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Contact:
Address: Büyükdere Cad.
105/9 34394 Mecidiyeköy, Şişli,
İstanbul, TURKEY
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

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Aims and Scope

Eurasian Journal of Medicine (Eurasian J Med), is the official journal of Atatürk University School of Medicine. The journal is a peer-reviewed, nonprofit scientific periodical. Three English-language issues have been published each year on February, June and October.

The aim of the Eurasian Journal of Medicine is to publish original research papers of the highest scientific and clinical value in all medical fields. The Eurasian J Med also includes reviews, case reports, editorial short notes, images of interest and letters to the editor that are related to recently published articles.

The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Eurasian Journal of Medicine is indexed in PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Scopus, EMCare, DOAJ, HINARI, EBSCO, CINAHL, Index Copernicus, GALE, ProQuest and Turkiye Citation Index.

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.eajm.org. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Atatürk University School of Medicine. Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Atatürk University School of Medicine, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

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Editor in Chief: Prof. Mecit Kantarcı
Address: Ataturk University School of Medicine, 25240, Erzurum, Turkey
Phone: +90 442 236 09 88
Fax: +90 442 236 09 68
E-mail: eajm@atauni.edu.tr

Publisher: AVES
Address: Büyükdere Avenue, 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
Web page: www.avesyayincilik.com

The Eurasian
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Official Journal of Atatürk University School of Medicine

Instructions for Authors

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Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to the Eurasian Journal of Medicine will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, releases signed by the patient or their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors

(ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are respon-

The Eurasian Journal of Medicine
Official Journal of Atatürk University School of Medicine

sible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Eurasian Journal of Medicine requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.eajm.org) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Eurasian Journal of Medicine requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

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MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2017 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.eajm.org. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

during the initial submission. These forms are available for download at www.eajm.org.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,

The Eurasian Journal of Medicine
Official Journal of Atatürk University School of Medicine

- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Materials and Methods, Results, and Discussion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Report, and Discussion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Image of Interest	250	No abstract	2	No tables	2 or total of 4 images
Letter to the Editor	500	No abstract	5	No tables	No media

The Eurasian Journal of Medicine
Official Journal of Atatürk University School of Medicine

comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Images of Interest: Our image section consists of a case report of 250 words, a few instructional points, a maxi- mum of two gures, and two references. We do ask that authors indicate that they have obtained patient consent if applicable. Image submissions should also include a title page, keywords and references. No additional legend subtitles for gures are necessary.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

DIGITAL IMAGE GUIDE

The Eurasian J Med requires that all digital artwork be prepared according to professional standards. Digital files must meet the Journal requirements to be accepted for publication.

Files that do not meet the guidelines will be rejected. Please refer to the instructions below when preparing images for publication.

A. Image Preparation Checklist. To verify that you have fulfilled the requirements for electronic image preparation, use the following checklist. Each category is expanded below the checklist (Table 3).

- Black-and-white images are saved in grayscale mode (not black and white).
- Photographic images are saved in RGB color mode (not CMYK or indexed color).
- Files are submitted in native TIFF or EPS and are not embedded in another program such as Microsoft Word, PowerPoint, or Excel.
- Charts or illustrations created in Microsoft Office (Word, PowerPoint, Excel) are submitted in native format and do not include embedded images.
- Charts created in SPSS, SigmaPlot or ChemDraw are submitted as EPS images.
- All graphics are sized to 100% of their print dimensions so that no scaling is necessary (3.2" wide for 1-column figures and 6.4" wide for 2-column figures).
- Images have been scanned according to our scanning guidelines.
- Files are named using our recommended naming conventions.

B. Color. When preparing digital images for publication, it is important to scan and save the electronic files in the correct color space.

1. Photographic images. Images such as photographs, angiograms, echocardiograms, etc., should be scanned and saved in RGB color mode, even if the images will be printed in grayscale. (The journal compositors will convert these images to their final grayscale or CMYK color modes.) Note: Printing in color is expensive and is not

The Eurasian Journal of Medicine
Official Journal of Atatürk University School of Medicine

always necessary. Please inform the Journal editors if an image requires color for clarity.

2. Line art. Black-and-white images, including line drawings, charts, graphs, and ECG and EEG tracings, should be scanned and saved in grayscale mode (not black-and white or color). (For charts created in SPSS, refer to Section C.2 on creating EPS file formats. For charts and graphs created in Microsoft Office, refer to Section C.3.)
3. Avoid ICC Profiles. Images should not contain any ICC profiles.

C. File Format. Submit only TIFF or EPS for electronic images. See instructions for submitting artwork that was created in Microsoft Office programs (Word, PowerPoint, Excel).

1. TIFF (Tagged Image File Format). TIFF is recommended for photographic images. When preparing TIFF images, be sure to refer to our scanning guidelines for the proper resolution. Note: The Journal accepts TIFF images that are saved with LZW compression; choosing this option will result in smaller files. In most software programs, a TIFF is made by choosing File/Save as… or Export/TIFF or TIF. For more information, consult the Help menu of your software.

2. EPS (Encapsulated Postscript). EPS is recommended for line art, charts, and illustrations that are created using professional drawing programs such as Adobe Illustrator, SPSS, ChemDraw, CorelDraw, SigmaPlot, etc. When submitting EPS files for publication, be sure to use the following guidelines:

- Convert text to outlines or include/embed fonts. Use only Journal-approved fonts.
- Flatten any layers.
- Use line weights greater than 0.5 points.
- Include an 8-bit preview/header at a resolution of 72 dpi.
- Save color images in RGB color mode.

In most drawing programs, an EPS file is made by choosing File/Save as … or Export/EPS. For more information, consult the Help menu of your software.

3. Microsoft Office (Word, Excel, PowerPoint). Charts and illustrations created in any Microsoft Office programs are accepted. Do not submit Microsoft Office files that contain embedded images. When creating charts and illustrations, use the following guidelines:

- Work in black and white, not color.
- Do not use patterns for fill color; use black, white, and shades of gray.
- Avoid 3-dimensional charts.
- Use only Journal-approved fonts.
- Use line weights greater than 0.5 points.
- Submit the grouped image so that the Journal compositors can access the datasheet.

4. AVOID THE FOLLOWING:

- Submitting graphics that are downloaded or saved from Web pages. The resolution will be too low, regardless of how the image looks on screen.
- Submitting GIF files. GIF files are never appropriate for publication. Scanning preprinted photographs (already published halftones). The printing process introduces distortion into the photograph that will transfer to the scan.
- Generating TIFFs within the Microsoft Office Document
- Scanning Program. This proprietary program changes the image formatting in such a way that the image cannot be opened in our image evaluation program.

D. Resolution and Scanning
1. Images must be scanned at the proper resolution to ensure print quality. Use the following guidelines to select the correct scanning resolution. Images that are scanned at lower resolutions will be rejected.

- Photographic images without text or arrows: 300 dpi/ppi
- Photographic images with text or arrows: 600 dpi/ppi
- Black-and-white line art: 1200 dpi/ppi

a. Scanning photographic images without text or arrows

- Scan in RGB mode.
- Scan at 300 dpi/ppi.
- Select a target width of 7.5 cm for 1-column figures and 15.5 cm for 2-column figures.
- Crop images tightly; do not scan the margins.
- Use the Eurasian J Med naming convention; save as a TIFF and apply LZW compression.

b. Scanning photographic images with text or arrows

- Scan in RGB mode.
- Scan at 600 dpi/ppi (even if text or labels will be added after the image is scanned).
- Select a target width of 7.5 cm for 1-column figures or 15.5 cm for 2-column figures.
- Crop images tightly; do not scan the margins.
- If adding labels, use an approved font. If the labels are pixilated, you may be asked for an unlabeled version.
- Use the Eurasian J Med naming convention; save as a TIFF and apply LZW compression.

c. Scanning black-and-white line art

- Scan in grayscale mode.
- Scan at 1200 dpi/ppi.
- Select a target width of 7.5 cm" for 1-column figures and 15.5 cm" for 2-column figures.

The Eurasian
Journal of Medicine
Official Journal of Atatürk University School of Medicine

- Images should be tightly cropped; do not scan the margins.
- If adding labels, use an approved font. If the labels are pixilated, you may be asked for an unlabeled version.
- Use the Eurasian J Med naming convention; save as a TIFF and apply LZW compression.

2. Scanning originals that are smaller than the target width

- Choose the correct color space for the photographic image or line art.
- Determine the correct resolution. If an image has a width smaller than the target width, it is necessary to compensate by increasing the scanning resolution. To increase the resolution, divide the actual width by the target width (either 7.5 cm or 15.5 cm). Multiply the answer by the target dpi and round up to the nearest hundred. The result will determine the scanning dpi. Use the following example: If an image is 2.4" wide and needs to be 300 dpi/ppi at 3" wide, then 3 divided by 2.4 = 1.251.25, 1.25 times 300 = 375, and round up to 400. Thus, if the 2.4" image is scanned at 400 dpi/ppi, the Journal can properly convert the image to be 3" wide at 300 dpi.
- Use the Eurasian J Med naming convention and save.

E. Naming Files

1. Naming convention. Please use the following naming convention for electronic images:

Author last name + figure number.file format
For example: Okur1.eps or Okur1A.tif

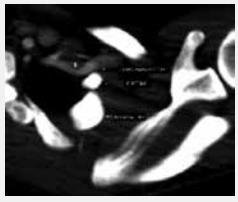
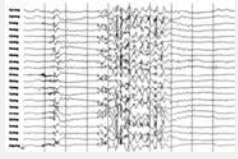
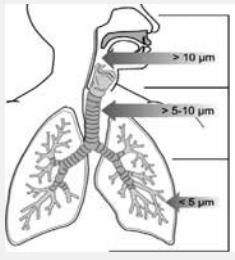
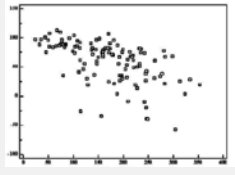
2. Revising images. Any time that you revise an image and resubmit it to the Journal, you need to add a version number to ensure that the image will be re-evaluated.

For example: Smith1.eps would be saved the next time as Smith1_v2.eps

Note: Always allow the software program to add the file format extension. Files that do not contain an extension will be rejected. To change a file format extension, you must use a software program; renaming a file extension does not properly convert a file. For example, simply renaming the JPG extension as TIFF does not convert the file to a TIFF image. Opening a JPG file in Photoshop (or in a comparable software program) and saving as a TIFF does properly convert the file.

Note: You can safely change the author last name + figure number (i.e., anything before the "dot-file format" portion) by using the Rename command.

F. Approved Fonts. Please use one of the following fonts for text in labels, graphs, and charts:

Type	Example	Format/Color Mode/Resolution
Photographic images without text or arrows		TIFF/RBG/300 dpi-ppi
Photographic images with text or arrows		TIFF/RBG/600 dpi-ppi
Black-and-white line art		TIFF/Grayscale/ 1200 dpi-ppi
Black-and-white line art from a professional drawing program such as Adobe Illustrator		EPS/Grayscale/ NA
Black-and-white chart or graph from Microsoft Office program		PPT or XLS/NA (Use blacks, whites and shades of gray.)/NA

- Adobe Garamond
- Arial
- Helvetica
- Symbol
- Times New Roman
- Univers LT

G. Labels

1. Do not place figure labels (A, B, C, etc.) on the digital images; include the letter in the figure file name (for example, Smith2B.tif).

The Eurasian Journal of Medicine
Official Journal of Atatürk University School of Medicine

2. If images are part of an A, B, C series, scan and submit each image separately.
H. How to Submit Images. To submit digital artwork, refer to the information in the Manuscript Submission section.

References
While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first three authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Ahn SS, Kim YJ, Hur J, et al. Preparing first-year radiology residents and assessing their readiness for on-call responsibilities: results over 5 years. AJR Am J Roentgenol 2009; 192: 539-44.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.
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Editor in Chief: Prof. Mecit Kantarcı
Address: Ataturk University School of Medicine, 25240, Erzurum, Turkey
Phone: +90 442 236 09 88
Fax: +90 442 236 09 68
E-mail: eajm@atauni.edu.tr

Publisher: AVES
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
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Preoperative Computerized Tomographic Assessment of Regional Lymph Node and Extramural Vascular Invasion in Colonic Cancer

Andrew T. W. McAvoy[1], Krishnan Gokul[1], Apam Chiphang[2], Dmitri Y. Artioukh[1]

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ORCID IDs of the authors:
A.T.W.M. 0000-0002-0534-5468;
K.G. 0000-0002-2551-6770;
A.C. 0000-0002-8859-8291;
D.Y.A. 0000-0002-8068-4128.

[1]Department of Surgery, Southport and Ormskirk Hospital, Southport, United Kingdom
[2]Department of Radiology, Southport and Ormskirk Hospital, Southport, United Kingdom

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Correspondence to: Andrew T W McAvoy
E-mail: andrew.mcavoy@hotmail.co.uk

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ABSTRACT

Objective: There have been recent attempts to transfer well-established principles of rectal cancer management to colonic cancer, thereby offering neoadjuvant chemotherapy to high-risk patients at least in the trial settings. Traditionally, postoperative chemotherapy is offered to patients with colonic tumors that metastasize into regional lymph nodes and have features of extramural vascular invasion (EMVI). If the same criteria are used for the selection of patients with colonic cancer for neoadjuvant chemotherapy, then their accurate preoperative detection becomes of paramount importance. The aim of the study was to establish the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the computerized tomographic (CT) assessment of lymph node involvement and EMVI in colonic cancer.

Materials and Methods: This retrospective study included 53 consecutive adult patients (35 males and 18 females; median age, 72 years) who had complete preoperative CT staging of colonic cancer followed by its surgical resection during a 12-month period from January 1, 2012, to December 31, 2012. Patients with rectal and colonic tumors presenting as an emergency who did not have complete preoperative CT imaging were excluded. Preoperative CT findings on regional lymph node status and EMVI were compared with the final histopathological staging of resected specimens calculating sensitivity, specificity, PPV, and NPV of the test.

Results: In predicting regional lymph node metastases, CT scan had a sensitivity of 85% and a specificity of 24%. PPV was calculated as 63% and NPV as 50%. In predicting EMVI, it had a sensitivity of 69% and a specificity of 49%. PPV was 37% and NPV was 78%.

Conclusion: Preoperative CT scan does not allow an accurate detection of regional lymph node metastases and EMVI and has a tendency to overstage colonic cancer.

Keywords: Colonic cancer, computerized tomography, extramural vascular invasion, neoadjuvant treatment

Introduction

Colorectal cancer is the fourth most common malignancy in the UK, with a crude incidence rate of 72 new cases for every 100,000 males and 56 for every 100,000 females, with almost three quarters of these tumors occurring in the colon [1]. Despite similar disease morphology, the treatment strategies for colonic and rectal cancer are different. In rectal cancer, neoadjuvant chemoradiation has a recognizable role aiming to downsize and/or downstage tumors that are at a risk of incomplete excision. More recently, there has been a tendency to transfer the successful and well-established principles of rectal cancer management to colonic cancer. Thus far, these took two directions mainly in the trial settings. First, more surgeons started to advocate the technique of total mesocolic excision similar to the total mesorectal excision in rectal cancer surgery [2]. Second, attempts have been made to offer neoadjuvant chemotherapy to patients with colonic cancers to improve survival, particularly in high-risk groups [3]. Traditionally, postoperative adjuvant chemotherapy has been offered to patients with colonic tumors that metastasize into regional lymph nodes (Dukes' C) and have features of extramural vascular invasion (EMVI) knowing that their 5-year survival rate does not exceed 60%–70% [1]. If the same criteria were to be used for the selection of patients with colonic cancer for neoadjuvant chemotherapy, then an accurate preoperative diagnosis of pathological regional lymphadenopathy and EMVI will become of paramount importance. Vascular spread is an important biomarker for the prediction of distant metastases. The detection of malignant cells in the intra- and peritumoral vessels may indicate the initiation of metastatic process, suggesting that systemic treatment would be beneficial in altering the prognosis.

Objectives

The aim of the study was to assess the accuracy of the computerized tomographic (CT) scan as the only widely used staging modality for colonic cancer in the preoperative detection of regional lymph node metastases and EMVI because these factors may potentially help in the selection of patients suitable for neoadjuvant chemotherapy.

Materials and Methods

All consecutive adult patients who underwent surgical resection for histologically proven invasive colonic cancer in a 12-month period between January 1, 2012, and December 31, 2012, were included. Basic demographic characteristics, including age and sex; the site of the tumor; and data on postoperative histological pTNM stage, Dukes' stage, and regional lymph node harvest were retrospectively collected. Patients with rectal and colonic tumors presenting as an emergency who did not have complete preoperative CT imaging were excluded. Preoperative thoracic and abdominal CT scan reports were also obtained, and the radiological TNM staging and EMVI status were recorded. Multi-detector CT scanner (64 slice GE scanner) was used to obtain the staging scan of the colon in the portovenous phase. An iodine-based contrast agent was injected via the intravenous route, and images were obtained 70 s post-contrast delivery. CT scans were performed with 2.5-mm slice thickness. CT characteristics of the metastatic lymph node involvement comprised its increased size (>10 mm), round as opposed to elliptical shape, irregular contour, cystic density suggestive of central necrosis, heterogenous post-contrast enhancement, and clustering of three or more lymph nodes. Regional lymph node metastases were described in accordance with the TNM classification of malignant tumors, 7th Edition, UICC [4]. The tumor was radiologically staged as N2 in the presence of more than three lymph nodes exhibiting the abovementioned characteristics. The radiological interpretation of EMVI was based on the presence of tumor "tongue" along the peritumoral veins, their stranding, nodular enlargement, or obvious blood vessel invasion (Figure 1-3). In some cases, the tumor tissue expanded the vessel, as shown in Figure 2. CT data on lymph node status and EMVI were compared with the findings on the histopathological examination of the resected specimens calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) as well as the accuracy of the preoperative CT staging. This retrospective study was using previously collected hospital, radiological, operative and histological data and

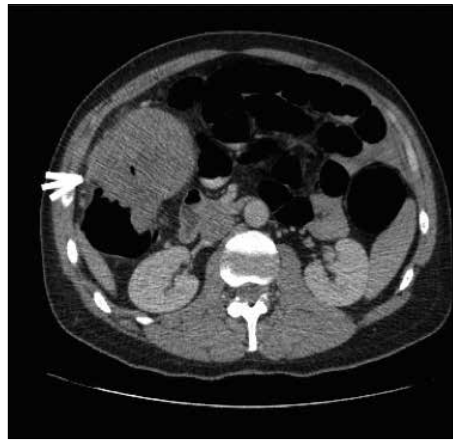

Figure 1. CT scan (axial view) showing tumor of the hepatic flexure of the colon with features of EMVI (blue arrow)

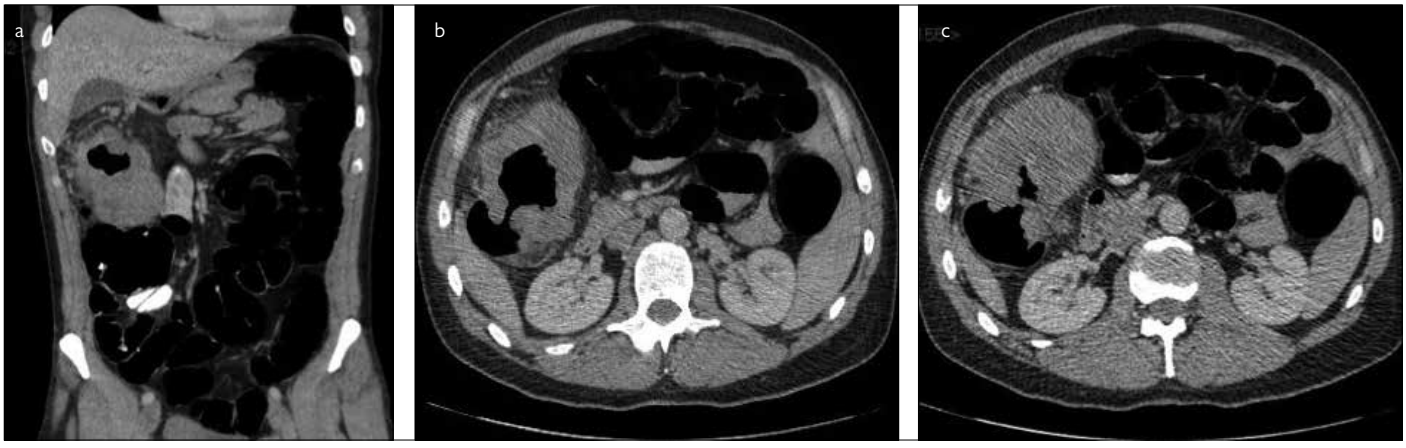

Figure 2. Coronal (a) and axial (b) CT post-contrast portovenous images of a stricturing hepatic flexure tumor with a prominent draining vessel [a key feature of extramural vascular invasion (red arrow), Axial CT portovenous phase images with nodal disease (green arrow) and hepatic flexure stricturing tumor (c)

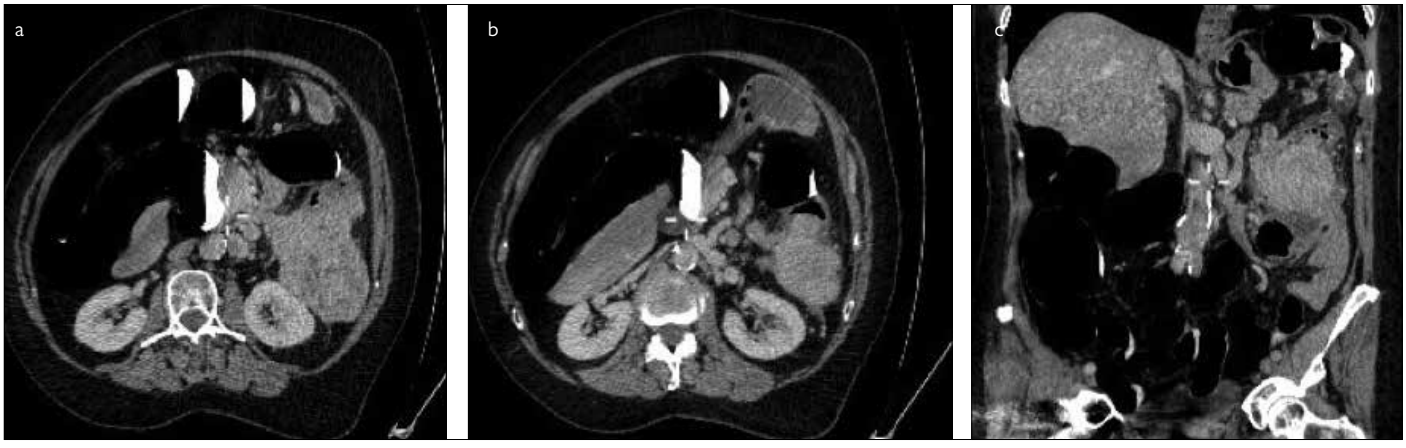

Figure 3. Axial CT portovenous phase with enlarged enhancing right retroperitoneal lymph node (green arrow) and a circumferential tumor of the descending colon (a), Axial CT in the portovenous phase (b) and coronal CT images (c) with dilated enhancing vessel and nodular outline features of extramural vascular invasion (red arrow)

did not require Ethics Committee approval. The study did not require specific consent apart from informed consent apart from informed written consent obtained from each patient at the time of surgical intervention.

Results

Fifty-three patients (35 males and 18 females) underwent resections for colonic cancer, as summarized in Table 1. Their median age was 72 (range, 46–93) years. Eleven (21%) patients had tumors located in the cecum, ten (19%) had tumors located in the ascending colon, three (6%) had tumors located in the hepatic flexure, nine (17%) had tumors located in the transverse colon, three (6%) had tumors located at the splenic flexure, three (6%) had tumors located in the descending colon, and fourteen (26%) had tumors located in the sigmoid colon. The histopathological staging was T1 in none (0%) of the patients, T2 in six (11%), T3 in 28 (53%), and T4 in 19 (36%). Lymph node status was N0 in 21 (40%), N1 in 16 (30%), and N2 in 16 (30%). The median lymph node harvest was 17 (range 5–40). Therefore, no patients had Dukes' A tumor, 21 (40%) had Dukes' B, 28 (53%) had Dukes' C, and 4 (7%) had Dukes' D cancer.

Table 1. Summary of patient and tumor characteristics

Characteristics	N=53 (%)
Age (median)	72 (46–93)
Sex	
Male	35 (66%)
Female	18 (34%)
Tumor Location	
Cecum	11(21%)
Ascending colon	10 (19%)
Hepatic flexure	3 (6%)
Transverse colon	9 (17%)
Splenic flexure	3 (6%)
Descending colon	3 (6%)
Sigmoid	14 (26%)
Tumor Stage	
T1	0
T2	6 (11%)
T3	28 (53%)
T4	19 (36%)
N0	21 (40%)
N1	16 (30%)
N2	16 (30%)
M1	4 (8%)
Dukes A	0 (0%)
Dukes B	21 (40%)
Dukes C	28 (53%)
Dukes D	4 (7%)
Median Lymph Node Yield	17 (Range: 5–40)

Table 2. Preoperative CT prediction of lymph node status and EMVI in comparison with histological examination of resected specimens

	Lymph Node Prediction	Extramural Vascular Invasion Prediction
Sensitivity	85%	69%
Specificity	24%	49%
Positive Predictive Value	63%	37%
Negative Predictive Value	50%	78%

Lymph node status prediction

CT imaging identified 43 lymph node-positive and 10 lymph node-negative patients. However, only 32 patients had histologically proven lymph node metastases. CT scan had a sensitivity of 85% and a specificity of 24% in the prediction of regional lymph node metastases. PPV was 63%, and NPV was 50% (Table 2).

Extramural vascular invasion prediction

CT imaging identified features of EMVI in 30 patients. Twenty-three patients were EMVI-negative. Postoperative histological examination revealed EMVI-positive tumors in 16 patients and EMVI-negative tumors in 37. CT prediction of EMVI had a sensitivity of 69% and a specificity of 49%. PPV was 37%, and NPV was 78% (Table 2).

Discussion

The choice of treatment of newly diagnosed malignancy depends on its accurate staging. Of the three main modalities [CT, magnetic resonance imaging (MRI), and positron emission tomography (PET)], CT and, to a lesser extent, PET scans have played the role of the exclusion of distant metastases in both colonic and rectal cancers, thereby allowing the selection of patients for potentially curative treatment. The use of MRI for the local staging of rectal tumors has greatly helped in identifying patients at a risk of incomplete tumor excision and in selecting them for neoadjuvant treatment [5]. Thus, in rectal cancer, downstaging and/or downsizing neoadjuvant chemoradiation has become a standard practice when the feasibility of complete excision is questioned because of the proximity of the tumor and/or pathologically enlarged lymph nodes to the mesorectal fascia ultimately forming the circumferential resection margin [6]. MRI has proved to be less accurate for the local staging of colonic cancer and has been of minimal clinical relevance thus far because after CT exclusion of distant metastases, the vast majority of patients with colonic cancer are offered immediate surgery. In contrast to rectal tumors, surgical resection has remained the main treatment for colonic tumors thus far, with 80% of patients receiving resection of the primary tumor as the first treatment step. Colonic resection can be followed by adjuvant chemotherapy (and occasionally radiotherapy) if adverse prognostic characteristics are identified on the histological examination of the resected specimen [7].

More recently, attempts have been made to advocate neoadjuvant chemotherapy to patients with colonic cancer [3]. Arguably, chemotherapy administered before surgery has a theoretical advantage of the early treatment of micrometastases, addresses adverse consequences of inevitable malignant cell shedding during surgical manipulation, allows better delivery of anti-neoplastic agents via undisturbed blood supply to the tumor, and is probably associated with better patient compliance [6]. Thus, neoadjuvant chemotherapy for locally advanced colonic cancer is currently being investigated by FOXTROT trial. Although the trial demonstrated downstaging in T3 and T4 tumors, neither nodal status nor the presence of EMVI was used in the inclusion criteria [3]. In addition to TNM staging, several other tumor-related factors are linked to adverse oncological outcomes, such as histological differentiation, mucin production, host lymphoid response to the tumor, tumor border configuration, absence of microsatellite instability, and loss of heterozygosity at chromosome 18q [8]. The features of EMVI and perineural invasion are also associated with adverse prognosis [9]. EMVI can be defined as the direct invasion of a blood vessel by the tumor. The presence of malignant cells in the intra- and peritumoral vessels, even if these developed because of the process of neovascularization, may indicate the initiation of systemic hematogenous spread, which indicates a poor prognosis [10] and warrants systemic chemotherapy. Angiogenesis, when proven, can also be used for targeted therapies [10].

Currently, the standard practice is to offer postoperative chemotherapy mainly to patients with histologically proven regional lymph nodes metastases and EMVI. If the same factors could be confidently established by accurate preoperative staging, then it could theoretically also aid in the selection of patients for neoadjuvant treatment.

Preoperative staging is both technology- and operator-dependent and, therefore, has variable results [11]. Currently, CT is the only practical tool for the staging of colonic cancer. Choi et al. [12] evaluated the preoperative CT assessment

of regional lymphadenopathy and reported a sensitivity of 88%, specificity of 66%, PPV of 59%, and NPV of 88%. A meta-analysis by Dighe et al. [13] included 19 studies comprising a total of 907 patients and found an overall CT sensitivity of 70% and specificity of 78% for the detection of regional lymph node involvement. The sensitivity of 85% in our series is in line with the abovementioned studies. CT detection of EMVI is even more challenging with an inter-observer variation between 54.5% and 61.0% and has reported sensitivity of 58%, specificity of 95%, and accuracy of 53% [14, 15]. Unlike in rectal cancer imaging, MRI and PET scans in colonic cancers have low sensitivity values [16-18]. Rollven et al. [16] compared high-resolution MRI with CT in the detection of the locally advanced stage, nodal, and EMVI positivity of colonic cancer and concluded that MRI may offer a slight advantage in accuracy. However, more recently, Hunter et al. [19] stated that they could not recommend that MRI should replace CT. PET/CT scan also proved to be inferior to CT scan alone in the detection of lymph node-positive disease [18].

Previous studies have suggested that the administration of neoadjuvant chemotherapy on a single criterion of the radiologically detected enlargement of the regional lymph nodes would result in overtreatment due to the lack of specificity; therefore, the search for additional indicators such as EMVI. Our results showed that the risk of neoadjuvant oncological overtreatment remained even when the selection was based on both the lymph node status and EMVI as judged on the preoperative CT scan. The future developments in this field will depend on whether the ongoing trials will prove the benefit of neoadjuvant chemotherapy to make it a standard of treatment in selected patients with colonic cancer and whether new diagnostic imaging modalities will become available to aid such a selection with more accuracy than the currently available CT scan.

In conclusion, the preoperative staging of colonic cancer by CT scan does not allow an accurate detection of regional lymph node metastases and EMVI.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Analysis of Intravenous Urography Findings in a Tertiary Reference Center

Hameed M. Aklan[1], Abdullah Mikhlafy[2]

ABSTRACT

Objective: To analyze intravenous urography (IVU) findings in a tertiary reference center.

Materials and Methods: A retrospective, observational study was conducted in a tertiary reference center. The radiology reports of 1,470 patients subjected to IVU in the period from January 2008 to December 2012 were retrieved from the tertiary reference center databases. Patients' demographic characteristics, type of care (inpatient or outpatient), and IVU radiologic findings were reviewed and analyzed.

Results: Of 1470 patients, approximately two-thirds were males. The mean age of the patients was 39.12±14.80 years (range: 2–95). Most of them were inpatients (92.9%; 1365/1470). The IVU findings were abnormal in 68.8% (1012/1470) of patients. Urinary tract calculi were the most frequent type of calculi observed among patients (36.8%; 541/1470), and the kidney was the most frequently affected organ by calculi (66.5%; 541/814). Hydronephrosis was the second most frequent finding, being observed in 29.7% (436/1470) of patients.

Conclusion: The presence urinary tract calculi was the most frequent IVU finding, revealing that urolithiasis could be the main indication for IVU.

Keywords: Intravenous urography, radiology, uroradiology

ORCID IDs of the authors:
H.M.A 0000-0002-4265-549X;
A.M. 0000-0001-6408-2154.

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[1]Department of Radiology, University of Science and Technology School of Medicine and Health Sciences, Sana'a, Yemen
[2]Department of Community Medicine, University of Science and Technology School of Medicine and Health Sciences, Sana'a, Yemen

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Correspondence to: Hameed M. Aklan
E-mail: hameedaklan@yahoo.com

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Introduction

Uroradiology emerged approximately a year after the discovery of X-rays in 1895, when it was first applied in the detection of urinary tract calculi. Following the discovery of various contrast materials that could be installed into the urinary tract, new applications were introduced, including cystography in 1903 and retrograde pyelography in 1906 [1].

Intravenous urography (IVU) was the most recommended radiologic examination for the diagnosis of urinary tract abnormalities until the end of the 20th century [2, 3]. In the late 1970s, ultrasonography started to be widely used in clinical practice. It was particularly useful to differentiate solid from cystic masses, thus avoiding direct cyst puncture [3]. Computed tomography (CT) scanning was introduced in the study and staging of renal masses in the 1980s [2]. Later, the diagnostic utility of CT imaging was improved by shortening the scanning time and radiation exposure as well as introducing multiplanar three-dimensional (3-D) reconstruction [4]. Nowadays, CT scanning is the "gold standard" of urologic imaging [4]. Multiphasic CT urography (CTU) has become the most suitable tool for the diagnosis of different urinary tract abnormalities, including congenital anomalies, infections, traumas, and tumors. In addition, its "one-stop-shop" use in the evaluation of vascular, parenchymal, and urothelial problems has a great impact on their management [5].

Reformatted 3-D CTU from thin-cut axial helical CT scans can create a coronal image similar to that of IVU. In addition to being easily interpreted by the clinicians unfamiliar with axial CT scan images, it improves the accuracy of diagnosing urinary tract abnormalities [6–8]. However, despite the recommendations by urology associations [9], IVU is still being requested by clinicians, particularly urologists, and is still being performed by radiologists, especially in the developing countries [9, 10]. Therefore, the aim of the present study was to retrospectively assess the trend of IVU use in the radiologic diagnosis of urinary tract abnormalities in patients attending a tertiary reference hospital in Sana'a city over a 5-year period.

Materials and Methods

Study Design and Data Collection

This retrospective, observational study was conducted at the Radiology Department of University of Science and Technology Hospital, a tertiary reference hospital in Sana'a, Yemen. Radiology reports of 1470 patients who were subjected to IVU in the period from January 2008 to December 2012 were retrieved from the hospital databases. Demographic characteristics of patients (e.g., age and gender), type of patient's care (inpatient or outpatient), and the IVU radiologic findings were collected and then analyzed.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software, version 18.0 (SPSS Inc., Chicago, IL, USA). Frequencies and percentages were used to present the data of categorical variables.

Ethical Approval

This study was approved by the Research Ethics Committee of the School of Medicine, University of Science and Technology, Yemen. All data were dealt with confidentially and were used anonymously and for research purposes only.

Results

Characteristics of the Study Population

Table 1 shows that approximately two-thirds of patients subjected to IVU for the radiological diagnosing of urinary tract abnormalities were males and 94.8% (1394/1470) were older than 18 years (94.8%; 1394/1470). Moreover, the majority of patients referred for the radiological diagnosis using IVU were from the hospital admitted patients (92.2%; 1365/1470).

Distribution of Abnormal IVU findings According to Certain Population Characteristics

Table 2 shows an overall abnormal IVU finding rate of 68.8% (1012/1470) in the urinary tract of patients undergoing IVU. There was a statistically significant difference in the abnormal IVU radiologic findings according to the gender and type of patient's care, wherein males and outpatients showed higher abnormality rates of 72.7% and 86.7%, respectively.

Distribution of Abnormal IVU Findings According to the Types of Affected Organs

Table 3 shows that the presence of calculi (36.8%; 541/1470) was the most frequent kidney abnormality, followed by hydronephrosis (29.7%; 436/1470). However, other structural and functional abnormalities of the kidneys were observed among 6.3% or less of patients undergoing IVU. Conversely, the presence of ureteral calculi was the most frequent abnormality in the ureters 17.6% (261/1470); however, the structural abnormalities of the ureter kinking and tortuous ureter were less frequently observed. Abnormalities in the urinary bladder were the least frequently observed IVU abnormalities of the urinary tract with diverticula being the most frequent finding among 1.0% (14/1470) of patients. According to the location of calculi in the urinary tract, most calculi were observed in the kidneys (66.5%; 542/814), followed by those in the ureters (31.9%; 260/814). However, bladder and pelvi-ureteric junction were the least frequently affected parts of the urinary tract with less than 1.0% of calculi being observed in each (Table 4).

Trend of IVU Use in the Tertiary Reference Hospital

Figure 1 shows an increasing trend of IVU use over the period of the study in a tertiary reference hospital, where most procedures (397) were performed in 2012.

Table 1. Characteristics of patients undergoing IVU*

Variable	n (%)
Gender	
Male	982 (66.8)
Female	488 (33.2)
Age (years)	
Mean±SD=39.12±14.80 (range: 2–95)	
<18	76 (5.2)
≥18	1394 (94.8)
Type of patient care	
Inpatients	1365 (92.9)
Outpatients	105 (7.1)

*Total number of patients is 1470; SD: standard deviation
IVU: Intravenous urography; n: number of patients

Table 2. Distribution of abnormal IVU radiologic findings among patients

		Abnormal IVU Findings
Variable	N	n (%)
Overall abnormal findings	1470	1012 (68.8)
Gender		
Male	982	714 (72.7)
Female	488	298 (61.1)
Type of patient care		
Inpatient	1365	921 (67.5)
Outpatient	105	91 (86.7)

IVU: Intravenous urography; N: total number of patients investigated; n: number of patients with abnormal IVU findings

Discussion

The advent of technology has led to the loss of the importance and relevance of some older techniques and their replacement with newer ones that are more sensitive and specific, less invasive, and cheaper [11]. Although IVU was the "gold standard" imaging procedure for the urinary tract, this role has been shifted to CT scanning as a result of its advent and subsequent improvements over the last 2 decades [4]. In the present study, however, the trend of IVU

Table 3. Types of abnormal IVU radiologic findings among patients according to the type of affected organs*

Organ	Type of Abnormality	n (%)
Kidney		
	Calculi	541 (36.8)
	Hydronephrosis	436 (29.7)
	Delayed secretion	92 (6.3)
	Small size	22 (1.5)
	Non-functioning kidney	15 (1.0)
	Poor secretion	13 (0.9)
	Large size	10 (0.7)
	Ectopic kidney	10 (0.7)
	Absence of kidney	10 (0.7)
	Agenesis	9 (0.6)
	Horseshoe kidney	8 (0.5)
	Sac-like kidney	2 (0.1)
Ureter		
	Calculi	260 (17.6)
	Ureteral kinking	6 (0.4)
	Tortuous ureter	2 (0.1)
Urinary bladder		
	Diverticula	14 (1.0)
	Irregular wall	12 (0.8)
	Neurogenic bladder	9 (0.6)
	Calculi	7 (0.5)
	Focal wall thickening	5 (0.3)

IVU: Intravenous urography; n: number of patients with abnormal IVU findings
*Total number of patients investigated was 1470

Table 4. Frequency distribution of urinary tract calculi among patients

Location of Calculi	n (%)
Kidney	541 (66.5)
Ureter	260 (31.9)
Bladder	7 (0.9)
Pelvi-ureteric junction	6 (0.4)
Total	814 (100)

n: number of patients with calculi

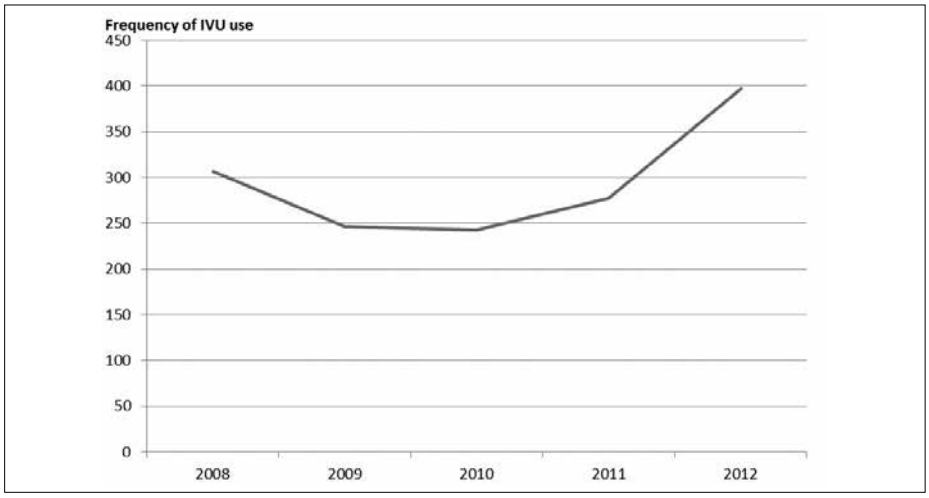

Figure 1. Trend of the IVU use as a diagnostic procedure among patients

use in a tertiary reference hospital in Sana'a has increased over the years. It is noteworthy that the tertiary reference hospital is one of the largest private tertiary care hospitals in Yemen with a 200-bed capacity and equipped with modern medical equipment, including those for sonography, CT scan, and magnetic resonance imaging.

The present finding that about two-thirds of patients subjected to IVU were males is consistent with those reported from Jordan and Pakistan, being 60.0% and 63.0%, respectively [10, 12]. However, it is in contrast to a finding reported from the United States, where most cases (73.0%) were those of females [4]. It is noteworthy that the higher proportion of females undergoing IVU in the latter study could be attributed to the fact that most IVU requests (38.0%) were from the Department of Obstetrics and Gynecology.

Although IVU is an unsafe radiologic procedure with side effects such as radiation exposure, possible allergic reactions, and nephrotoxicity [13], most radiologic findings usually appear normal with varying percentages from one study to another. In the present study, the IVU findings were normal in 31.2% of patients. This is comparable to those reported from Pakistan and Brazil, being 26.0% and 23.1%, respectively [10, 11]. In contrast, a study conducted in Ireland reported higher proportion of IVU normal findings (77.0%) than our study [14].

The finding that 5.2% of IVU patient cases in the present study were younger than 18 years is consistent with that reported among Brazilian patients subjected to IVU, in which 3.6% of them were younger than 18 years [10]. The low proportion of children undergoing IVU in the present study reveals that Yemeni pediatric patients are exposed to the risk of radiation during the IVU procedures despite the availability of low-dose and ultra-low-dose CT protocols.

In the present study, the presence of urinary tract calculi was the most frequent IVU finding, and this reveals that urolithiasis could be the main indication of IVU. In 2011, the European Association of Urology (EAU) recommended that non-contrast-enhanced CT (NCCT) should be used to confirm calculi in patients presenting with acute flank pain because of its superiority to IVU and that in patients with a body mass index (BMI) of <30, low-dose NCCT protocols should be used [9]. Moreover, in its updated guidelines in April 2014, EAU recommended NCCT for the evaluation of patients to be treated for renal stones because it enables the 3-D reconstruction of the collecting system in addition to the measurement of stone density and skin-to-stone distance [15].

Although the IVU use shows a downward trend worldwide, the present study reveals its upward use in tertiary care hospitals in Yemen. Contrary to the findings of the present study, a study conducted in a single medical center in the United States showed a threefold decrease in the use of IVU over the period from July 1995 to February 2006 [16]. Similarly, the use of IVU substantially decreased from 323 cases in 1999 to 17 cases in 2006 in the Montefiore Medical Center, Bronx, USA, and IVU has not been performed in the Brigham and Women's Hospital, Boston, Massachusetts since 2000 [3]. The upward trend of IVU use in the present study could be attributed to the fact that clinicians do not fully appreciate that a more accurate delineation of the urinary tract can be performed using other alternative techniques such as CT scanning. In fact, CT is more sensitive and specific for the majority of urinary tract pathological conditions not just for flank pain and urolithiasis but also for hematuria and renal masses as well as the assessment of regional lymph nodes, where it has been found to be superior to all other imaging modalities [4, 17]. Recently, Hale et al. [4] found that 48.0% of patients who had undergone IVU went through additional radiologic studies within 30 days for a further evaluation of unresolved issues related to their initial complaint (i.e., persistent symptoms and/or no clear diagnosis with IVU). In addition, 36.0% of patients had either differing or additional diagnostic information that could lead to a change in medical decision making. Therefore, the need for these additional studies and their added information further demonstrates the diagnostic limitations of IVU and superiority of CT scanning [4].

Despite the higher radiation dose in conventional helical CT compared with IVU, this problem can be overcome by the use of new low-dose and ultra-low-dose helical CT protocols [18]. Therefore, exposure to radiation can be reduced to levels below those associated with IVU (0.97–1.9 millisievert "mSv" for low-dose NCCT compared with 1.3–3.5 mSv for IVU), while still remaining highly sensitive and specific for urinary abnormalities [18]. Low-dose CT has been shown to have a sensitivity level of 86.0% for detecting ureteric calculi smaller than 3 mm and 100% for calculi larger than 3 mm in patients with BMI <30 [18]. In addition, low-dose CT shows a pooled sensitivity of 96.6% and specificity of 94.9% for the diagnosis of urolithiasis in a meta-analysis of prospective studies concerning its diagnostic performance [19]. Conversely, cost could be supposed as another drawback of CT, where some clinicians still believe that IVU is more cost-effective. However, taking into consideration other factors such as the longer IVU procedure, cost of the room, and the personnel and follow-up tests required, IVU becomes more expensive than CT. This was confirmed by Pfister et al. [20], who found that NCCT can be a better alternative to IVU because of its higher diagnostic accuracy and better economic impact as a result of its higher effectiveness, faster performance, lower cost, and less risk compared with IVU. In addition, it also enables the detection of various additional renal and extra-renal pathological conditions [20].

Although the present retrospective study is limited by the fact that it was conducted in one hospital, the large sample size and length of the study duration can give clinicians and radiologists clear-cut prospects about the uroradiologic practice in the country for the sake of shifting to better radiodiagnostic alternatives.

In conclusion, IVU is still used excessively in Yemen. The presence of urinary tract calculi was the most frequent IVU finding, which reveals that urolithiasis could be the main indication for IVU.

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Sexual Dysfunction Is Associated with Depression and Anxiety in Patients with Predialytic Chronic Kidney Disease

Serkan Guven[1], Funda Sari[2], Ayca Inci[2], Ramazan Cetinkaya[2]

ABSTRACT

Objective: We aimed to determine the prevalence of sexual dysfunction and clarify the relationship between sexual dysfunction and depressive mood state, drugs, and disease activities in patients with predialytic chronic kidney disease (CKD).

Materials and Methods: In total, 150 patients with CKD who had an estimated glomerular filtration rate of 15–60 mL/min were included; 65 healthy controls were selected. A detailed medical and sexual medical history was taken from individuals in the control and patient groups by applying the Golombok–Rust Inventory of Sexual Satisfaction and Hospital Anxiety and Depression Scale.

Results: Sexual frequency (p=0.027), impotence (p<0.001), and premature ejaculation scores (p<0.001) in male patients and sexual frequency (p=0.004), communication (p=0.004),, satisfaction (p<0.001), avoidance (p=0.008), orgasmic dysfunction (p<0.001), sensuality (p=0.002), and total sexual dysfunction scores (p<0.001) in female patients with CKD were found to be higher compared with the control group. In female patients, the depression scores of patients with stage 3 CKD were found to be higher than those of patients with stage 4 CKD (p=0.028). The avoidance scores of male patients with depression (p=0.006) were high. In contrast, the communication score of female patients with depression was high (p=0.004). It has been detected that the factors that affect the sexual dysfunction score of patients with CKD in males are age (p=0.006), hypertension (p=0.008), anxiety (p=0.003), and depression (p=0.002) and those in female patients are age (p=0.034), anxiety (p<0.001), and depression (p=0.001).

Conclusion: Patients with predialytic CKD substantially have sexual dysfunction. The most important factors that affect sexual dysfunction are age, hypertension, anxiety, and depression.

Keywords: Chronic kidney disease, depression, anxiety, predialysis, sexual dysfunction

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[1]Department of Internal Medicine, Antalya Training and Research Hospital, Antalya, Turkey
[2]Division of Nephrology, Department of Internal Medicine, Akdeniz University School of Medicine, Antalya, Turkey

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Correspondence to: Funda Sari
E-mail: fundasari@ymail.com

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Introduction

Chronic kidney disease (CKD) is a worldwide public health issue. CKD is a chronic and progressive disease affecting every organ system of the body. It also affects the social, economic, and psychological status of patients [1-3]. In patients with impaired renal function, depression and anxiety disorders may develop because of loss of physical and mental capabilities and and their roles in the business life, family, and society; depression may thus be triggered in these patients by their initial disease. In studies investigating the psychiatric effects of organ failure in patients with CKD, the most frequently reported psychiatric disorder was depression [4-6].

Sexual function disorders are also frequently encountered in patients with CKD. However, these complaints are generally not reported to the physician mainly because of social and traditional reasons. Only 22% of patients with sexual dysfunctions inform their physicians about these complaints [4, 7-11].

Studies investigating sexual dysfunction in patients with CKD are quite limited, particularly during the predialysis period of the disease. In the present study, our aim was to determine the frequency of sexual dysfunctions in patients with predialytic CKD of stages 3, 4, and 5 and to determine the relation between sexual dysfunctions with depressive mood and anxiety.

Materials and Methods

This study was performed with a total of 150 sexually active patients (90 males and 60 females) with their partners who were followed up at the nephrology clinic for at least 6 months, who

had an estimated glomerular filtration rate (eGFR) of 10–60 mL/min/1.73 m^2, who were capable of understanding the study questions and expressing their thoughts, and who voluntarily participated in the study. A healthy control group of 65 individuals (30 males and 35 females) was selected from volunteers without any systemic disease, with a regular sexual life, and matching age and gender characteristics with the patient group. Participants in both groups were informed about the study, and written consent was obtained. The study was approved by the local ethics committee (ethics committee decision date and number: 03 April 2014, 38/10).

Complete blood count and ferritin, proteinuria, blood urea nitrogen, glucose, creatinine, uric acid, total protein, albumin, parathyroid hormone, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, carbon dioxide, sodium, potassium, calcium, and phosphorus levels were assessed.

The detailed sexual history of subjects in both groups was evaluated using the Golombok–Rust Inventory of Sexual Satisfaction (GRISS) scale. GRISS is a 28-item, Likert-type, self-report scale that evaluates the presence and severity of sexual dysfunctions. Two separate forms are developed for men and women. It not only provides overall scores of the quality of sexual functioning but also examines seven dimensions of sexual activity. Sexual frequency, communication, avoidance, sensuality, and satisfaction are the shared dimensions among both men and women. Men are additionally assessed for impotence and premature ejaculation. Vaginismus and orgasmic dysfunction are dimensions specific to women. High scores indicate greater severity of sexual dysfunctions [12].

The severity of anxiety and depression symptoms of the participants was evaluated using the Hospital Anxiety Depression Scale (HADS). HADS is a 14-item, Likert-type, self-report scale. Seven items of HADS measure depressive symptoms severity and seven items assess the severity of anxiety symptoms. Higher scores indicate greater psychopathology [13].

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 (IBM Corp.; Armonk, NY, USA) software package. Descriptive parameters were expressed as frequency, percentage, mean, standard deviation (SD), median, minimum (min), and maximum (max). Relations between categorical variables were analyzed using the Fisher's exact test or Pearson's chi-square test.

To test normality, the Shapiro–Wilk test was used when the number of samples in the group was less than 50, whereas the Kolmogorov–Smirnov test was used when the number of samples was greater than 50. Normality hypothesis was controlled using the Shapiro–Wilk test to analyze the differences between the measured values of the two groups. The Mann–Whitney U test was used for non-normally distributed data, whereas the Student's t test was used for normally distributed data. The Kruskal–Wallis test was used for non-parametric comparisons between more than two groups, whereas the Bonferroni–Dunn test was used in the post-hoc analysis of significant cases. Analysis of Variance (ANOVA) test was used for comparison between groups when the assumption of normal distribution was met, and the Šidák test was used for paired comparisons. Linear regression analysis was used to predict sexual dysfunction scores by including variables that exhibited significant differences in the single-variable analysis. A p value of <0.05 was considered as statistically significant.

Results

The comparison of the demographic parameters between patients with CKD and the control group are shown in Table 1. The location of residence and level of education was statistically significantly different between the groups (p<0.001 and p<0.001, respectively). A greater ratio of patients with CKD lived in the rural areas compared with the control subjects (p<0.001). Patients with CKD also had a higher ratio of elementary school graduates (p<0.001) and a lower ratio of higher education graduates (p<0.001) compared with the control subjects (Table 1).

The most frequent causes of CKD were hypertension (HT) (32%), diabetes mellitus (DM) (25.3%), and glomerulonephritis (GN) (22%). The rate of comorbidity among patients with CKD was 76.7%. The most common comorbidities were HT (64%) and DM (13.3%). Calcium channel blockers (CCBs) (59.3%) and angiotensin-converting enzyme inhibitors (ACEIs; 42%) were the most commonly used drugs by the patients. The rates of comorbid diseases (HT and DM) were not different between the kidney failure stages (p>0.05). Moreover, there was no significant difference between the types of drugs (beta-blockers, CCBs, and ACEIs) used between the kidney failure stages (p>0.05).

Male patients with CKD had higher sexual frequency (p=0.027), impotence (p<0.001), and premature ejaculation (p<0.001) scores. Female patients with CKD had higher sexual frequency (p=0.004), communication (p=0.004), satisfaction (p<0.001), avoidance (p=0.008), sensuality (p=0.002), orgasmic disorders (p<0.001), and total sexual dysfunction (p<0.001) scores, while also having lower vaginismus scores (p=0.018; Table 2).

In the CKD group, patients aged below and above 50 years were compared with regard to anxiety, depression, and sexual dysfunction parameters. The test results indicated significant differences in the depression scores between males of the two age groups and in the communication scores between females of the two age groups. Male patients aged below 50 years had lower depression scores (p=0.032), whereas female patients aged above 50 years had higher communication scores (p=0.027).

The anxiety, depression, and sexual dysfunction parameters did not significantly differ among

Table 1. Demographic parameters of patients and control groups

			Control		CKD		
			n	%	n	%	p
Sex		Male	30	46.2	90	60.0	0.06
		Female	35	53.8	60	40.0	
Age	Female	Mean±SD	48.51±7.1		50.42±8.94		
		Med (min-max)	47 (40-64)		51 (27-65)		0.066
	Male	Mean±SD	50.2±8.67		53.61±8.61		
		Med (min-max)	48 (40-65)		56 (35-65)		0.145
Place of residence		Rural	4	6.2	43	28.7	<0.001
		Urban	61	93.8	107	71.3	
Educational status		Illiterate	0	0.0	8	5.3	
		Primary school	18	27.7	73	48.7	
		Secondary school	8	12.3	22	14.7	<0.001
		High school	15	23.1	32	21.3	
		Academy	24	36.9	15	10.0	

CKD: chronic kidney disease; SD: standard deviation

male patients with CKD with respect to education level; however, among female patients with CKD, the anxiety (p=0.014), satisfaction (p=0.022), and orgasmic disorder (p=0.034) scores as well as the total score (p=0.033) significantly differed with respect to education. These scores were lower among patients with high school level of education or higher compared with those with secondary school level of education or below (p<0.001).

The anxiety, depression, and sexual dysfunction parameters were also compared with respect to the patients' location of residence. These parameters did not significantly differ among male patients; in contrast, the communication score was higher (p=0.013) among female patients and the satisfaction score was lower (p=0.009) among those living in rural areas.

When comorbidities were independently evaluated, it was determined that the total sexual dysfunction score was higher in male patients with DM than in those without DM (p=0.038). Among male patients with HT, the avoidance (p<0.001) and sensuality (p=0.003) scores as well as the general total score (p=0.003) were determined to be higher than those of patients without HT. In male patients with coronary artery diseases (CAD), the mean satisfaction score was found to be lower than that of patients without CADs (p=0.042). Female patients could not be similarly compared because of insufficient sample size.

When CKD causes were independently evaluated, it was observed that the avoidance (p=0.005), sensuality (p=0.008), impotence (p=0.02), and total (p=0.002) scores among males significantly differed in at least one of the groups. The results of the paired comparisons indicated that patients whose CKD was due to HT had lower avoidance scores than those with DM (p=0.005) and GN-related CKD (p=0.044). Furthermore, patients whose CKD was due to HT had lower sensuality scores than those with DM-related CKD (p=0.008); patients whose CKD was due to HT had lower impotence score than those with DM-related CKD (p=0.017). The evaluation of the total scores indicated that patients with CKD due to HT had lower total scores than those with DM-related CKD (p=0.002). The sexual function parameters were not different in female patients in terms of CKD causes (p>0.05).

The anxiety, depression, and sexual dysfunction parameters were also compared with respect to the drugs used by the patients. The premature ejaculation score was found to be higher among male patients receiving beta-blockers (p=0.005), whereas the communication (p=0.003), satisfaction (p=0.002), and sensuality (p=0.028) scores were determined to be lower among female patients receiving beta-blockers. Among males receiving CCBs, only the anxiety (p=0.025) and depression (p=0.019) scores were statistically significantly

Table 2. Anxiety, depression, and sexual dysfunction parameters of male and female patients in the CKD and control group

		n	Mean	SD	Median	Min	Max	p	
	Anxiety	Control	30	6.23	3.87	6.00	.00	14.00	0.426
		CKD	90	5.84	4.33	5.00	.00	21.00	
	Depression	Control	30	5.30	3.75	4.00	.00	16.00	0.775
		CKD	90	5.59	3.95	5.50	.00	21.00	
	Sexual frequency	Control	30	3.63	2.04	4.00	.00	8.00	0.027
		CKD	90	4.54	1.86	4.00	.00	8.00	
	Communication	Control	30	3.67	2.55	3.50	.00	8.00	0.746
		CKD	90	3.50	2.62	3.00	.00	8.00	
	Satisfaction	Control	30	6.67	3.28	7.00	.00	12.00	0.053
		CKD	90	5.69	2.82	6.00	.00	13.00	
	Avoidance	Control	30	3.47	2.89	3.00	.00	10.00	0.094
		CKD	90	2.44	2.40	2.00	.00	9.00	
	Sensuality	Control	30	3.37	2.74	2.50	.00	9.00	0.881
		CKD	90	3.29	2.72	3.00	.00	13.00	
	Impotence	Control	30	3.77	2.14	4.00	.00	8.00	<0.001
		CKD	90	5.96	2.99	6.00	.00	14.00	
	Premature ejaculation	Control	30	4.93	2.90	5.00	.00	11.00	<0.001
		CKD	90	7.98	3.09	8.00	.00	14.00	
Male total sexual dysfunction score		Control	30	33.00	11.68	32.00	11.00	56.00	0.076
		CKD	90	37.84	13.20	39.00	6.00	72.00	
	Anxiety	Control	35	7.34	4.98	7.00	.00	21.00	0.126
		CKD	60	8.70	4.81	8.00	.00	20.00	
	Depression	Control	35	6.66	4.87	6.00	.00	20.00	0.477
		CKD	60	7.42	4.75	7.00	.00	20.00	
	Sexual frequency	Control	35	4.14	2.22	4.00	.00	8.00	0.004
		CKD	60	5.43	1.77	6.00	1.00	8.00	
	Communication	Control	35	3.80	2.22	3.00	.00	8.00	0.004
		CKD	60	5.23	2.39	5.00	.00	8.00	
	Satisfaction	Control	35	5.34	3.66	5.00	.00	12.00	<0.001
		CKD	60	8.45	3.79	8.00	.00	16.00	
	Avoidance	Control	35	3.89	3.08	3.00	.00	12.00	0.008
		CKD	60	6.35	4.28	5.50	.00	16.00	
	Sensuality	Control	35	4.60	3.55	4.00	.00	12.00	0.002
		CKD	60	7.30	4.07	7.00	.00	16.00	
	Vaginismus	Control	35	6.43	2.75	7.00	.00	10.00	0.018
		CKD	60	5.25	3.02	5.00	1.00	16.00	
	Orgasmic dysfunction	Control	35	5.57	3.41	4.00	.00	14.00	<0.001
		CKD	60	8.10	3.09	8.00	2.00	16.00	
Female total sexual dysfunction score		Control	35	39.29	18.16	38.00	4.00	70.00	<0.001

CKD: chronic kidney disease; SD: standard deviation

higher. The satisfaction (p=0.042) and total sexual dysfunction scores (p=0.024) were higher among female patients using diuretics. The avoidance (p=0.015), sensuality (p=0.006), and impotence (p=0.001) scores as well as the general total score (p=0.006) were higher among male patients receiving insulin; as for female patients, insulin use was associated with a lower vaginismus score (p=0.01). Among patients using statin, it was observed that males exhibited higher impotence scores (p=0.034), whereas females had lower communication scores (p=0.04).

Table 3. Predictors of sexual dysfunction score in male patients (Model 1)

	Unstandardized coefficients		Standardized coefficients			95% Confidence interval	
	Beta	Standard error	Beta	t	p	Lower limit	Upper limit
(Constant)	9.536	7.416		1.286	.201	−5.157	24.230
Age	.367	.130	.247	2.827	.006	.110	.624
Diabetes mellitus	6.224	3.731	.145	1.668	.098	−1.168	13.615
Hypertension	7.604	2.813	.294	2.703	.008	2.031	13.176
Insulin	2.586	3.060	.079	.845	.400	−3.476	8.649
Anxiety	.810	.267	.263	3.035	.003	.281	1.338

Table 4. Predictors of sexual dysfunction score in male patients (Model 2)

	Unstandardized coefficients		Standardized coefficients			95% Confidence interval	
	Beta	Standard error	Beta	t	p	Lower limit	Upper limit
(Constant)	8.797	7.487		1.175	.242	−6.035	23.629
Age	.388	.131	.261	2.954	.004	.128	.648
Diabetes mellitus	5.911	3.735	.137	1.583	.116	−1.488	13.310
Hypertension	7.664	2.805	.297	2.732	.007	2.106	13.221
Insulin	3.069	3.033	.094	1.012	.314	−2.940	9.078
Depression	.894	.289	.269	3.095	.002	.322	1.467

Table 5. Predictors of sexual dysfunction score in female patients (Model 1)

	Unstandardized coefficients		Standardized coefficients			95% Confidence interval	
	Beta	Standard error	Beta	t	p	Lower limit	Upper limit
(Constant)	3.510	14.883		.236	.814	−26.066	33.086
Educational status	1.535	4.197	.038	.366	.716	−6.807	9.876
Age	.473	.220	.203	2.151	.034	.036	.911
CCBs	6.734	4.687	.172	1.437	.154	−2.581	16.049
Diuretic	5.511	5.959	.088	.925	.358	−6.333	17.354
Anxiety	1.416	.383	.357	3.693	<.001	.654	2.178

CCBs: calcium channel blockers

Table 6. Predictors of sexual dysfunction score in female patients (Model 2)

	Unstandardized coefficients		Standardized coefficients			95% Confidence interval	
	Beta	Standard error	Beta	t	p	Lower limit	Upper limit
(Constant)	14.766	13.991		1.055	.294	−13.037	42.570
Educational status	−.859	4.124	−.021	−.208	.835	−9.055	7.337
Age	.357	.218	.153	1.635	.106	−.077	.790
CCBs	4.916	4.753	.126	1.034	.304	−4.529	14.361
Diuretic	3.556	6.113	.056	.582	.562	−8.591	15.703
Depression	1.288	.384	.317	3.354	.001	.525	2.051

CCBs: calcium channel blockers

When the anxiety, depression, and sexual dysfunction parameters were compared with respect to disease stage, the premature ejaculation score was found to be higher among male patients with stage 5 CKD compared with those with stages 3 (p=0.018) and 4 (p=0.037) CKD. The number of female patients with stage 5 CKD was not sufficient to perform a similar evaluation (n=2). The depression score of patients with stage 3 CKD was found to be higher than those with stage 4 CKD (p=0.028).

Anxiety and depression scores were found to be highly inter-related; hence, in the regression models developed to predict sexual dysfunction scores in the patients, these two variables were not included in the same model to avoid multicollinearity problems. Therefore, two models were developed for both males and females. All variables included in the model were primarily determined by considering the significant results obtained in the single-variable analysis. When anxiety was included into the model for male patients, age, HT, and anxiety were determined to be significant parameters (Table 3). When depression was included in the model, age, HT, and depression were determined to be significant parameters (Table 4). When anxiety was included in the model for female patients, age and anxiety were determined to be significant parameters (Table 5), and when depression was included in the model, only the depression parameter was found to be significant (Table 6).

Discussion

Sexual dysfunction is frequently observed in both male and female patients with chronic uremia, as observed in our study [4, 9-11, 14]. Furthermore, many patients believed that their sexual lives had to end with the beginning of dialysis, whereas patients who continued having an active sexual life had lower sexual satisfaction levels than the normal population [11]. A meta-analysis published by Navaneethan et al. [9] comprising 50 studies with a total of 8343 patients described that almost all studies reported a higher prevalence of erectile dysfunction. The ratio of erectile dysfunction was estimated to be 70%, whereas the rate of sexual dysfunction in female patients was determined to be 30%–80%. Erectile dysfunction is reported to be the most frequent problem among male patients, whereas decreased satisfaction and orgasm is most frequently reported among

female patients [4]. In our study, sexual frequency, impotence, and premature ejaculation scores among male patients with CKD were found to be higher than those of the control group. In female patients with CKD, sexual frequency, communication, satisfaction, avoidance, and orgasmic disorder scores as well as the total sexual dysfunction score were comparatively higher, whereas the vaginismus score was lower compared with the control subjects.

It is still unclear whether sexual dysfunction is related with organic or psychogenic causes in the natural course of CKD. This is a natural consequence of the metabolic and hormonal disorders caused by uremia [7, 8, 10, 15]. Sexual dysfunction in patients with CKD was determined to be associated with the stage of CKD, dialysis treatment, advanced age, DM, and depression [10, 14-19]. In our study, patients in the predialysis period were evaluated. When anxiety, depression, and sexual dysfunction parameters of the patients were compared between the stages of the disease, the premature ejaculation score was found to be higher in male patients with stage 5 CKD than in those with stages 3 and 4 CKD. These results show that sexual dysfunction might be affected as the kidney disease progresses, albeit at a limited level.

The number of female patients with stage 5 CKD was not sufficient for evaluation (n=2); however, the depression score of patients with stage 3 CKD was found to be higher than that in female patients with stage 4 CKD. This result can be associated with the adaptation of CKD progression in female patients.

Advanced age is an important factor of sexual dysfunction in patients with CKD [10, 14-19]. Age-related physiological and psychological changes in women mainly occur during menopause. Decreases in libido, sexual responsiveness, comfort level, and sexual frequency may accompany the changes in sexual function. Low testosterone levels during the premenopausal period may cause decreased libido, decreased touch sensibility, and fatigue [20]. In addition, age-related changes in males include decreases in ejaculation frequency, erection, and sexual willingness as well as decreases in the level of testosterone production [21]. We also determined that age was one of the factors that affected sexual dysfunction.

Sexual dysfunction in patients with CKD was determined to be associated with anxiety and depression [10, 14-19]. The following factors accounted for the causes of depression in male patients with CKD: job loss, loss of male self-image, shame due to social pressures (leading to the avoidance of help-seeking behavior), and difficulty in urination. In the general population, there is the established notion that men are and should always be ready for sexual intercourse, which has the effect of lowering performance and causing significant anxiety. This in turn may lead to sexual unwillingness and avoidance of sexual intercourse. Such a cycle of unrealistic expectations and avoidance may create a depressive state in the individual [22-24]. In the study by Kurdoğlu et al. [25], depressive symptoms in predialysis patients was found to be 6 and 3.8 times more prevalent, respectively, compared with control subjects and hemodialysis patients. Moreover, sexual dysfunction was 24 times more common in predialysis patients with depressive symptoms compared with patients without depressive symptoms [25, 26]. In our study, male patients with anxiety had lower sexual frequency scores and higher avoidance scores, whereas female patients with anxiety had higher avoidance and sensuality scores as well as higher total scores. Male patients with depression had higher avoidance scores, whereas female patients with depression had higher communication scores. In addition, in our study, anxiety and depression were determined to be independent factors that affect sexual dysfunction in both males and females.

In an epidemiological study conducted in the Netherlands with 7076 patients, it was determined that anxiety and depression disorders are correlated to female, age of 25–34 years, low level of education, living alone, unemployment, family history of psychiatric diseases, and traumas during childhood [24]. When the anxiety, depression, and sexual dysfunction parameters were compared with respect to the level of education, no differences were identified in males, whereas the anxiety, satisfaction, and orgasmic dysfunction scores and the total scores significantly differed among female patients according to their level of education. These scores were found to be lower in patients with high school level education and above compared with patients with secondary school level education or below. These results indicated that sexual dysfunction decreases with increasing level of education.

A high ratio of patients with CKD, approximately 80%–85%, had HT. Many recent studies have demonstrated that sexual dysfunction develops as a consequence of comorbidities, such as HT, CAD, and DM [27-29]. In our study, the avoidance and sensuality scores, as well as the general total scores, were higher among male patients with HT compared with those without HT. Moreover, in our study, HT was determined to be another factor that affects sexual dysfunction in males.

Sexual dysfunction is highly frequent in male and female patients with DM. Diabetic genitourinary autonomic neuropathy causes serious disorders, such as bladder dysfunction, retrograde ejaculation, erectile dysfunction, and dyspareunia (due to decreased vaginal lubrication). Loss of trabecular smooth muscle, particularly in the cavernous tissue, is believed to be responsible for this condition in males. The development of cardiovascular complications has also been reported to be a possible cause [28, 30, 31]. Consistent with the findings of previous studies, we determined that total sexual dysfunction scores were higher in both male and female patients with DM.

In addition to coexisting diseases in patients with CKD, certain cardiovascular and antihypertensive medications (beta-blockers, thiazide diuretics, etc.) may also play a role in the development of sexual dysfunction [32]. In our study, the premature ejaculation score was higher in male patients receiving beta-blockers, whereas the communication, satisfaction, and sensuality scores were lower in female patients using beta-blockers. Only the anxiety and depression scores were found to be higher in male patients receiving CCBs. In female patients using diuretics, the satisfaction score and the total sexual dysfunction score were determined to be higher.

One of the limitations of our study is the relatively small size of the study population, particularly females and patients with stage 5 CKD. Another limitation of this study is that the diagnosis of anxiety and depression is solely based on self-reported scales.

In conclusion, it is observed that patients with predialytic CKD substantially have sexual dysfunction. The most important factors that affect sexual dysfunction are age, HT, anxiety, and depression.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Antalya Training and Research Hospital Ethic Committee (03 April 2014, 38/10).

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The Role of Ionic Homeostasis in Cisplatin-Induced Neurotoxicity: A Preliminary Study

Cigdem Cengelli Unel, Kevser Erol

ABSTRACT

Objective: The aim of the present study was to investigate the role of ionic homeostasis in cisplatin (cis-diamminedichloroplatinum (II), CDDP)-induced neurotoxicity. CDDP is a severely neurotoxic antineoplastic agent that causes neuronal excitotoxicity. According to some studies, calcium influx increases, whereas potassium efflux decreases neuronal death. Nimodipine and glibenclamide were used to analyze the role of ionic flows in CDDP-induced neurotoxicity in rat primary cerebellar granule cell (CGC) culture.

Materials and Methods: CGC culture was prepared from the cerebella of Sprague Dawley 5-day-old pups. The submaximal concentration of CDDP was determined and then given with 1, 10, or 50 μM of drugs into culture. Neurotoxicity was investigated using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole) assay. One-way analysis of variance, Kruskal–Wallis H test, and Tukey test were applied for statistical analysis.

Results: CDDP induced neurotoxicity in a concentration-dependent manner. Neither nimodipine nor glibenclamide was able to protect CGCs against CDDP neurotoxicity.

Conclusion: By blocking L-type voltage-gated calcium channels, nimodipine did not prevent CDDP neurotoxicity in CGCs. Ca^{2+} influx via these channels seemed to be insufficient to cause a change in CDDP-induced neurotoxicity. Similarly, glibenclamide failed to prevent CDDP neurotoxicity. Further studies are needed to elucidate the mechanisms of these preliminary results.

Keywords: Cerebellar granule cells, glibenclamide, KATP channels, nimodipine

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ORCID IDs of the authors:
C.C.U 0000-0001-7680-0141;
K.E. 0000-0002-8808-6616.

Department of Pharmacology, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey

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Correspondence to: Cigdem Cengelli Unel
E-mail: cigdemcengelli@gmail.com

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Introduction

Cisplatin (cis-diamminedichloroplatinum (II), CDDP) is a platinum-based antineoplastic agent widely used against a variety of cancers [1]. However, its clinical benefits are limited owing to its adverse effects, such as ototoxicity, nephrotoxicity, cardiotoxicity, hepatotoxicity, and central and peripheral neurotoxicity [2]. Neurotoxicity is an important dose-limiting adverse effect that may cause not only dose reduction or drug cessation during therapy but also reduction of the quality of life of patients. The neurotoxicity induced by CDDP is found to have active neuronal cell death features and also has glutamate-dependent excitotoxic features [3]. CDDP affects calcium homeostasis and causes increased intracellular calcium concentrations [4]. However the knowledge about the neurotoxicity of cerebellar granule cells (CGCs) induced by CDDP is limited.

The ion movements are crucial for neurotoxic or neuroprotective mechanisms in antineoplastic agent therapy. Particularly, calcium and potassium ions may have critical roles in neuronal cell death [5]. Calcium ions are fundamental for performing normal cellular functions and for cellular survival. However, calcium concentration may reach critical levels in pathological conditions, such as ischemia or brain damage, leading to cellular damage or cell death [6, 7]. Increased intracellular calcium levels are caused by release from internal stores and calcium influx via channels in the membrane. The dysregulation of calcium homeostasis and calcium signaling is known to contribute to the neurotoxic side effects of CDDP. Particularly, voltage-gated calcium channels are believed to play a role in CDDP-induced neurotoxicity [4]. Thus, the aim to buffer excess intracellular calcium may be achieved by using calcium antagonists that block voltage-gated calcium channels [8].

K_{ATP} channels belong to Kir channels characterized by inward rectification by allowing more current to flow inward than outward. These channels are important ion channels that regulate many cellular functions, neuronal signaling, and membrane excitability according to both electrical activity and metabolic status of the cell. In many cell types, it was shown that they may have a role in neuroprotective mechanisms [9]. However, there is a controversy in the results of studies about the contribution of these channels to neuroprotective strategies. In previous studies, the blockade of K_{ATP} channels protects the dopamine neurons from degeneration; however, the activation of K_{ATP} channels can also protect mesencephalic neurons from MPP^+ cytotoxicity [10, 11]. Moreover, K_{ATP} channel activation was found to protect CGCs from oxidative stress [11].

In previous CGC neurotoxicity studies, neuronal death was shown to arise from several reasons, such as excess glutamate release, changes in Ca^{2+} homeostasis, deficiency of K^+, reactive oxygen species production, and caspase activation [8, 12]. Any change in the concentrations of these molecules may cause cell death. Although molecular mechanisms of pathological cell loss have been extensively investigated in many studies, the contribution of the disruption of ionic homeostasis to cell death is still unknown. However, excitotoxicity was found to be increased by calcium influx and decreased by potassium efflux in different cell types [13].

The evaluation of neurotoxicity can be achieved by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole) assay, which is widely used in cytotoxicity studies. The MTT assay is a colorimetric viability test based on the enzymatic reduction of the MTT (thiazolyl blue tetrazolium bromide) molecule to formazan crystals in the presence of viable cells. This enzymatic reduction concludes with a change in color that can be easily detected by an ELISA reader system in terms of absorbance values [14].

CDDP was found to activate excitotoxic mechanisms and also trigger active neuronal death [3]. It is widely known that calcium influx increases, whereas potassium efflux decreases excitotoxicity [13]. The aim of this preliminary study was to evaluate the potential roles of the channels that regulate calcium and potassium ions in the neurotoxicity of CDDP. To determine the effect of calcium ions, the cells were treated with nimodipine (L-type calcium channel blocker). The cells were also treated with glibenclamide (K_{ATP} channel blocker) to evaluate the potential therapeutic effect of K_{ATP} channels in CDDP neurotoxicity.

Materials and Methods

Primary cultures of CGCs were prepared from 5-day-old newborn Sprague–Dawley rats with modifications in the method described by Xu and Wojcik [15]. Approval was obtained from the local ethics committee for animal experimentations. In addition, informed consent was obtained from the participants of the study, and the institution's ethics committee approved the study (protocol number: 273/2012). The animals were procured from the Medical and Surgical Research Center in Eskişehir Osmangazi University. Briefly, newborn rats were decapitated, and the cerebellum was removed. To prevent contamination, the cerebellum was washed twice with calcium-free Hank's Balanced Salt Solution (HBSS) (HyClone Thermo Scientific, Germany). Then, it was suspended in 5 ml calcium-free HBSS containing 2 ml of trypsin–EDTA (0.25% trypsin–0.02% EDTA; Sigma Aldrich, USA) at 37°C for 40 min. Trypsin digestion was attenuated by adding 5 ml of fresh Dulbecco's Modified Eagle Medium (DMEM) (Sigma Aldrich, Germany). DMEM solution comprised 10% fetal calf serum (FCS) (HyClone Thermo Scientific, Germany), 50 µg/mL penicillin, and 0.2 mM L-glutamine (Sigma Aldrich, Germany). After centrifugation at 1000 rpm for 5 min, the resulting pellets were suspended. After enzymatic disintegration, the cell suspension was pipetted up and down using Pasteur pipets with soft-headed tips that provide mechanic disintegration called trituration.

The bases of 25 cm^2 polypropylene tissue culture flasks were covered with poly-D-lysine (Sigma Aldrich, Germany). Twenty-four hours before the experiment, 0.1 mg/mL poly-D-lysine (30,000–70,000 MW) was dissolved in phosphate-buffered saline, and the bases of 96-well plates were also covered with the same solution. After keeping at room temperature (25°C) for 5 min, excess poly-D-lysine was vacuumed and left to dry at 4°C overnight. Then, the cell suspension was transferred into covered flasks to allow adherence to the surface, and culture flasks were incubated at 37°C and humidified at 95% air and 5% CO_2. After 30 min, the media was changed to eliminate non-adherent cells, and fresh DMEM containing 10% FCS was added into the flasks. Culture media was changed twice a week, and neurons were used for neurotoxicity experiments following an 8-day in vitro incubation.

The dye exclusion method was applied to stain the cells with 0.4% trypan blue for counting live cells. An inverted light microscope was used to examine stained and non-stained cells immediately. Approximately 10,000 cells per well were plated in 96-well culture plates in drug-free DMEM medium overnight. CDDP (100, 200, and 500 µM) (Sigma Aldrich, USA) was applied to wells at gradually increasing concentrations. After applying the drug into cell suspensions, the plates were incubated overnight at 37°C and humidified at 95% air and 5% CO_2. The toxic effects of CDDP were evaluated using the drug alone or with nimodipine (Sigma Aldrich, USA) or glibenclamide (Sigma Aldrich, USA) at concentrations of 1, 10, and 50 µM.

The MTT assay was used for cytotoxicity determination. MTT was dissolved in HBSS at a final concentration of 1 mg/mL. Briefly, at the end of the incubation period, the cells inside the 96-well culture plates were incubated with MTT solution at 37°C for 4 h. After vacuuming the incubation solution, the cells were lysed with 150 µL dimethyl sulfoxide and subjected to the measurement of optical density at 540 nm as reference on an ELISA system (Thermo Lab Systems Multiscan EX, USA) [16, 17].

Results were evaluated using the ELISA reader system (Thermo Lab Systems, Germany). Drug applications to 96-well plates were handled at different times so each plate was evaluated according to its control data. Data were analyzed using SPSS 15.0 statistical package program (IBM SPSS Inc., Chicago, IL, USA). The percentage of cell death scores was calculated, and the results were statistically analyzed using Kruskal–Wallis H and Tukey tests. A p-value<0.05 was considered significant.

Results

The percentage of cell death according to each group was calculated using the following formula: [relative cell death = 1 − (n / nK ort)]. As expected, CDDP induced neuronal cell death concentration dependently (Figure 1). The minimum inhibitor concentration of CDDP was determined as 200 µM ($p<0.01$) (Table 1, Figure 1). Nimodipine and glibenclamide combinations were performed together with 200 µM of CDDP.

The difference between the CDDP group and the CDDP–nimodipine combination groups was not significant. In addition, nimodipine did not induce any toxicity at all concentrations (1, 10, and 50 µM). Thus, nimodipine neither increased nor decreased the neurotoxicity of CDDP (Table 2, Figure 2). CDDP neurotoxicity did not significantly change when it was applied together with glibenclamide. However, 10 µM

glibenclamide increased CDDP neurotoxicity ($p<0.001$). In addition, glibenclamide alone was not toxic to the CGCs at all concentrations applied (Table 2, Figure 3).

Discussion

The present study investigated the effects of L-type Ca^{2+} channel blocker nimodipine and K_{ATP} channel blocker glibenclamide in CDDP-induced neurotoxicity using primary CGCs. Neither nimodipine nor glibenclamide significantly changed CDDP neurotoxicity.

An increase in intracellular calcium concentration is a common mechanism for the neurotoxic side effects of CDDP. Calcium channels are mainly of L-type (60%–70%) in 1-week old CGC culture [18]. Thus, calcium influx via these channels may be believed to be critical for neuronal cell death. However, our results were quite the opposite. The blockade of L-type calcium channels via nimodipine could not protect the cells. Neuronal L-type calcium channels have different gating properties identified in a variety of neurons, including CGCs [19]. This difference in gating properties of L-type calcium channels may be due to nimodipine ineffectiveness. Moreover, nimodipine-sensitive L-type current contributed to 15% of the total current, and the prevention of calcium influx via nimodipine-sensitive calcium channels may be inadequate to prevent CDDP neurotoxicity [20].

The other calcium influx routes may be responsible for CDDP neurotoxicity rather than the L-type calcium channels. In the past, an increase in intracellular calcium was known to be responsible for neurotoxicity, whatever way calcium goes into the cell; however, recent studies focused on the way of calcium influx and the involved second messenger systems [21]. Similarly, in hippocampal neurons, calcium influx via L-type calcium channels was found to be harmless, but calcium influx via N-methyl-D-aspartate (NMDA) receptors was toxic for the cells [22]. Thus, the blockade of L-type calcium channels was suggested to be unable to prevent toxic calcium influx in our study. The increase in toxicity may be relevant to other calcium routes (e.g., NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, kainate receptors, and

Table 1. Concentration-dependent cytotoxicity induced by cisplatin (Cis100, Cis200, and Cis500: cisplatin 100 µM, 200 µM, and 500 µM, ***p<0.001)

		n	Mean±SE	Median (25%–75%)	p*	Pairwise comparisons
1	Control	33	0.265±0.028	0.240 (0.115–0.360)		
2	Cis100	23	0.351±0.036	0.388 (0.193–0.450)	<0.001	1–3***, 1–4***
3	Cis200	72	0.591±0.017	0.619 (0.497–0.701)		
4	Cis500	24	0.759±0.006	0.760 (0.749–0.782)		

*Kruskal–Wallis one-way analysis of variance on ranks (median 25%–75%)

Table 2. Relative cell death values for the cisplatin/nimodipine combination groups (Cis200: cisplatin 200 µM; N1, N10, and N50: nimodipine 1, 10, and 50 µM, *p<0.05, **p<0.01, ***p<0.001)

		n	Mean±SE	Median (25%–75%)	p*	Pairwise comparisons
1	Cis200	72	0.591±0.017	0.619 (0.497–0.701)		
2	Cis200+N1	12	0.657±0.014	0.646 (0.626–0.698)		
3	Cis200+N10	47	0.676±0.014	0.696 (0.603–0.746)		1–5**, 1–6**,
4	Cis200+N50	24	0.658±0.030	0.680 (0.648–0.727)	<0.001	1–7**, 2–5*,
5	N1	8	0.167±0.040	0.177 (0.053–0.261)		3–6***, 4–7***
6	N10	11	0.206±0.060	0.120 (0.027–0.412)		
7	N50	18	0.272±0.032	0.270 (0.196–0.367)		

*Kruskal–Wallis one-way analysis of variance on ranks (median 25%–75%)

Table 3. Relative cell death values for the cisplatin/glibenclamide combination groups (Cis200: cisplatin 200 µM; G1, G10, and G50: glibenclamide 1, 10, and 50 µM, **p<0.01, ***p<0.001)

		n	Mean±SE	Median (25%–75%)	p*	Pairwise comparisons
1	Cis200	72	0.591±0.017	0.619 (0.497–0.701)		
2	Cis200+G1	12	0.695±0.020	0.703 (0.648–0.737)		
3	Cis200+G10	36	0.726±0.011	0.745 (0.685–0.769)		1–5**, 2–5***,
4	Cis200+G50	12	0.687±0.033	0.727 (0.590–0.770)	<0.001	1–7***, 4–7***,
5	G1	9	0.233±0.048	0.177 (0.100–0.388)		1–6**, 3–6***,
6	G10	12	0.296±0.048	0.276 (0.153–0.439)		1–3***
7	G50	23	0.274±0.038	0.231 (0.126–0.385)		

*Kruskal–Wallis one-way analysis of variance on ranks (median 25%–75%)

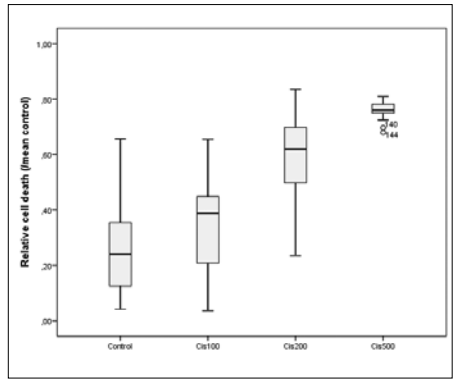

Figure 1. Cisplatin neurotoxicity at 100, 200, and 500 µM concentrations
cis: cisplatin

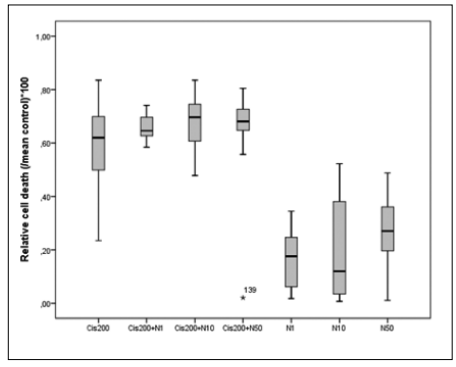

Figure 2. Cisplatin neurotoxicity at 100, 200, and 500 µM concentrations
cis: cisplatin

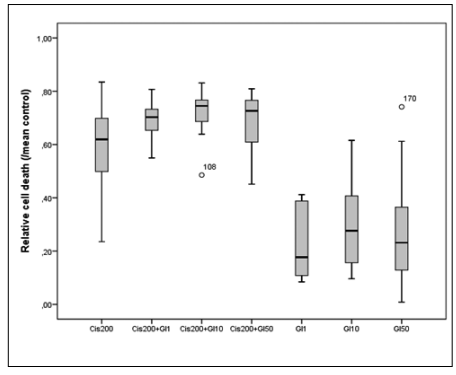

Figure 3. The relative cell death values of cisplatin and glibenclamide combination groups
cis: cisplatin, GI: glibenclamide

Na^+/Ca^{2+} exchanger) rather than L-type calcium channels as shown in a previous study [22].

L-type calcium channels were shown to couple with Ca^{2+}/CaM kinase II (CaMKII), enabling the channels to play a primary role in CaMKII activation [23]. The inhibition of CaMKII was shown to cause neurotoxicity via dysregulation of glutamate/calcium signaling and enhanced neuronal excitability [24]. CaMKII can also regulate cAMP response element-binding protein (CREB) phosphorylation, which is crucial for neuronal survival. Thus, blockade of L-type calcium channels with nimodipine may cause inactivation of CaMKII and disruption of CREB phosphorylation, leading to neurotoxicity and neuronal cell death [25]. Future studies should aim to investigate the roles of these molecules.

The physiology of calcium signaling also differs from cell to cell. Both Purkinje neurons and cerebellar granule neurons may have different signaling mechanisms [22]. Hence, unsuccessful inhibition of neurotoxicity by voltage-gated channels may have originated from their different calcium signaling mechanisms. However, previous studies have shown that nimodipine protects CGCs from intracellular calcium increase induced by NMDA and hydrogen sulfur neurotoxicity [26, 27]. In our previous study, we also studied CDDP neurotoxicity with different types of neuronal cells, including dorsal root ganglion neurons. CDDP also induced physiological alterations related to calcium dynamics in the cell. Nimodipine was able to protect the dorsal root ganglion neurons from the toxic effects of CDDP [28]. However, CGCs were different from the dorsal root ganglion neurons because the cerebellum is one of the regions of the central nervous system that develops postnatally [29]. CGC progenitors still migrate into the internal granular layer of the cerebellum even during early postnatal period [30]. Thus, at that time, CGCs undergo rapid growth and may be more vulnerable to the devastating effects of drugs. Because injury may generate some structural changes in this region. For example, Piccolini et al. [31] noticed that CDDP induces alterations in matrix metalloproteinase expression in the developing rat cerebellum. The information related to such physiological changes in CGCs in the presence of a neurotoxic drug CDDP is limited.

In addition, the capability of nimodipine to block channels can be based on the state of the channels, and channels bind nimodipine with different affinities according to their state [32]. The nimodipine-sensitive current is most probably responsible for the increase of calcium as determined by prolonged depolarizations in these cells. Thus, the sensitivity of voltage-gated calcium channels to nimodipine may be different based on the type of cells and condition.

In excitable cells, such as neurons, the regulation of potassium ion movements is fundamental for the regulation of membrane potential and electrical activity. Any change in the concentration of potassium ions that occurred in intracellular or intercellular compartments contributes to the activation of cell death mechanisms. K_{ATP} channels deliver potassium inside or outside of the cell according to the membrane potential. K_{ATP} channels decrease membrane excitability by regulating K^+ ion flow direction. Thus, they may be the candidate ion channels for the protection of cells from excitotoxicity [33].

At normal physiological status, K_{ATP} channels are closed; however, in the presence of a toxic agent, the membrane is depolarized [33]. This causes an excitation in the cells. K_{ATP} channels open, and K^+ ions flow through the outside of the membrane to defeat excitation and then hyperpolarization occurs. If K_{ATP} channels are exogenously closed, excitation cannot be blocked and excitotoxicity occurs in the cells.

In the study, to investigate the relationship between the neurotoxicity of CDDP and K^+ ion movement across the membrane through K_{ATP} channels, glibenclamide (blocker of K_{ATP} channel) at 1, 10, and 50 μM concentrations was applied with CDDP. Glibenclamide did not cause any significant change in CDDP neurotoxicity.

First, in the presence of a neurotoxic agent, K_{ATP} channels are opened to suppress excitation; however, later, the loss of excess potassium ion from the cell may contribute to the toxicity of CDDP. If the level of potassium decreases, some enzymes, such as caspases and endonucleases, may get activated, leading to induction of apoptosis [34].

Similarly the efflux of K^+ ions and the loss of intracellular potassium are also critical in apoptosis, like in case of Ca^{2+} influx and the accumulation of intracellular calcium [5]. Physiological concentrations of intracellular potassium act as a suppressor on proapoptotic molecules. If the loss of potassium is greater than the cell can tolerate, caspases, cytochrome C, and endonucleases would be activated, and then apoptotic cascade starts for these cells. Moreover, the cells lose water with potassium efflux, and this may cause shrinkage of the cells by decreasing cell volume, which is one of the characteristic features of apoptosis. Potassium ion is abundant in the cells, and even if tens of mM loss can be tolerated, a 50% loss cannot be tolerated by the cells. Thus, high potassium loss must be considered for causes of cell death. Therefore, the contribution of K_{ATP} channels to CDDP neurotoxicity was so complex. Mitochondrial K_{ATP} channels may be more effective to decrease toxicity as shown in a previous study [13]. K_{ATP} channels of neonatal rats in our study might be inadequate to protect the neurons from cell death. In an earlier study, Xia and Haddad showed that the formation of K_{ATP} channels and sulfonylurea receptors (subunit of K_{ATP} channels) occurs postnatally, and it is the highest level at maturation. Thus, K_{ATP} channel activation in the mature period may be more protective against the neurotoxic reaction [35].

The present study has some limitations. First, the content of the study was restricted to only one type of calcium and potassium channels. In addition, only the cytotoxicity test was performed to investigate the effects of drugs. MTT assay is an absorbance-based assay that provides information about the viability of the cells and how well they metabolize the component. It is not always comparable to % growth inhibition. In future studies, electron microscopy techniques may also be included in the study to detect the histopathological features of CDDP-induced neurotoxicity.

Finally, this preliminary study provides an insight for future studies in CDDP-induced neurotoxicity. It is difficult to explain the exact mechanisms of the interaction between the neurotoxicity of CDDP and calcium/potassium ion movements in CGCs. The results of the previous studies are also complicated to understand the missing points related to ionic homeostasis and neurotoxicity. The mechanisms of the interaction between the effects of CDDP and intracellular ionic homeostasis are complex and multidirectional phenomena that must be comprehensively investigated.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eskişehir Osmangazi University (273/2012).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.E.; Design - K.E., C.C.U.; Supervision - K.E.; Resources - K.E., C.C.U.; Materials - K.E., C.C.U.; Data Collection and/or Processing - C.C.U.; Analysis and/or Interpretation -

K.E., C.C.U.; Literature Search - K.E., C.C.Ü.; Writing Manuscript - C.C.U.; Critical Review - K.E.

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Association Between the Subtypes of Stroke and the Various Risk Factors of Cerebrovascular Accidents: A Cross-Sectional Study

Samad Shams Vahdati[1], Alireza Ala[2], Seyed Ali Mousavi Aghdas[3], Ali Adib[2], Mohammad Mirza-Aghazadeh-Attari[4], Fatemeh Aliar[2]

ORCID IDs of the authors:
S.S.V. 0000-0002-4831-6691;
A.A. 0000-0001-8231-2937;
S.A.M.A. 0000-0001-9408-3596;
A.A. 0000-0003-1613-7653;
M.M.A.A. 0000-0001-7927-6912;
F.A. 0000-0002-3544-132X.

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[1]Department of Emergency, Emergency Medicine Research Team, Tabriz University of Medical Sciences, Iran
[2]Department of Emergency Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Students Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Institute of Aging Research, Tabriz University of Medical Sciences, Tabriz, Iran

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Correspondence to:
Mohammad Mirza-Aghazadeh-Attari
E-mail: mirza-aghazadeh-attari@tbzmed.ac.ir

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ABSTRACT

Objective: Stroke is a common heterogeneous disease classified into two subtypes: ischemic and hemorrhagic. Many risk factors have been associated with stroke, and the most well-known is hypertension. Although the relation between stroke and these risk factors has been emphasized before, there is inconclusive evidence about the relation between the different risk factors and the subtypes of stroke. The present study aims to fill this gap.

Materials and Methods: In the present retrospective, cross-sectional study, 827 patients with diagnosed stroke were included. Demographic data and the acquired risk factors were determined using pre-designed questionnaires. Statistical analysis was conducted using chi-square test, Student t-test, and Pearson correlation coefficient.

Results: Among the included 827 patients, 432 (52.2%) were men and 395 (47.8%) were women. The mean±standard deviation of age was 68.41±12.46 y in men and 67.89±11.85 y in women, respectively, and the difference was not significant. Of all the patients, 672 had ischemic strokes and 155 had hemorrhagic strokes. The most common risk factor in the patients was hypertension with a prevalence of 66.7%. Of all the risk factors, only hypertension, atrial fibrillation (AF), age, and a positive family history were significantly related to a subtype of stroke.

Conclusion: Knowing that the prevalence of hypertension, AF, age, and positive family history are significantly different between the two subtypes, the patients having these risk factors can be entered into more specified public health measures, which puts more emphasis on the subtype that they are more prone to.

Keywords: Emergency medicine, neurology, stroke

Introduction

Stroke is an amalgamate disease with two subtypes: ischemic and hemorrhagic [1]. It is estimated that 6.8 million American adults have suffered from stroke, and that 610,000 people experienced it for the first time during 2013. Stroke is the second most common debilitating disease in the United States and financially is a massive burden on the health system [2]. A recent large-scale study has revealed that>90% of the burden of stroke is attributed to the modifiable risk factors, including behavioral (e.g., smoke), metabolic (hypertension, diabetes, hypercholesterolemia, low glomerular filtration rate, and high body mass index), and environmental (air pollution and lead exposure) factors [3].

Arterial hypertension (AH) causes hyaline degeneration and fibrinoid necrosis in the weak and short arteries supplying the base of the brain, including the thalamus, basal ganglia, brain stem, cerebellum, and internal capsule. Other different mechanisms of hypertension contributing to stroke are likewise well-discussed [4, 5]. The patients with diabetes mellitus (DM) are also at an increased risk of recurrent and disabling/fatal lacunar infarcts, which makes them susceptible to ischemic and hemorrhagic strokes [6, 7]. Also, according to two recent meta-analyses, DM and smoking habits differently affect gender in terms of an increase in the risk of stroke. Female diabetic or smoker patients are predisposed to a higher risk of stroke in contrast to males [8, 9]. As another metabolic factor, the elevated levels of low-density lipoprotein particles are related to an increased risk of ischemic strokes [10]. Smoking is implicated in higher stroke mortality, functional disability, and experiencing stroke at younger ages [11]. A meta-analysis reporting on

11,658 stroke patients has shown newly diagnosed atrial fibrillation (AF) [12] in nearly 25% of all the patients, detected by the combination of sequential cardiac monitoring [13]. The patients with AF have a 5-fold increased risk for embolic strokes [14].

Considering the high prevalence of emergency referrals and hospitalizations due to stroke, it seems that a vast evaluation of the relevant risk factors and their demography is valuable [15]. To the best of our knowledge, there is limited evidence in this field, and it is not well understood if all risk factors contribute as much to the different subtypes of stroke. Understanding the different patterns of the risk factors could benefit policy makers in constructing measures to accurately address the needs of the patients at high risk of stroke. Herein, we have investigated the relation among the above-mentioned risk factors, central and peripheral vascular syndromes, and the subtypes of stroke.

Materials and Methods

Patients

In this retrospective cross-sectional study, we assessed all patients with diagnosed stroke admitted to a referral medical educational hospital. The inclusion period was from January 2015 to January 2017. A total of 846 patients were detected; of which, we excluded those who left the hospital untreated (discharged with personal consent) or who had incomplete documents, i.e., the items of our study. After the exclusion, a total of 827 patients were assessed. The collected data were extracted from the patients' documents according to the variables predetermined in our questionnaire. The variables comprised the demographic data of the patients such as sex, age, stroke subtype (ischemic or hemorrhagic), risk factors (hypertension, diabetes, hyperlipidemia, smoking habits, alcohol consumption, Atrial fibrillation (AF), oral contraceptive use, a history of previous transient ischemic attacks, cerebrovascular accidents (CVAs), acute coronary syndromes, familial predisposition), and the presence of central or peripheral vascular syndromes (strokes, limb arterial thrombosis, and mesenteric artery thrombosis). The risk factors and vascular syndromes were determined by the results of a physical examination during the period in which the patient was hospitalized and by referring to the patient's medical records

Statistical Analysis

The data were analyzed using SPSS® (version 23.0.0, IBM Corp.; Armonk, New York, USA). To describe the sample population, we used mean±standard deviation, frequency, cumulative frequency, frequency distribution table, and cluster bar graphs. For the evaluation of our assumptions regarding the differences among the independent groups, chi-square test, Student t-test, and Pearson correlation coefficient were used. In all items, $p<0.05$ was considered statistically significant. Power of the study was set at 80%.

Ethical Considerations

The present study was approved by the Ethical Board of the University of Medical Sciences wherein the study was conducted. The collected data were anonymously entered in this study. No personal information was extracted from the files; we have provided only general data (not individualized) about our study population. The collected data were recorded in real and non-perverted forms, without selecting particular individuals, to achieve the desired results. To avoid any bias, the assumptions were written in a double-sided layout.

Results

In the present study, of the 846 patients, 827 patients with diagnosed stroke from January 2015 to January 2017 were included.

Of the 827 patients, 432 (52.2%) were males and the remaining 395 (47.8%) were females (sex ratio of 1.09:1), and the difference was not statistically significant (p=0.21).

The mean±standard deviation of age was 68.16±12.38 y with a median of 68 and a mode of 65 y (min=26 and max=95). The age distribution examined with the Kolmogorov–Smirnov test showed that the data distribution was not normal ($p<0.01$) and had a negative skew (skewness=−0.041), showing a higher incidence rate in older patients (Figure 1).

The mean±standard deviation of age in male patients was 68.41±12.46 y and 67.89±11.85 y for female patients, respectively, showing no statistically significant difference (p=0.29).

A total of 672 patients had ischemic stroke (81.3%), leaving the prevalence of hemorrhagic strokes at 18.7% (155 of 872 patients). There was no statistically significant correlation in terms of sex and the subtype of stroke (p=0.47). More information is presented in Figure 2.

The mean age of the patients having ischemic stroke was 68.64±12.41 y, and it was 66.11±12.06 y in patients with hemorrhagic stroke. The difference was statistically significant (p=0.02).

The most common risk factor for stroke was hypertension (66.7%). The other risk factors are presented in Figure 3.

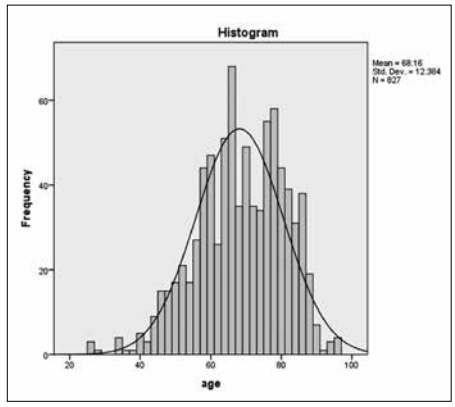

Figure 1. Distribution of age in patients included in the study

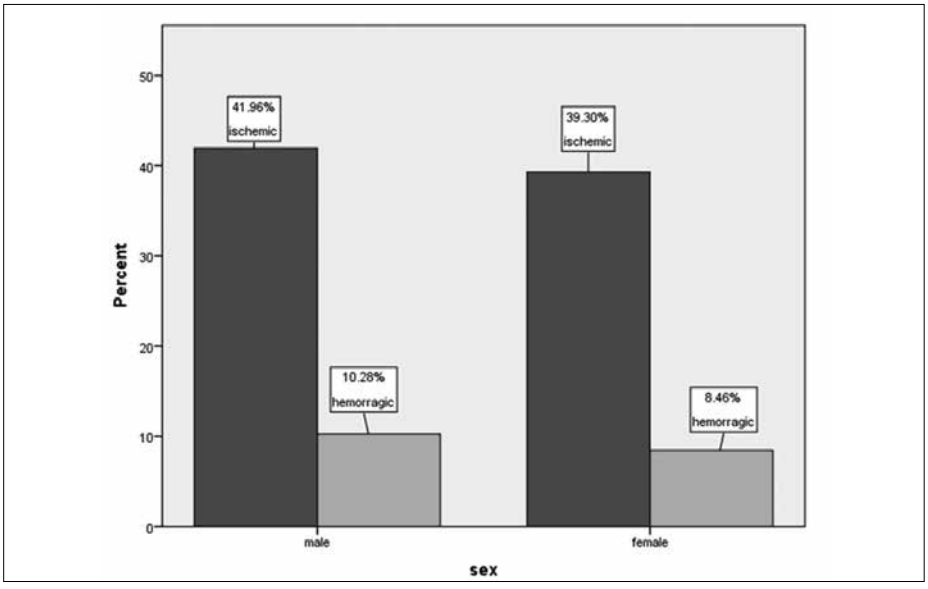

Figure 2. Distribution of patients based on the subtype of stroke separated according to sex

The determination of a relation between the risk factors and the subtypes of stroke showed that there was a significant relation between AH, AF, age, and family history and the subtype of stroke. The other risk factors had no significant relation. More information is presented in Table 1.

Of all the patients, 123 (14.9%) and 26 (3.1%) had peripheral and central vascular syndromes (PVS and CVS), respectively. CVS is defined as the involvement of the vasculature of the central nervous system by any means. Further analysis of the CVSs showed that the most prevalent etiology was the previous episodes of stroke (14.9%). While studying the PVSs, we found that the thromboses of extremity and mesenteric veins with a prevalence of 19 (2.3%) and 7 (0.8%), respectively, were the main causes of PVSs in these patients.

A history of previous stroke(s) was more common in patients with hemorrhagic strokes than that in the patients with ischemic strokes (20.6% vs. 13.4%; p=0.02). The incidence of thrombosis in the extremities was 2.4% in ischemic strokes and 1.9% in hemorrhagic strokes (p=0.73), respectively; further, the incident rate of mesenteric veins thrombosis was 0.7% and 1.3% in the ischemic and hemorrhagic strokes, respectively (p=0.5). There was no statistically significant correlation between the PVSs incidents and the subtype of stroke (p=0.9)

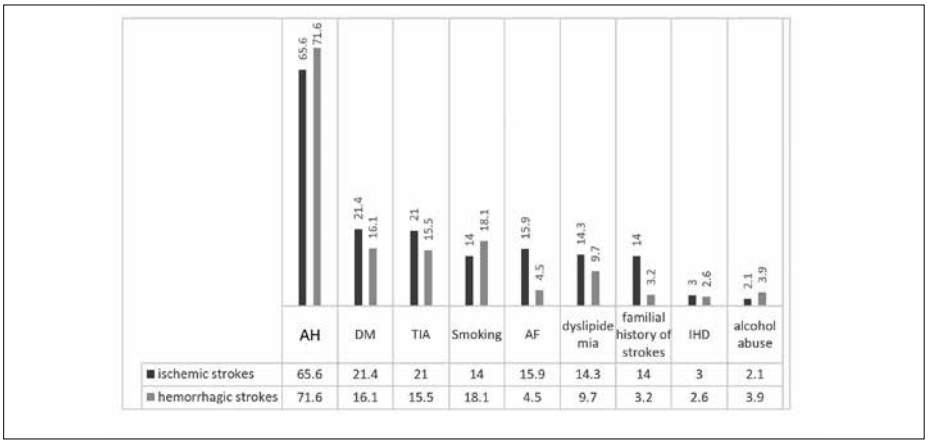

Figure 3. Prevalence of different risk factors in the included patients

Table 1. Relevance of stroke risk factors in accordance with the subtypes of stroke

		B	S.E.	Wald	DF	Sig.	Exp[B]
Variables	DM	−.290	.264	1.203	1	.273	.749
	AH	.680	.220	9.555	1	.002	1.974
	HLP	−.418	.330	1.607	1	.205	.658
	Smoke	.348	.278	1.569	1	.210	1.417
	Alcohol	.910	.598	2.318	1	.128	2.485
	Family History	−2.243	.520	18.627	1	.000	.106
	IHD	−.066	.587	.013	1	.910	.936
	AF	−1.442	.415	12.092	1	.001	.236
	TIA	−.360	.254	2.006	1	.157	.698
	Age	−.035	.008	17.346	1	.000	.966
	Sex	.171	.201	.725	1	.395	1.187
	Constant	.698	.572	1.491	1	.222	2.010

Variable(s) entered on step 1: DM (Diabetes mellitus), AH (Arterial Hypertension), HLP (Hyperlipidemia), Smoke, Alcohol, Familial history, IHD (Ischemic heart disease), Atrial fibrillation (AF), TIA (Transient ischemic attack), age, sex

Discussion

The frequency of ischemic and hemorrhagic strokes was 81.2% and 18.8%, respectively. These findings were in compliance to those of various previous studies, including Andersen et al. [16], Hajat et al. [17], and Zhang et al. [18] who stated that the prevalence of hemorrhagic strokes was between 5% and 25%.

In the study of the stroke risk factors, 64.4% and 20.1% of patients had AH and DM, respectively. The most common risk factors among the patients in Zhang's study were AH and hyperlipidemia. According to these results, the controlling and preventing chronic illnesses such as AH and DM are of high importance while controlling CVAs, particularly now that the prevalence of these conditions is increasing in different societies [19].

According to our study, old age, a history of AF (15.7% vs 3%), and a familial history of CVAs (13.6% vs. 5.2%) were more common among the patients with ischemic strokes. There was no significant difference between the subtype of stroke in terms of sex and the other risk factors. Other studies such as Anderson et al. found that the risk factors such as age, sex, and blood pressure were not predictive of the subtype of stroke [16]. On the other hand, Hajat et al., in a study of 1254 stroke patients that reviewed the risk factors and subtypes of strokes, found that there is a correlation between increased age and the incidence of ischemic strokes [17]. The same results were obtained in the studies performed by Zhang et al. and Grysiewicz et al. [18, 20]. Bilic et al. [21], studying the differences between hemorrhagic and ischemic strokes, found a higher prevalence of AH, an older age, atherosclerotic diseases, and AF in patients suffering from ischemic strokes. The results of the study conducted by Kimura et al. show the predictive value of old age in the occurrence of a second ischemic stroke [22]. All these studies show a positive relation between older age and the incidence of stroke, which is aligned with the findings of the current study, although there were some studies failing to show a correlation among these two factors.

Jørgensen et al. [23] found no correlation between AF and the occurrence of stroke, but there were studies stating that there is a higher risk of having an ischemic stroke, particularly among the patients with a history of AF, and another study showed an overall higher risk of suffering from strokes regardless of the subtype in patients with a history of AF [17, 18, 21, 22, 24]. Focusing on these results and the fact that AF has a prevalence of 19% in patients with a history of stroke and that this rate increases to 40% with an increase in age, we notice the importance of an early diagnosis and the treatment of AF in preventing strokes, particularly the ischemic subtype [25].

Age, sex, race, and a familial history of stroke are all risk factors of ischemic strokes, which cannot be changed, cured, or prevented [20].

In a study performed by Zhang et al., it was shown that having a familial history of stroke was suggestive of experiencing an ischemic stroke rather than a hemorrhagic stroke (9.8% vs. 3.3%) [18]. The results of the current recent study show a correlation between ischemic strokes and a familial history of strokes. These results were proven by Yamada et al. [26]at a cellular and molecular level, suggesting a genetic basis for ischemic strokes.

An evaluation of the PVSs and CVSs showed a history of these conditions in 3.1% and 14.9% of the cases, respectively. Zhang et al. [18] reported only a history of peripheral vascular diseases equivalent to 1.8% in patients with ischemic strokes. A history of past strokes in patients suffering from hemorrhagic strokes was more common as compared with that in patients suffering from ischemic ones (20.6% vs. 13.4%) with a p-value of 0.02. No correlations were found between the incidence of PVSs and the subtypes of stroke. In a study, Skaf et al. [27] showed that the prevalence of venous thromboembolism was higher in the patients with hemorrhagic strokes than that in the patients with ischemic strokes. Another study performed by Turnipseed et al. [16] reported five cases of stroke and two cases of transient ischemic attacks in 160 patients referred with peripheral vascular problems [28].

There is also a study that showed a 22.5% risk of experiencing a second episode of stroke in 5 years after experiencing the first stroke, which risk is particularly higher in the first 6 months following the initial incident. According to this study, the incidence rate of the second stroke is in correlation with the hemorrhagic index [28], and Baily et al. [29] claimed that 75% of the strokes in the patients experiencing a second episode were hemorrhagic rather than ischemic.

The present study aimed to address the differences between the two main subtypes of stroke and their different risk factor patterns. A limitation of this study is that the sample population was not large enough to make definite conclusion on the risk factors and the subtypes; it rather provides preliminary information on the subject. Also, all patients in the present study were from a single tertiary care, referral center. Multicenter studies would be of more merit. Needless to say, cohort studies focusing on the risk factors would help in constructing a definite correlation.

Most of the patients had an ischemic-subtype stroke. The age difference between the ischemic and hemorrhagic stroke group was statistically significant, suggesting a need for intense public health measures in the elderly. The most common risk factor among the patients was AH, emphasizing the importance of tight control of this factor. The only factors associated with the stroke subtype were AH, AF, age, and family history. The other risk factors were not significantly associated with a particular subtype of stroke.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics board of research deputy of Azad University School of Medicine, Tabriz branch.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Computed Tomography-Based Diagnosis of Gastric Vein Invasion in Patients with Gastric Cancer

Emre Unal, Ali Devrim Karaosmanoglu, Mustafa Nasuh Ozmen, Deniz Akata, Musturay Karcaaltincaba

ABSTRACT

Objective: The objective of this study was to demonstrate computed tomography (CT)-based diagnosis of venous invasion in patients with gastric cancer and its prognostic value.

Materials and Methods: Medical records and CT examinations of 530 patients with gastric cancer diagnosed after biopsy from February 2003 to December 2015 were included in this retrospective study. An imaging-based diagnosis of venous invasion was established when one of the following criteria were satisfied: 1) tumoral enhancement in the lumen of the vein, 2) tumor protruding through the course of a vein, and 3) distention of the vein due to extension of the gastric tumor. CT-based diagnosis of gastric vein invasion was established in 11/530 patients.

Results: Histopathological examination revealed poorly differentiated gastric adenocarcinoma (n=10) and neuroendocrine carcinoma (n=1). The median survival of the patients after the initial CT was 153.5 (range: 6–1275) days. Tumor invasion was observed at the aberrant left gastric vein (n=2), right gastroepiploic and superior mesenteric vein (n=2), gastric vein (n=4), and short gastric vein (n=3). Two of the three patients with short gastric vein invasion died 6 and 7 days after the initial CT, respectively.

Conclusion: All draining veins of the stomach can be invaded by gastric cancer; CT can enable diagnosis that may be important for prognosis and surgical planning. The presence of short gastric vein invasion detected by CT may be associated with poor prognosis.

Keywords: Gastric cancer, prognosis, venous invasion, CT, gastric vein

ORCID IDs of the authors:
E.U. 0000-0002-1520-2487;
A.D.K. 0000-0003-0027-9593;
M.N.O. 0000-0002-9910-4808;
D.A. 0000-0002-1318-0085;
M.K. 0000-0002-3384-0909.

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Department of Radiology, Hacettepe University School of Medicine, Ankara, Turkey

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Correspondence to: Musturay Karcaaltincaba
E-mail: musturayk@yahoo.com

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Introduction

Gastric cancer is still the cause for a considerable amount of cancer-related deaths worldwide [1-3]. Surgery is the main treatment option for patients with gastric cancer, and for almost 2 decades, laparoscopic surgery has gained great interest, particularly for early-stage gastric cancer [4-9]. Complex perigastric vascular anatomy can be a challenging issue during surgery [6-8]. Moreover, a high rate of anomalous course of the perigastric vessels may distress surgeons. However, recent advances in multidetector computed tomography (MDCT) scanners have enabled visualization of the precise course of perigastric vessels. The efficacy of computed tomography (CT) in assessing perigastric vascular anatomy and its application in the preoperative period has been indicated by several studies [5-10]. Despite curative and successful surgery, there are several tumor-related prognostic factors affecting survival. In a study by Nakanishi et al. [11], histological differentiation, depth of tumor invasion, presence of metastases, and venous invasion were found to be main prognostic factors of overall survival in patients with gastric carcinoma. Although the usual late presentation of the disease is also responsible for the poor survival rate, the presence of venous invasion is further reported to be a reliable independent prognostic factor in early-stage gastric cancer [12, 13]. Lee et al. [12] reported that lymphovascular invasion was an independent negative prognostic factor in node-negative patients, and the prognosis was similar to that of the N1 group (involvement of 1 to 2 nodes). Araki et al. [13] concluded that moderate or marked venous invasion was an independent predictor of relapse-free and overall survival in patients with stage IB node-negative gastric cancer. Moreover, several molecular markers have been found to be useful in predicting poor prognostic factors related with venous invasion in gastric cancer [14-16]. Previous studies have been based on histopathological/surgical findings, and there has been no study regarding CT-based diagnosis of venous invasion in gastric cancer. Histopathological diagnosis

of venous invasion is a well-recognized prognostic factor in patients with gastric cancer; however, CT-based diagnosis of venous invasion by gastric cancer is a rare entity. In this study, we aimed to demonstrate CT-based diagnosis of venous invasion in patients with gastric cancer and its prognostic value.

Materials and Methods

Ethics

This retrospective study has been approved by the local ethics committee of Hacettepe University (GO 16/112-17). Informed consent was waived because of the retrospective nature of the study.

Patients

Medical records and CT examinations of 530 patients diagnosed with gastric cancer from February 2003 to December 2015 were retrospectively reviewed in the study. This was a retrospective analysis of a prospectively collected database of patients with gastric cancer from a single tertiary care institution. The exclusion criterion was lack of CT-based diagnosis of gastric vein invasion according to imaging criteria given below. Imaging-based diagnosis of venous invasion was established in 11 patients. CT findings and clinical data of the patients are summarized in Table 1.

CT Technique and Image Analysis

Abdominal CT was performed using a 16-detector row CT scanner (Somatom Sensation 16, Siemens, Germany). All patients received 100 ml of iodinated contrast material (Ultravist 300/100 mg/mL; Bayer Schering Pharma, Berlin, Germany) at a flow rate of 4 mL/s using a power injector. CT images were obtained 70 s after the injection of the contrast.

The location of the gastric cancer, extension of the tumor, and tumoral invasion through the course of draining veins of the stomach were reviewed on CT images. An imaging-based diagnosis of venous invasion was established when one of the following criteria were satisfied: 1) tumoral enhancement in the lumen of the vein, 2) tumor protruding through the course of a vein, and 3) distention of the vein due to extension of the gastric tumor. Right and left gastric veins, aberrant left gastric vein (ALGV), right and left gastroepiploic veins, superior mesenteric vein (SMV), short gastric veins, and the portal vein were evaluated for tumoral invasion (Figure 1). Right and left gastric veins were evaluated as a gastric vein because the mass located at the lesser curvature of the stomach prevented assessment (Figure 2). Pathology reports of the patients were retrieved from the hospital information system.

Statistical Analysis

Statistical Package for Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. Descriptive statistics are provided as median (minimum-maximum). Statistical significance is deemed to occur when a p value is <0.05.

Results

The study cohort comprised six men and five women, with a median age of 60 (range: 48-83) years. In all patients, diagnosis of gastric carcinoma was established by histopathological examination. Only three patients (27%) underwent surgical treatment. In two of the three patients, bland thrombus was observed at follow-up after chemotherapy, whereas residual tumoral thrombus was detected in the remaining one patient. The median survival of the patients after the initial CT was 153.5 (range: 6-1275) days. One patient was still alive 6 months after the initial CT, i.e., at the time of the study. Although no postmortem examination was performed to verify the cause of death, there was no evidence in any of the patients supporting the presence of a metastasis that could be the cause of sudden cardiopulmonary arrest (e.g., brain, mediastinal, and heart metastases). In addition, none of the patients had advanced stage of comorbid diseases (e.g., severe cardiac arrhythmia and significant heart-kidney-lung-

Table 1. CT findings and clinical data of the study cohort

Age (years)	Gender	Pathology	Dissemination	Invaded vein	Survival (days)	Surgery
58	M	Poorly differentiated adenocarcinoma	Liver–bone left adrenal metastases, perigastric and periportal lymphadenopathy	Short gastric vein	6	-
53	F	Poorly differentiated adenocarcinoma with signet ring cell formation	Disseminated lymphadenopathy	Short gastric vein	7	-
66	F	Poorly differentiated adenocarcinoma	Disseminated lymphadenopathy	Gastric veina	60	-
60	F	Poorly differentiated adenocarcinoma	Liver invasion, disseminated lymphadenopathy, and peritoneal involvement	ALGV	105	-
83	F	Poorly differentiated adenocarcinoma	No sign of metastases	SMV via the right gastroepiploic vein	120	Distal gastrectomy
48	M	Poorly differentiated adenocarcinoma	Liver invasion, perigastric and periportal lymphadenopathy	ALGV	187	-
66	M	Poorly differentiated adenocarcinoma	Pancreatic invasion and perigastric lymphadenopathy	Short gastric vein	256	-
78	M	Poorly differentiated adenocarcinoma	Disseminated lymphadenopathy and peritoneal involvement	Gastric veina	439	-
74	M	Large-cell neuroendocrine carcinoma	Perigastric and periportal lymphadenopathy	Portal vein via the gastric veina	537	Total gastrectomy
58	F	Poorly differentiated adenocarcinoma	Perigastric and periportal lymphadenopathy	SMV via the right gastroepiploic vein	1275b	-
54	M	Poorly differentiated adenocarcinoma	Perigastric and periportal lymphadenopathy	Portal vein via the gastric veina	N/Ac	Total gastrectomy

ALGV: aberrant left gastric vein; SMV: superior mesenteric vein
[a]Differentiation of right and left gastric veins from each other was not possible, [b]The only patient with regression, [c]Alive at the time of the study.

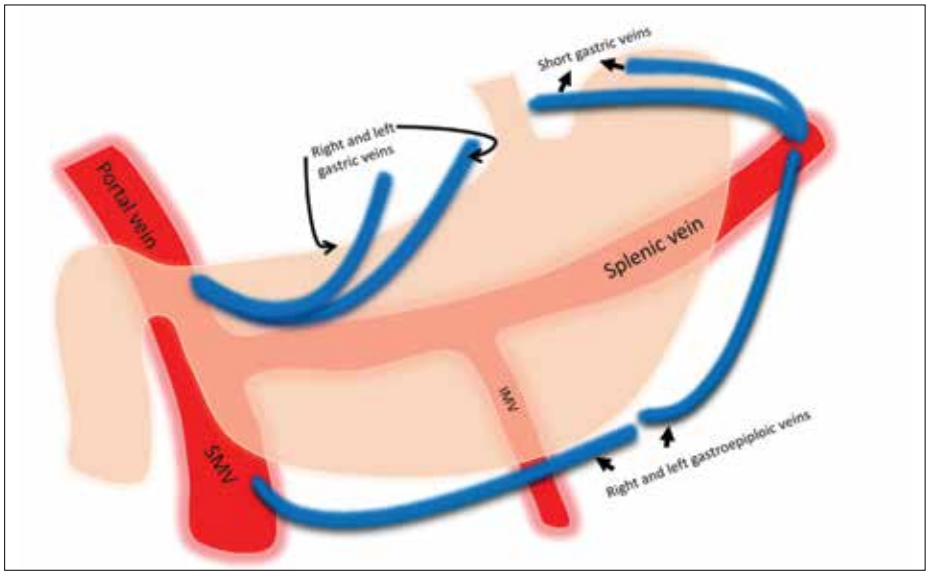

Figure 1. Schematic drawing showing courses of primary veins of the stomach
SMV: superior mesenteric vein, IMV: inferior mesenteric vein

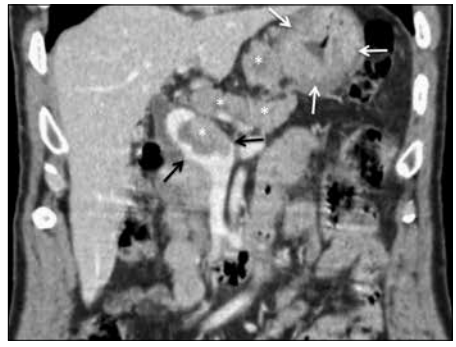

Figure 2. A 74-year-old man with gastric cancer invading the gastric veins. Coronal reformatted contrast-enhanced computed tomography (CT) image showing malignant thickening of the stomach wall (white arrows) and tumoral invasion through the course of the gastric vein (asterisks). Marked portal vein dilatation is seen at the site of gastric vein drainage because of luminal filling of the main portal vein with tumor (black arrows)

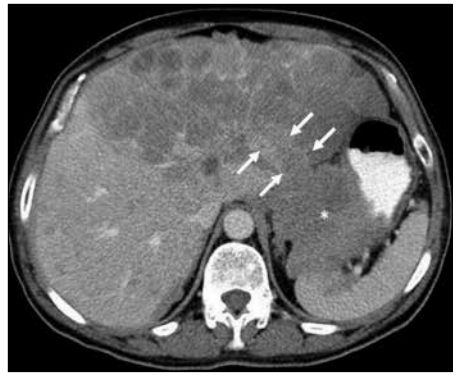

Figure 3. A 48-year-old man with gastric cancer invading the liver. Axial contrast-enhanced CT image demonstrating gastric cancer (asterisk) invading the left lobe of the liver via an aberrant left gastric vein (ALGV). Tumoral invasion of ALGV (arrows) and multiple liver metastases are seen

liver failure). Therefore, deaths of these patients were primarily attributed to gastric cancer.

Pathological examination revealed poorly differentiated adenocarcinoma in 10 out of the 11 patients (91%). Of these 10 patients, one had signet ring cell formation. In the remaining one patient, a large-cell neuroendocrine carcinoma was diagnosed. Although statistical analysis could not be achieved because of the small patient group of our study, survival rates of the patients with ALGV (Figure 3) and short gastric vein (Figure 4) invasion were low. Two patients with ALGV invasion died 105 and 187 days after the initial CT, respectively. Furthermore, two of the three patients with short gastric vein invasion died 6 and 7 days after the initial CT, respectively. These four patients had poorly differentiated adenocarcinoma, and the patient who died 7 days after CT had signet ring cell formation. The patient who died 1275 days after diagnosis had poorly differentiated adenocarcinoma invading SMV via the right gastroepiploic vein and the tumor in SMV almost totally regressed after chemotherapy; this was the only patient who was responsive to chemotherapy (Figure 5).

Discussion

The present study evaluated the value of CT-based diagnosis of venous invasion in patients with gastric cancer. Although our study had a small patient cohort as a major drawback for further analysis, survival rates of patients with ALGV and short gastric vein invasion were significantly low. Therefore, we can argue that the presence of ALGV or short gastric vein invasion on CT of a patient with gastric cancer may indicate poor prognosis. Advanced gastric cancer has a poor prognosis with a median survival time of 3-5 months in patients who are untreated and<12 months in those who have undergone the current chemotherapy protocols [2, 3]. In the present study, the median survival of patients after the initial CT was 153.5 days despite chemotherapy, and in seven patients, survival was <9 months, suggesting that venous invasion detected on CT is a poor prognostic factor of gastric cancer. One patient was still alive 6 months after the initial CT, i.e., at the time of the study.

Surgery is the main accepted treatment option for patients with operable gastric cancer with or without adjuvant chemotherapy depending on the stage of the disease [2, 3, 12, 13]. However, there is still a debate regarding the treatment of gastric cancer with venous invasion. Lee et al. [12] suggested that an individualized and comprehensive treatment approach should be considered in the presence of lymphovascular invasion because they found out that lymphovascular invasion was an independent negative prognostic factor of node-negative gastric cancer. Moreover, Araki et al. [13] determined that venous invasion was the only independent prognostic factor of relapse-free and overall survival in stage IB node-negative gastric cancer. They further concluded that adjuvant chemotherapy could be used for improving outcomes in patients with early-stage gastric cancer, particularly in the presence of venous invasion [13]. Nevertheless, authors of both studies also pointed out that further clinical trials are needed for confirming their results. In the present study, two patients had SMV invasion via the right gastroepiploic vein. One of these two patients underwent distal gastrectomy because there was no evidence of any metastases and pathological examination also revealed lack of lymph node metastasis. On the other hand, the other patient was followed up with chemotherapy. The patient who underwent distal gastrectomy was 83 years old and died 3 months postoperatively because of postoperative complications. However, the other patient who had inoperable gastric cancer responded to the treatment, and the main tumor and venous invasion were significantly reduced in size at follow-up. The anomalous course of the left gastric vein (LGV) has been recently described [17]. The efficacy of MDCT in depicting the perigastric vessel anatomy was investigated in several studies; authors have reported that MDCT is a useful and effective method for preoperative visualization of the

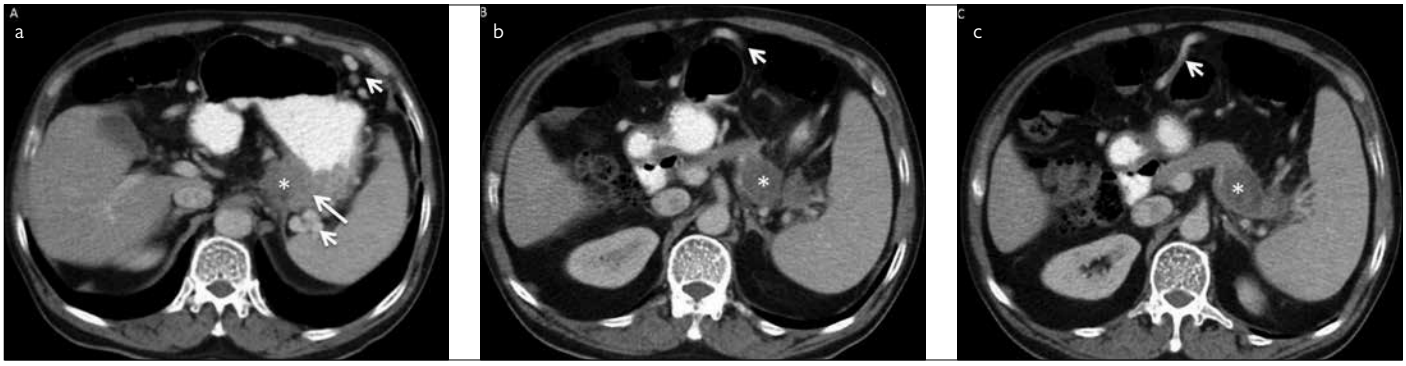

Figure 4. a-c. A 66-year-old man with gastric cancer extending through the course of short gastric veins. Serial axial contrast-enhanced CT images demonstrating the main tumor (long arrow, a), and tumor infiltrating through the course of short gastric veins (asterisks, a-c). Tumoral occlusion of the splenic vein is clearly seen (asterisk, c). Dilated collateral veins due to splenic vein occlusion (short arrows, a-c)

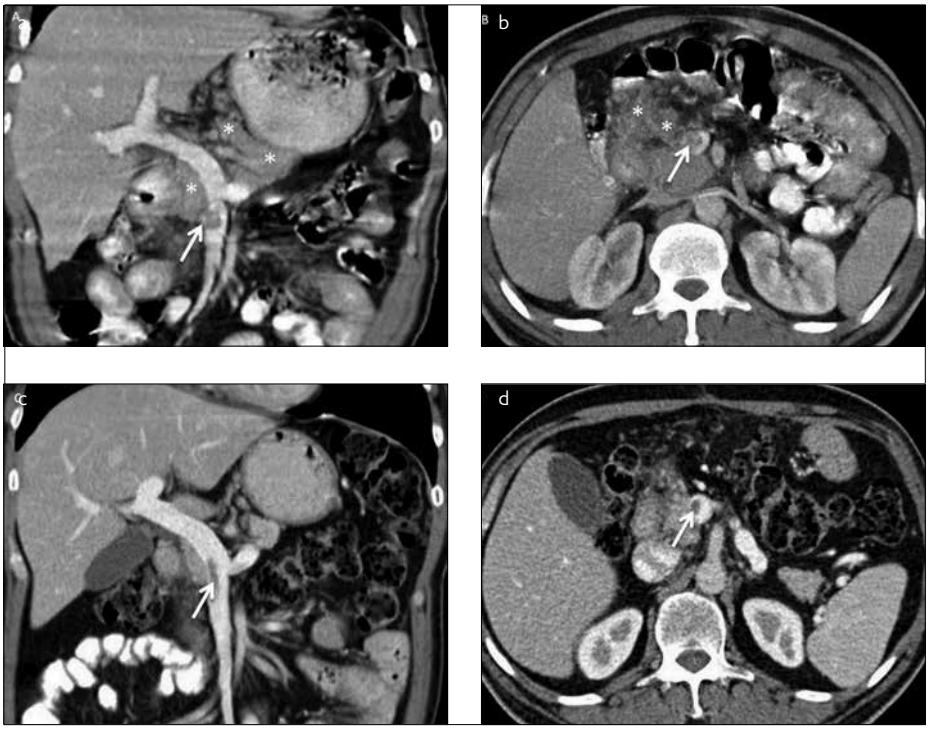

Figure 5. a-d. A 58-year-old woman with gastric cancer invading the superior mesenteric vein. Coronal (a) and axial (b) CT images demonstrating tumoral infiltration through the course of the right gastroepiploic vein (asterisks, a, b). Superior mesenteric vein invasion is also seen at the side of gastroepiploic vein drainage (arrows, a, b). Follow-up CT (c, d) after chemotherapy reveals marked tumoral regression at the course of the right gastroepiploic vein. Residual bland thrombus is seen without any sign of enhancing the soft tissue mass (arrows, c, d)

perigastric vessel anatomy [5-10]. Furthermore, preoperative demonstration of the vascular anatomy by MDCT can contribute to reduction of intraoperative blood loss, particularly during laparoscopic surgery [5, 6]. Identifying the course of LGV is important because LGV may demonstrate variations in the course, and injury to LGV may lead to significant blood loss [6]. On the other hand, ALGV develops because of morphogenetic changes during the developmental process in early embryonic life and has a unique course through the ligamentum venosum [17]. ALGV directly connects the stomach and liver, leading to venous drainage of lesser curvature into the liver. Therefore, direct spread of gastric cancer into the liver can occur in the presence of ALGV. In the present study 2 of 11 patients had ALGV invasion.

The most significant finding in our study was the survival time of patients with short gastric vein invasion; two of the three patients with short gastric vein invasion died within 1 week after CT. Perineural invasion was significantly associated with lymphatic venous invasion [12, 18]. Short gastric veins are adjacent to more important nerves (e.g., vagus nerve, phrenic nerve, and sympathetic-parasympathetic nervous system adjacent to the upper one third of the stomach) than the other veins of the stomach. Moreover, Jiang et al. [18] also reported that the incidence of perineural invasion was higher in the upper one third of the stomach. They considered that the presence of larger autonomic nerves and larger perineural spaces located in this area could be responsible [18]. In light of this information, we speculate that sudden cardiopulmonary arrest because of perineural invasion could be the cause of death, particularly in two patients with short gastric vein invasion. We acknowledge that the small sample size of our study prevents further analysis; thus, further studies are warranted for confirming our results. Nevertheless, our findings tend to agree with the above-mentioned studies that individual treatment options rather than standard protocols are more appropriate for managing gastric cancer, particularly in patients with venous invasion.

One of the major reasons for poor survival rates of gastric cancer is the late presentation of the disease. Nevertheless, it has also been reported that the presence of venous invasion on pathological examination could be used as a reliable prognostic marker in the early stage of the disease, particularly in patients with node-negative gastric cancer [12, 13]. Routine histopathological examination is occasionally insufficient for evaluating the presence of lymphatic and venous involvement in gastric cancer; therefore, researchers investigated the significance of molecular marker expression in predicting the presence of venous invasion [14-16]. However, Sekiguchi et al. [4] suggested that using immunohistochemistry in routine practice was not feasible in terms of the cost and workload. They reported that deeper invasion, the presence of an undifferentiated-type adenocarcinoma component, and a macroscopically elevated type were independent risk factors of venous involvement in gastric cancer. They also found out that a larger size (>20 mm), deeper invasion, the presence of a papillary

adenocarcinoma component, and the presence of an undifferentiated-type adenocarcinoma component were independent risk factors of lymphatic involvement as well [4]. Based on their results, Sekiguchi et al. [4] suggested that identification of these risk factors contributes to efficient use of immunohistochemistry stains in high-risk patients. On the other hand, it should be emphasized that CT can miss microscopic venous invasion. Moreover, smaller size of RGV and metastatic lymph node compression of LGV may result in non-visualization of these veins [9].

Our study had several limitations. First, the study cohort was small. However, CT-based diagnosis of venous invasion in gastric cancer is an uncommon finding in daily routine practice. Second, it was a retrospective, case-control study performed at a single institution. Third, pathological examination information regarding the presence of venous invasion was not available for patients who did not undergo surgery.

In conclusion, venous invasion of gastric cancer can be detected on CT and the presence of short gastric vein and ALGV invasion may be associated with poor prognosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University (GO 16/112-17).

Informed Consent: Written informed consent was waived because of the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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Evaluation of the Relationship between Carcinoembryonic Antigen and TNM Stage in Colorectal Cancer

Omer Topdagi[1], Aysu Timuroglu[2]

ABSTRACT

Objective: We aimed to examine the relationship between carcinoembryonic antigen (CEA) levels in the preoperative period and TNM (T: primary tumor, N: lymph node, M: distant metastasis or metastasis) staging in patients with colorectal cancer in our region.

Materials and Methods: In the present study, 752 cases diagnosed with colorectal cancer between January 1992 and December 2010 we analyzed retrospectively.

Results: Data of 752 patients diagnosed with colorectal cancer between 1992 and 2010 were evaluated; of the 752 patients, 427 (56.8%) were males and 325 (43.2%) were females with the mean age of 56.8±14.9 years. CEA levels of 316 cases were measured; 52.2% of the samples were within normal limits. Cases with CEA ≤5 ng/mL were majorly in Stage III, whereas those with CEA >5 ng/mL were predominantly in Stage IV. The TNM stage, tumor diameter, and differentiation levels were defined, and no statistically significant relationship was detected between these parameters and CEA levels.

Conclusion: While the CEA levels of 52.2% of participating cases were within normal limits, there was no statistically significant relationship between the CEA levels and differentiation level of tumor, tumor diameter, and TNM staging. According to the data, CEA levels may be within normal limits in the majority of patients with colorectal cancer. Therefore, normal levels of CEA will not rule out colorectal cancer diagnosis, and it can be concluded that these patients should be investigated in detail.

Keywords: Colorectal cancer, carcinoembryonic antigen, disease stage

ORCID ID of the corresponding author:
O.T. 0000-0002-9690-4447

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[1]Department of Internal Medicine, Atatürk University School of Medicine, Erzurum, Turkey
[2]Department of Internal Medicine, Erzincan University School of Medicine, Erzincan, Turkey

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Correspondence to: Omer Topdagi
E-mail: omertopdagi@hotmail.com

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Introduction

Colorectal cancer is an important cause of mortality and morbidity worldwide [1]. It is the fourth cancer type among women and men, and it ranks second among cancer-related deaths [2]. Serum carcinoembryonic antigen (CEA) is a glycolyzed antigen, which is secreted into the lumen after expression on the apical surface of colonic epithelial cells [3]. It is an oncofetal antigen, and its serum levels are increased at a rate of 75% in colorectal cancer recurrence. While CEA levels are highly sensitive in hepatic and retroperitoneal metastases, local recurrences are less sensitive in peritoneal and lung metastases [4]. Preoperative CEA levels in patients with colorectal cancer may be normal or high, and high CEA levels are reported to be closely related to recurrence and poor prognosis [5].

In our study, the presence of a relationship between preoperative CEA levels and tumor stage was investigated in patients with colorectal cancer.

Materials and Methods

Patients diagnosed with colorectal cancer as pathological results of examinations performed in our institution between 1992 and 2010 were retrospectively screened. The tumor, node, metastasis (TNM) stage of 320 patients were defined. The TNM classification (T: primary tumor, N: lymph node, M: distant metastasis or metastasis) of American Joint Committee on Cancer/ Union for International Cancer Control was used in colorectal cancer staging. Patients with colorectal cancer were classified as Stage I (presence of tumor without lymph node involvement extending to subserosa), Stage II (presence of tumor without lymph node involvement extending beyond subserosa), Stage III (presence of tumor without lymph node involvement without metastasis), and Stage IV (metastatic tumor) by using this method. The CEA levels of patients

Table 1. Median age, gender, tumor localization, and TNM stages of cases

Median age, years	56 (21-92)
Gender	
Male	427 (56.8%)
Female	325 (43.2%)
Total	752 (100%)
Tumor localization	
Cecum	33 (4.4%)
Ascending colon	66 (8.9%)
Transverse colon	21 (2.8%)
Descending colon	81 (10.9%)
Sigmoid colon	134 (18%)
Rectum	410 (%55)
Total	745 (%100)
TNM staging	
I	22 (6.9%)
II	68 (21.3%)
III	100 (31.3%)
IV	130 (40.6%)
Total	320 (100%)

T: primary tumor; N: lymph node; M: metastasis

Table 2. CEA levels and frequency values

CEA	Frequency	%
≤5 ng/mL	188	59.5
>5 ng/mL	128	40.5
Total	316	100

CEA: carcinoembryonic antigen

were also measured in the preoperative period. According to the reference range of our institution's hormone laboratory, values <3.4 ng/mL were accepted as normal, whereas those >3.4 ng/mL were accepted as high.

The Statistical Package for Social Sciences (SPSS Inc.; Chicago, IL, USA) 15.0 program was used in data analysis. Statistical analysis of mean ($\bar{X}$), frequency value (F), p value, Chi square (X^2), and t test were used in the analyses. The p values were obtained as the results of statistical analysis of data, and the level of significance was accepted as

All participants were informed about the study and written consent was obtained. The ethics committee approved the study protocol.

Results

In the present study, data from 752 patients diagnosed with colorectal cancer between 1992 and 2010 were evaluated. Of the 752 patients, 427 (56.8%) were males and 325 (43.2%) were females. The mean age was 56.8±14.9 years, and the median age was 56 years. The youngest patient was 21 years old, whereas the oldest was 92 years old. Patient data are summarized in Table 1.

The CEA levels of 316 patients could be defined; the CEA levels of samples were within normal limits (CEA= 0-3.4 ng/mL). When literature was reviewed generally, it was observed that patients were classified according to CEA levels below or about 5 g/mL. Therefore, the second classification was performed in the study and it was defined that 59.5% of cases had CEA ≤5 ng/mL (Table 2).

The relationship between CEA levels and TNM staging of patients is shown in Table 3. Cases with CEA ≤5 ng/mL were predominantly in the Stage III, whereas those with CEA >5 ng/mL were intensely in the Stage IV. Chi square analysis was performed, and no statistically significant correlation was detected between TNM staging and CEA levels (p>0.05; Table 3).

Table 3. CEA levels and TNM staging

CEA	TNM staging									
	Stage I		Stage II		Stage III		Stage IV		Total	
	Freq.	%	Freq	%	Freq	%	Freq	%	Freq	%
≤5 ng/mL	13	8.7	34	22.8	53	35.6	49	32.9	149	100
>5 ng/mL	6	6.1	21	21	25	25.5	46	46.9	98	100
Total	19	7.7	55	22.3	78	31.6	95	38.5	247	100

T: primary tumor; N: lymph node; M: metastasis; CEA: carcinoembryonic antigen; Freq: frequency

Table 4. CEA level and differentiation degree

	Differentiation degree				
CEA	Mild	Moderate	Well	Undifferentiated	Total
≤5 ng/mL	9	60	22	1	92
>5 ng/mL	10	32	5	1	48
Total	19	92	27	2	311

CEA: carcinoembryonic antigen

Table 5. CEA level and tumor diameters

	CEA level		
Tumor diameter	≤5 ng/mL	>5 ng/mL	Total
< 3 cm	32	29	61
3-6 cm	58	31	89
6-9 cm	31	21	52
>9 cm	29	16	45
Total	150	97	247

CEA: carcinoembryonic antigen

When CEA levels were evaluated with tumor differentiation degrees, no statistically significant correlation was detected between cases with CEA ≤5 ng/mL and those with >5 ng/mL in the Chi square analysis (p>0.05; Table 4).

When the correlation between CEA levels and tumor diameters of patients was compared, no statistically significant correlation was detected in the Chi square analysis (p>0.05; Table 5).

Discussion

CEA, which was first defined by Gold and Feedman in 1965, is an intracellular protein, and can be defined normal at low concentrations in the embryonic and fetal intestines or normal adult human cells. CEA can be detected at high levels in breast and lung cancers as well as in the serum levels are detected high at 90% of primary colorectal cancer cases. CEA is an important structure regulating promoter functions in intracellular adhesion and aggregation. Therefore, it has been believed that CEA has an important role in tumor invasion and in defining metastasis [5, 6]. Filiz et al. [7] reported in their study on 151 colorectal cancer patients in 2009 that 58.8% of patients had normal preoperative CEA levels. No statistically significant correlation was detected between tumor size, localization, and differentiation degree and preoperative CEA levels in that study. In another study conducted by Duffy [8], correlation between CEA levels of patients and differentiation degree was investigated. While CEA levels were high in cases with well and moderately differentiated tumors, they were low in the cases with poor and mild differentiations. This condition was believed to be due to low CEA levels in patients with undifferentiated or poorly differentiated tumors at the advanced stage. When CEA levels and differentiation degrees of patients were compared in the aforementioned study, it was observed that tumor differentiation was mild or undifferentiated in patients with CEA levels of >5 ng/mL; it was generally well or moderate in cases with CEA levels of <5 ng/mL. However, the condition was not statistically significant.

Huh et al. [5] investigated the correlation between CEA levels and TNM staging in 474 patients with colorectal cancer. Patients were divided into two groups according to CEA levels of above or below 5 ng/mL. However, only patients with non-metastatic colorectal cancer were included in the study. As result of the study, a statistically significant correlation between CEA levels and TNM staging of patients was defined. While CEA levels were high in 33.1% of patients preoperatively, they were normal in the rest of patients. No significant correlation was detected between CEA levels, tumor localization, and differentiation degrees of patients. Lee et al. [6] accepted a preoperative CEA level of 5 ng/mL as the cut-off value. CEA levels were low among patients with Stage I and II TNM classification (66%), but they were high in patients with more advanced disease; the correlation was statistically significant. In our study, CEA levels were detected within normal limits in 52.2% of cases; no statistically significant correlation was detected between CEA levels and tumor differentiation degree, tumor diameter, and TNM staging. In the light of this information, it should be considered that CEA levels may be within normal limits in many patients with colorectal disease; hence, in suspected cases for colorectal cancer, normal levels of CEA cannot rule out colorectal cancer diagnosis. Moreover, a clear correlation between CEA levels and TNM staging of patients has not been revealed, clearly indicating that further studies are required about this issue.

Retrospective design is a limitation of this study. And inadequate care in keeping patient records is another limitation of our study.

In conclusion, colorectal cancer is a cancer type, in which more studies should be performed because it is an important mortality and morbidity cause in the world and in our country. There is a meaningful link between TNM stage and CEA level.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Atatürk University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept - O.T., A.T.; Design - O.T., A.T.; Supervision - O.T., A.T.; Resources - O.T., A.T.; Materials - O.T., A.T.; Data Collection and/or Processing - O.T., A.T.; Analysis and/or Interpretation O.T., A.T.; Literature Search - O.T., A.T.; Writing Manuscript - O.T., A.T.; Critical Review O.T., A.T.; Other - O.T., A.T.

Conflict of Interest: Authors have no conflict of interest to declare.

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Frequency and Significance of Perforating Venous Insufficiency in Patients with Chronic Venous Insufficiency of Lower Extremity

Ismet Tolu, Mehmet Sedat Durmaz

ABSTRACT

Objective: The aim of this study was to reveal the frequency and impact of perforating venous insufficiency (PVI) in chronic venous insufficiency (CVI) of lower extremity (LE).

Materials and Methods: Between 2012 and 2017, a total of 1154 patients [781 females (67.68%) and 373 males (32.32%), 228 (19.76%) unilateral and 926 (80.24%) bilateral LE] were examined using Doppler ultrasound (US). A total of 2080 venous systems of LEs [31.4% male (n=653) and 68.6% female (n=1427); 1056 left LEs (50.77%) and 1024 right LEs (49.23%)] were examined. All patients had symptoms of venous insufficiency (VI).

Results: PVI was revealed in 27.5% (n=571) of LEs. Varicose veins (VVs) related with perforating vein (PV) were revealed in 44.7% of LEs (n=929). PVI was observed in 50.91% of patients with chronic deep venous thrombosis (DVT), 64.41% with deep venous insufficiency (DVI), 59.81% with great saphenous vein (GSV) insufficiency, 68.49% with small saphenous vein (SSV) insufficiency, 58.65% with accessory GSV insufficiency, and 58.77% with PV associated with VVs. There was a statistically significant relationship between PVI and chronic DVT, DVI, GSV, SSV, and accessory GSV insufficiency ($p<0.001$). A significant relationship was observed between the increase in PV diameter and the presence of PVI ($p<0.001$).

Conclusion: PVI is quite common in combined VI, and PV evaluation should be a part of LE venous system examination.

Keywords: Chronic venous insufficiency, doppler ultrasound, perforating venous insufficiency, varicose veins

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ORCID IDs of the authors:
İ.T. 0000-0002-1161-9998;
M.S.D. 0000-0002-1340-2477.

Department of Radiology, Health Sciences University Training and Research Hospital, Konya, Turkey

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Correspondence to: Mehmet Sedat Durmaz

E-mail: dr.msdurmaz@gmail.com

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Introduction

Chronic venous insufficiency (CVI) may lead to many physical and cosmetic problems that compromise the quality of life [1]. Preoperative color Doppler ultrasound (US) evaluation of the deep venous system (DVS) and superficial venous system (SVS) in terms of insufficiency and varicose veins (VV) has been considered as a routine procedure [2, 3]. Approximately half of all VIs occur in multiple levels or is combined [1, 4]. Although there are 150 perforating veins (PVs) in the lower extremity (LE), only a few of them are clinically significant [5]. Perforators are located between the deep and the superficial veins [great saphenous vein (GSV), small saphenous vein (SSV), anterior or posterior accessory GSV or VVs]. Because PVs drain into SVS from DVS by penetrating the muscle fascia, any failure in the valves of these structures directly leads to SVS insufficiency and VV [6, 7]. PV may play a critical role in the development of VV and non-healing venous ulcers by becoming the reason of venous hypertension. Despite the fact that there are many studies on PVs in the literature, its effects on hemodynamics are still controversial [6, 8, 9]. The role of PVs in the etiology and management of VVs and CVI continues to be debated [10]. The aim of this study was to assess the impact and frequency of perforating venous insufficiency (PVI) in combined CVI of LE detected by Doppler US.

Materials and Methods

This study was approved by the local research ethics committee. All patients were contacted by post, and written informed consent was obtained from each patient prior to the Doppler US examination. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable

ethical standards. This prospective controlled study was performed from April 2012 to July 2017. A total of 1154 patients [781 females (67.68%) and 373 males (32.32%)] with complaints or symptoms of venous insufficiency (VI; such as leg edema, pain, ulcers, cramps, itching, thickening of the skin, color change around the ankles of the skin, having VVs, or feeling of tension in the legs) were included in this study.

All LE venous Doppler US examinations were performed by a single radiologist who had 10 years of experience in Doppler US (M.S.D.). The patients were in the age range of 14–87 years (mean, 46 years). All patients were evaluated using Doppler US examinations: unilateral LE was examined in 228 of them and bilateral LEs were examined in the remaining 926. A total of 2080 venous systems of LEs were examined. In total, 168 patients, including patients with acute superficial vein thrombosis (SVT) and deep vein thrombosis (DVT), elderly patients who could not stand up, and patients who did not cooperate to Valsalva's maneuver, were excluded from the study.

Doppler US was performed with a high-frequency (7.5 MHz) linear array transducer TOSHIBA Aplio 300 (Toshiba Medical System Corporation, Tokyo, Japan). All the pathological findings and levels were recorded separately. The Doppler US examination for reflux began with a standard US examination of the DVS performed with the patient in the supine position to exclude DVT and SVT. Then, the patients were evaluated while they were in an upright position, in terms of deep venous insufficiency (DVI) and superficial venous insufficiency (SVI). The patient was requested to support her/his body weight to the side that was not being examined. In this way, by shifting one's body weight, a patient could relax the muscle of the leg under examination and so the presence of reflux could be detected. The Valsalva's maneuver was used to evaluate the valvular competence of DVS. Valvular competence of SVS and PVs was evaluated at rest with the Valsalva's maneuver and on compression of the distal parts of the calf. GSV, SSV, and anterior/posterior accessory GSV territory from the thigh to calf were evaluated. Moreover, "the thigh perforators" include the medial thigh (hunter's PV), anterior thigh, and posterior thigh PVs; "the knee perforators" include the medial knee (Boyd's PV) and popliteal fossa PVs; and "the leg perforators" include the paratibial (Sherman PV), posterior tibial (Cockett's PVs), anterior leg, lateral leg, and posterior leg (medial and lateral gastrocnemius, intergemellar) PVs that were evaluated as shown in Figure 1. PVs were assessed in the transverse and oblique scanning planes, and the diameter of PVs as detected by US was noted. Maximal diameters of PVs were measured at the suprafascial–subfascial connection level (Figure 2). Augmentation of blood flow by compression of the limb below the perforator and Valsalva's maneuver was used to assess valvular integrity (Figure 3). Reflux flow of more than 0.5 s was used as criterion for significant VI and in PVs, DVS, and SVS on spectral Doppler imaging. DVI, GSV, SSV, and PVI were recorded (Figure 4). Anterior and posterior accessory GSV insufficiency were separately noted. Moreover, it was evaluated whether the relationship between the PVI or other VI existed. The duration of the examination was approximately 20 min for each LE venous system. The US reports and images were saved on a digital US database and later to a computer media (23-inch, full HD, 1920×1080 resolution, Dell, Intel Corporation, US).

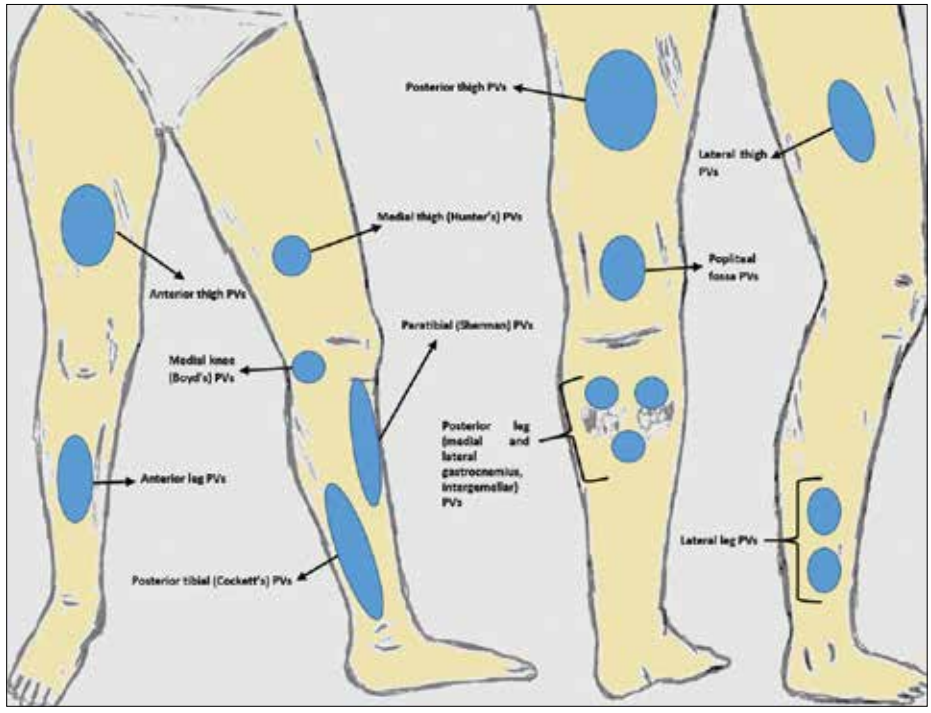

Figure 1. Schematic images of the main groups of PVs in LE

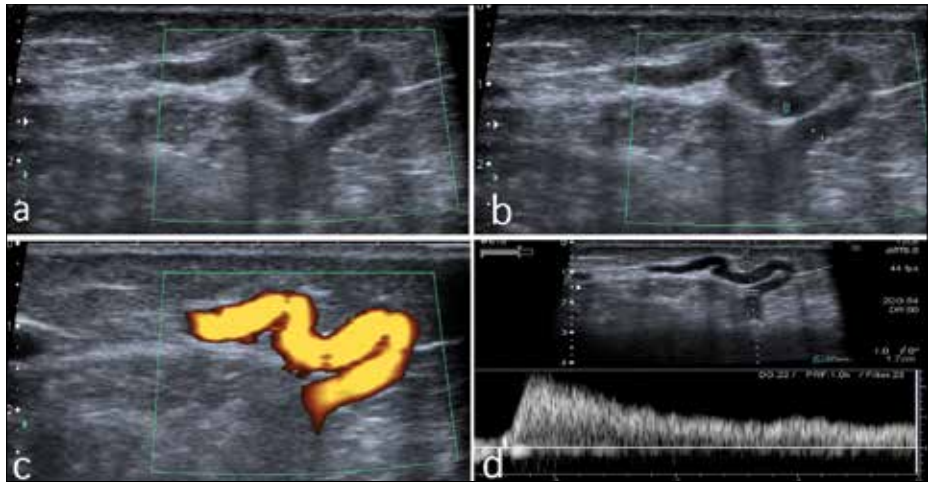

Figure 2. a-d. Sonographic evaluation of PV. PV obliquely perforates the deep muscular fascia and associates the with the superficial vein (a), diameter of PV measured at the suprafascial–subfascial connection level (b), augmentation of blood flow by compression of the limb below PV and Valsalva's maneuver are used to assess valvular integrity with color flow imaging (c), and spectral Doppler imaging (d)

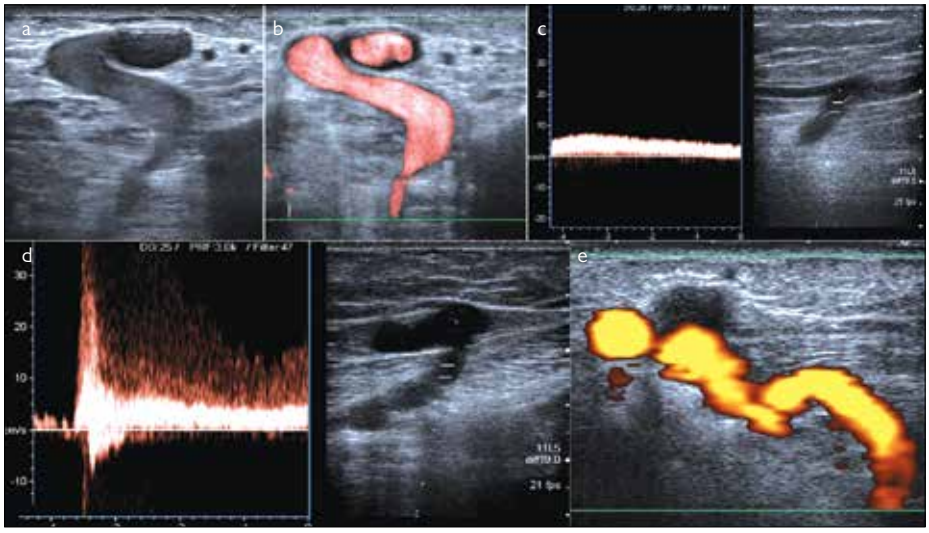

Figure 3. a-e. Sonographic imaging of perforating vein (PV) associated with varicose vein and saphenous veins. Enlarged posterior tibial (Cockett's) PV obliquely perforates the deep muscular fascia and connects with the crural varicose vein (a). Power Doppler imaging showing reflux both in the posterior tibial PV and in the varicose vein following a Valsalva's maneuver (b). Spectral Doppler imaging showing significant reflux in the paratibial (Sherman) PV following a Valsalva's maneuver (c). Spectral Doppler imaging showing significant reflux in the medial thigh (Hunter's) PV associated with saphenous vein following compression of the distal parts of the calf (d). Power Doppler imaging showing reflux in the posterior leg (lateral gastrocnemius) PV associated with small saphenous vein following a Valsalva's maneuver (e)

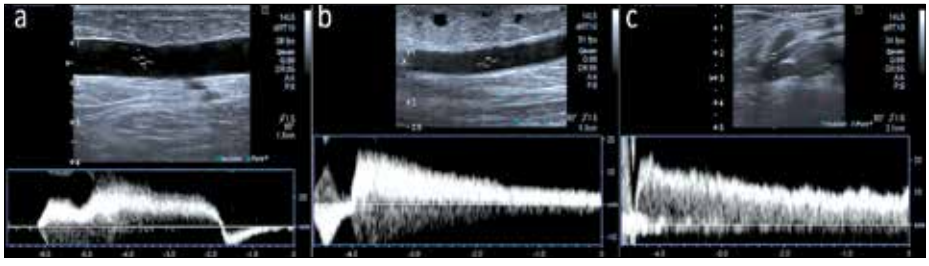

Figure 4. a-c. Reflux in saphenous veins. Longitudinal view and spectral Doppler imaging show significant reflux in the great saphenous vein at the level of distal thirds of the thigh following a Valsalva's maneuver (a). Spectral Doppler imaging showing significant reflux in the great saphenous vein at the level of distal thirds of the thigh (b) and in the small saphenous vein distal to the saphenopopliteal junction in the proximal cruris, following compression of the distal parts of the calf (c)

Table 1. Number of incompetent PVs

Perforating vein	Number (Percent)
Medial thigh (Hunter's) perforating veins	104 (8.25 %)
Anterior thigh perforating veins	26 (2.06 %)
Posterior thigh perforating veins	78 (6.20 %)
Medial knee (Boyd's) perforating veins	188 (14.92 %)
Popliteal fossa perforating veins	89 (7.06 %)
Paratibial (Sherman) perforating veins	116 (9.20 %)
Posterior tibial (Cockett's) perforating veins	325 (25.80 %)
Anterior leg perforating veins	35 (2.77 %)
Lateral leg perforating veins	34 (2.70 %)
Posterior leg (medial and lateral gastrocnemius, intergemellar) perforating veins	265 (21.03 %)
Total	1260 (100 %)

Statistical analysis

Statistical analysis to evaluate the data was performed using SPSS packet program (Statistical Package for Social Sciences, version 15, SPSS Inc., Chicago, Illinois, USA). Normal distribution of continuous variables was tested using the Kolmogorov–Smirnov test. Primarily, the definitive statistics related to the variables were evaluated. Descriptive statistics were expressed as mean, standard deviation, frequency, and percentile. Statistical analysis was performed using the chi-square and Mann–Whitney U tests. The chi-square test was used to determine the relationship between PVI and PV associated with VVs, chronic DVT, DVI, GSV insufficiency, SSV insufficiency, and accessory GSV insufficiency. The Mann–Whitney U test was used to determine the relationship between the presence of PVI and the increase in PV diameter. Values of $p<0.05$ were considered significant.

Results

In total, 2080 venous systems of LEs were examined. PVI was observed in 1260 PVs and 27.5% (n=571) of LEs. Significant reflux was most commonly detected in the posterior tibial, posterior leg, and medial knee PVs (Table 1). VVs related with PVs were revealed in 44.7% of LEs (n=929). Doppler US examination showed reflux in these VVs. PVI was observed in 546 of the 929 LEs (58.77%) in which LEs PVs were associated with VVs. The reflux started from an incompetent PV located directly at the peripheral side of VVs. There was a statistically significant relationship between PVs associated with VVs and PVI ($p<0.001$) (Table 2). Chronic DVT was observed in 2.6% (n=55) of LEs. PVI was also observed in 50.91% of patients with chronic DVT. There was a statistically significant relationship between chronic DVT and PVI ($p<0.001$).

DVI was revealed in 295 (14.2%) of LEs. DVI was observed only in the main femoral vein (FV) 172 (58.3%), only in the FV 21 (7.12%), only in the deep FV 3 (1.02%), only the in popliteal vein 27 (9.15%), in multiple veins 72 (21.24%) of 295 LEs with DVI. PVI was observed in 190 (64.41%) of 295 LEs with DVI. There was a statistically significant relationship between DVI and PVI ($p<0.001$).

GSV insufficiency was revealed in 34.80% (n=724) of LEs. PVI was observed in 59.81% (n=433) of patients with GSV insufficiency. There was a statistically significant relationship between GSV insufficiency and PVI ($p<0.001$).

SSV insufficiency was revealed in 10.5% (n=219) of LEs. PVI was observed in 150

Table 2. Degrees of association between duration of hemodialysis and clinical measurements in CKD group

		Perforating vein associated with varicose veins			
		Absent	Present	Total	p
Perforating venous insufficiency	Absent	1126	383	1509	<0.001
	Present	25	546	571	

p<0.05 was considered to be statistically significant.

Table 3. Relationship between PV insufficiency and chronic DVT, DVI, GSVI, SSVI, and accessory GSVI

		Perforating venous insufficiency		
		Absent	Present	p
Chronic deep venous thrombosis	Absent	1482	543	<0.001
	Present	27	28	
Deep venous insufficiency	Absent	1404	381	<0.001
	Present	105	190	
Great saphenous vein insuffiency	Absent	1218	138	<0.001
	Present	291	433	
Small saphenous vein insuffiency	Absent	1440	421	<0.001
	Present	69	150	
Accessory great saphenous vein insufficiency	Absent	1466	510	<0.001
	Present	43	61	
Total		1509	571	

p<0.05 was considered to be statistically significant.

(68.49%) patients with SSV insufficiency. There was a statistically significant relationship between SSV insufficiency and PVI (p<0.001).

We also found anterior and/or posterior accessory GSV insufficiency in 5% (n=104) of LEs. PVI was observed in 58.65% (n=61) of patients with accessory GSV insufficiency. There was a statistically significant relationship between accessory GSV insufficiency and PVI (p<0.001). PVI frequency increased with increasing number of veins with VI in deep and superficial veins, and a statistically significant relationship was found (p<0.001).

The smallest diameter of PV with insufficiency was 2.0 mm, and the largest diameter was 5.1 mm. The mean diameter of PVs with insufficiency was 3.24 mm. PVs that were detected during US examination but were not insufficient had a mean diameter of 1.85 mm. A significant relationship was observed between the increase in PV diameter and the presence of PVI (p<0.001).

In conclusion, we found a statistically significant relationship between PVI and PV associated with VVs, chronic DVT, DVI, GSV, SSV, and accessory GSV insufficiency (p<0.001). These parameter values related to PVI are presented in detail in Table 3. Moreover, PVI frequency increased with increasing number of veins with VI, and a statistically significant relationship was found (p<0.001).

Discussion

PVs connect collecting and saphenous veins with tibial, femoral, popliteal, and sinusoidal deep veins by obliquely perforating the deep muscular fascia [6, 11]. Large PVs contain valves that direct flow from superficial vessels to deep veins and generally run along the perforated artery [11]. Among many PVs, the medial calf perforators are probably the most important [5, 12]. PVs have varying appearances in terms of size and distribution. The prevalence of PVI increases linearly as the severity of DVI and SVI increases [13]. PVI is most frequently associated with reflux in SVS, followed by reflux in both SVS and DVS. DVI is rarely the primary cause. The correlation between the occurrence of insufficiency of GSV and PVs has been revealed [6, 14-17]. In many studies and our study, PVI was found to be most frequently associated with insufficiency in deep veins, GSV, SSV, anterior/posterior accessory GSV, and chronic DVT. We found statistically significant relationship between PVI and chronic DVT, DVI, GSV insufficiency, SSV insufficiency, and accessory GSV insufficiency (p<0.001). There was a statistically significant correlation between PVI and PV related with VVs (p<0.001). These results have indicated that incompetent PVs play a critical role in CVI. We detected a meaningful relationship between PV associated with VVs and PVI (p<0.001). PVs, especially those associated with VV, should be examined for reflux, regardless of whether they are enlarged or not. We found a significant relationship between the increase in PV diameter and the presence of PVI (p<0.001). However, PVs in which reflux was detected had a very small diameter, whereas PVs in which reflux was not detected in our study had a diameter >4 mm. Because of this, the size cannot be considered as the only criterion for PVI diagnosis.

Mechanism of valve dysfunction of PVs leading to CVI and hemodynamic role of PV has not yet been completely elucidated [13, 18, 19]. One of the asserted mechanisms of the incompetency is enlargement of the diameter, in which incompetent PVs may serve as the re-entry point for superficial blood flow into DVS of patients with VVs [20, 21]. The other proposed mechanism of incompetency is dysfunction due to irreversible valvular damage [19, 21, 22]. Irreversible valvular damage of incompetent PVs might be associated with recurrence of VVs after operating SVI; therefore, this type of incompetent PVs may require simultaneous treatment with SVI [19, 21, 22].

The presence of incompetent PVs after treatment of SVI has been defined as a major risk factor for non-healing and recurrent leg ulcers and for recurrence of varicosities in patients with CVI. Residual incompetent PVs associated with failure of treatment and aggressive procedures to manage incompetent PVs have improved the surgical outcome. The experiences gathered in clinical studies have also demonstrated that incompetent PVs are likely to be more important in the development of VVs [2, 10, 23]; if incompetent PVs can be selectively treated, more satisfactory results could be achieved [19, 22]. Several authors suggest treating incompetent PVs in cases of focal swelling, pain, associated VVs, focal skin irritation, discoloration, venous ulceration in the area of the incompetent PVs, clinical severity, etiology, anatomy, and pathophysiology score more than four [24]. In particular, treatment of incompetent PV is recommended in which the VV is non-saphenous and starts from the

periphery of incompetent PV. PVI is important for the development and maintenance of these peripherally located VV [19]. Some patients have enlarged incompetent PVs and severe limb symptoms, including ulceration. In the treatment of venous ulcers that are located above the ankle, it is recommended to include treatment of incompetent PV in combination with SVI therapy [19, 25]. In patients with a combination of SVI and PVI, routine PVI treatment is recommended by some authors, along with SVI treatment because of the risk of recurrence [6, 25-27]. Incompetent PVs can be treated with surgical ligation, US-guided sclerotherapy, endovascular thermal, laser therapy, or radiofrequency ablation [24]. It is still not known whether preoperative identification of PVI could facilitate more effective treatment. If the radiologists are not aware of the importance of PVI and do not mention it in their reports and only SVI is treated, recurrences in this group of patients will be inevitable. Because of these reasons, evaluation of PVs should be a part of LE venous system examination, and radiologists should indicate the presence of any PVI in the reports.

Color Doppler US has become a major diagnostic tool in the evaluation of patients with VI symptoms [28]. Gray-scale US examination with color Doppler and spectral analysis have become increasingly important and are now more frequently used for the diagnosis and treatment of VI [12]. Doppler US examination for reflux begins with a standard US examination of DVS performed with the patient in the supine position for excluding DVT. Doppler US assessment of VI should always be performed with the patient in the standing position [28]. The examination of deep, superficial, and PVs should be performed at the same time because all of them will play an important role in the patient's diagnosis and future treatment [2, 28, 29].

The limitation of the study is that interobserver variation could not be evaluated because of the length of the examination time and all patients were observed by a single experienced radiologist. In conclusion, our study showed that PVI is quite common in combined VI and that there is a statistically significant relationship between PVI and chronic DVT, DVI, GSV, SSV, and accessory GSV insufficiency. PVI frequency increased with increasing number of veins with VI, and a statistically significant relationship was found. Incompetent PVs play a significant role in CVI. Doppler US is a safe and effective technique for evaluating LE CVI before planning the treatment course. PV evaluation should be a part of LE venous system examination in VI, and size alone cannot be the criterion for PVI diagnosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selçuk University (2017/19-2017/319).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.S.D.; Design - M.S.D., İ.T.; Supervision - İ.T.; Resources - M.S.D.; Materials - M.S.D.; Data Collection and/or Processing - İ.T., M.S.D.; Analysis and/or Interpretation - M.S.D.; Literature Search - İ.T., M.S.D.; Writing Manuscript - M.S.D., İ.T.; Critical Review - İ.T., M.S.D.

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The Role of GnRH Analogues in Improving Outcome in Women Undergoing Superovulation and Intrauterine Insemination after Surgical Correction of Mild Endometriosis: A Randomized Controlled Trial

Piyush Bansal[1], Kavita Khoiwal[2], Neena Malhotra[1], Vatsla Dadhwal[1], Aparna Sharma[1], Dipika Deka[1]

ABSTRACT

Objective: Treatment with laparoscopic surgery, gonadotropin-releasing hormone analog (GnRHa) therapy, superovulation (SO), and intrauterine insemination (IUI) have individual benefits in improving fertility outcomes in women with endometriosis. The aim of the study was to evaluate the role of GnRHa in improving outcome in women undergoing SO and IUI after surgical correction of mild endometriosis.

Materials and Methods: This was a randomized controlled trial conducted in the Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India, over a period of 2 years and 6 months. Ninety women who were diagnosed with mild endometriosis on laparoscopy using the revised American Society for Reproductive Medicine criteria were included in the study. The patients in the study group (n=45) received a single dose of 3.75 mg GnRHa subcutaneously within 48 h of the surgery, and those in the control group (n=45) did not receive GnRHa. Thereafter, patients in both arms received SO and IUI from the next menstrual cycle. Four patients in the study group and three patients in the control group were lost to follow-up before the first cycle of ovulation induction. Primary outcomes measured in our study were live birth rates and clinical pregnancy rate. Secondary outcome measures were number of follicles>18 mm, endometrial thickness, dose and days of gonadotropin stimulation.

Results: Baseline characteristics, such as age and body mass index, were comparable in both groups. The SO and IUI cycles were comparable between the two groups with regard to the secondary outcome parameters. Pregnancy rate in the first cycle was 17.1% in the study group and 19.1% in the control group (p=0.81). The overall pregnancy rate was similar in both groups (study group=21.9%, control group=23.8%; p=1). As no patient had miscarriage or any other complication during pregnancy, live birth rate was similar to the clinical pregnancy rate.

Conclusion: Adding GnRHa for the suppression of mild endometriosis has shown no significant improvement in the surgical management of women undergoing SO and IUI.

Keywords: Mild endometriosis, GnRH analog, superovulation, intrauterine insemination

ORCID IDs of the authors:
P.B. 0000-0003-0222-9661;
K.K. 0000-0002-3156-7486;
N.M. 0000-0001-7837-5361;
V.D. 0000-0003-0280-5833;
A.S. 0000-0002-7369-2007;
D.D 0000-0001-5126-4362.

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[1]All India Institute of Medical Sciences, New Delhi, India
[2]All India Institute of Medical Sciences, Rishikesh, Uttrakhand, India

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Correspondence to: Neena Malhotra
E-mail: malhotraneena@yahoo.com

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Introduction

Endometriosis is a common condition affecting 5%–10% of the general population [1]. Approximately 30%–50% of women with endometriosis are infertile, and 50% of infertile women suffer from endometriosis [2]. It is defined as the growth of endometrium-like tissue outside the uterus, which induces a chronic inflammatory reaction [3]. In women with unexplained subfertility, its prevalence is reported to be as high as 50% [4]. Despite its high prevalence, endometriosis remains an enigmatic disease, especially the association of minimal and mild disease with infertility.

The precise physiologic mechanism involved in the development of endometriosis lesions in the pelvis and abdominal cavity has not been elucidated. Furthermore, the exact mechanism by which endometriosis impairs fertility remains speculative. There is a lack of sufficient data to establish a significant correlation between those non-anatomical alterations and reproductive failure in humans with endometriosis. This is currently attributed to the altered immunologic milieu of peritoneal fluid by cytokines, proteases, prostaglandins, reactive oxygen species, IgG, IgA, lymphocytes, and autoantibodies [2]. These may lead to impaired ovulation, fertilization, embryo development, and implantation. Moderate-to-severe disease is known to cause

anatomic distortion and hence interferes with fecundity. Surgical treatment of the lesions is proven to improve the chance of pregnancy even in minimal and mild disease [5-7]. Following surgical treatment, expectantly awaiting conception or moving to ovarian stimulation and intrauterine insemination (IUI) remains a debatable issue. However, considering improvements in surgical corrections would be best garnered with active interventions in the first few cycles including superovulation (SO) and IUI, which have shown improved live birth rates (LBRs) [8]. However, in vitro fertilization (IVF), which has the best outcome, is generally offered after failed attempts at SO and IUI, particularly in minimal and mild disease.

Gonadotropin-releasing hormone agonists (GnRHa) have an established role in pain management [9], but its role in fertility improvement is uncertain. It has shown to improve results when administered before IVF [10], but its use before ovarian stimulation and IUI has not been explored. Laparoscopic surgery, GnRHa therapy, SO, and IUI have individual benefits in improving fertility in women with endometriosis, but they have not been studied together in a prospective manner. The aim of our study is to evaluate the role of GnRHa in improving outcome in women undergoing SO and IUI after surgical correction of mild endometriosis.

Materials and Methods

The study was a randomized controlled trial conducted in the Department of Obstetrics and Gynecology at All India Institute of Medical Sciences, New Delhi, India, over a period of 2 years and 6 months. Approval for the study was obtained from the institute's ethics committee board.

Patients with unexplained infertility and suspected endometriosis were recruited from the gynecology and infertility clinic after a basic workup for infertility, which included a detailed history, examination, and investigations for the couple. Optimum investigations for the evaluation of infertility included detailed semen analysis (to exclude male factor); endometrial biopsy (to exclude tuberculosis); baseline serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), thyroid-stimulating hormone (TSH) levels on days 2–5 of the menstrual cycle (to exclude ovarian failure, hyperprolactinemia, and thyroid dysfunction); hysterosalpingogram during the follicular phase to exclude tubal and uterine factor defects; and ultrasonography (USG) of the pelvis to rule out any associated pelvic pathology. Informed written consent was obtained from the patients after thorough counseling.

Women older than 36 y who had pelvic inflammatory disease including genital tuberculosis, polycystic ovarian syndrome, diminished ovarian reserve (serum FSH level>10 mIU/mL, Antimullerian hormone <1.1 ng/mL), or factors advocating outright IVF as in moderate or severe endometriosis, and recurrent endometriosis and cases of severe male factor infertility were excluded from the study. Besides, patients with conditions that could impede implantation as in endometrial polyp or submucous myoma or thin endometrium were also excluded.

All patients underwent a standard three-port laparoscopy under general anesthesia by a single surgeon to evaluate the cause of infertility. Women who were diagnosed with endometriosis on laparoscopy were staged using the revised American Society for Reproductive Medicine (ASRM) criteria [11]. Women with ASRM stage II or mild endometriosis (score, 6–15) at laparoscopy were included in the study. These women underwent fulguration of endometriotic peritoneal implants, resection with fulguration of endometriotic nodules, and cystectomy with fulguration of endometriotic ovarian cysts. Bipolar cautery was used for fulguration.

Thereafter, patients were randomized into two groups, study (group A) and control groups (group B), based on computer-generated random numbers. Randomization was done by one of the data entry operators from the department who was not involved in the study and not by any of the clinicians involved during surgery or treatment cycles post-surgery. Patients in the study group (group A) received a single dose of 3.75 mg GnRHa–leuprolide acetate subcutaneously within 48 h after surgery, whereas the control group (group B) did not receive GnRHa. The injection leuprolide acetate (injection Leuprodex depot) was given free of cost. The pharmaceutical company Bharat Serums and Vaccines Limited, Mumbai, India, declared no conflict of interest for the same. Thereafter, patients in both arms underwent SO and IUI beginning at the next menstrual cycle.

Ovarian stimulation was performed in all women using a combination of clomiphene citrate and urinary human menopausal gonadotropin (hMG) in a sequential therapy, wherein clomiphene citrate (50 mg; Siphene, Cipla Pharmaceuticals Limited, Mumbai, India) was started on day 3 of the menstrual cycle for 5 days. hMG injection (150 IU; HUMOG, Bharat Serum and Vaccines Limited, Mumbai, India) was given intramuscularly on days 7 and 9 of the menstrual cycle. Serial transvaginal sonography was started on day 10 of the cycle to track follicular development and endometrial thickness (ET) and to check treatment response. An additional dose of hMG was given when the response on follicular tracking was sub-optimal (<10 mm follicle on day 10 scan). Once follicle size reached ≥18 mm and ET ≥7 mm, human chorionic gonadotropin injection (5000 IU; hCG, HUCOG, Bharat serum and vaccines limited, Mumbai, India) was given intramuscularly to

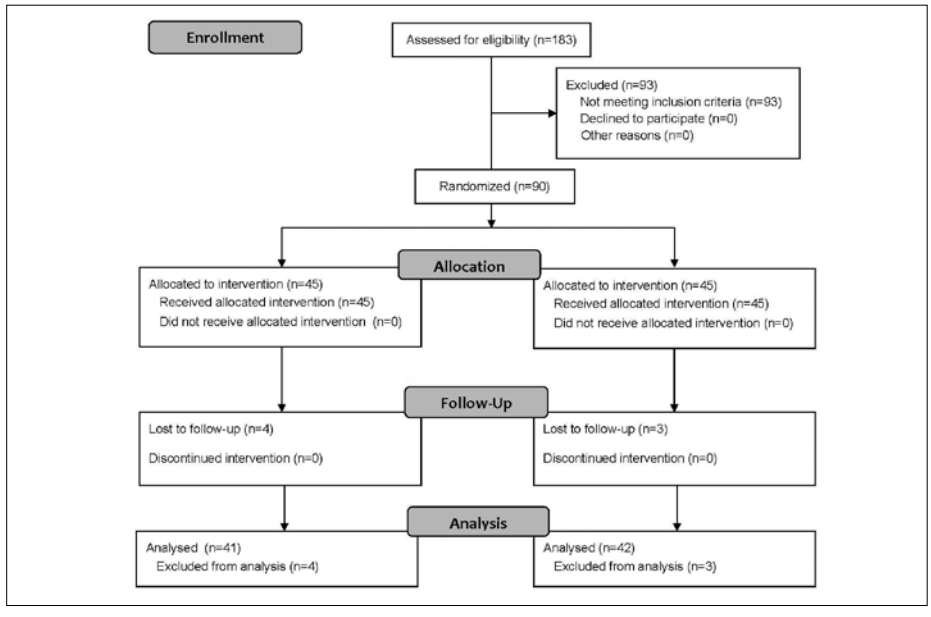

Figure 1. Flowchart of the study

trigger ovulation. IUI was performed 36 h after injecting hCG. The cycle was canceled if more than four dominant follicles developed on days 10–12 on monitoring or if there was no response with clomiphene citrate and increasing doses of hMG until day 16 of stimulation.

The outcome measures were compared between cases and controls at the end of the first cycle of SO followed by IUI, as the effects of GnRHa would prevail for approximately 4 weeks that is up to the first cycle. Subsequent cycles would not have a bearing of the GnRHa effect. However, up to three cycles of SO+IUI were given to patients in both groups as is the practice of our fertility units before moving to IVF.

Primary outcomes measured were LBRs and clinical pregnancy rate. A urine pregnancy test was performed 14 days after IUI or in case the patient missed her period. A quantitative serum beta-hCG test was performed followed by a USG at 6 weeks to confirm pregnancy. Clinical pregnancy was defined as the presence of a viable intrauterine pregnancy during scans performed at 6 weeks. All pregnant women were then further followed up during their pregnancy until delivery. A live birth was defined as the delivery of fetus after 26 weeks.

Sample Size Calculation

Using the software Stata 9.0 (Stata Corp 4905, Texas, USA) and based on the study by Rickes et al. [12], to achieve a power of 80% with an alpha error of 5%, an estimated sample size of 40 per group was established. Rickes et al. [12] only documented clinical pregnancy rates and did not measure LBRs. In women with mild endometriosis, they found higher pregnancy rate with postoperative GnRHa therapy followed by IUI than with surgery alone (86% vs. 58%). Considering 10% loss to follow-up, we recruited 45 patients per group.

Secondary outcome measures assessed were the number of follicles>18 mm in diameter, ET, dose and days of gonadotropin stimulation.

As shown in Figure 1, a total of 183 women who presented to our gynecology or infertility clinic were assessed for eligibility. Of these women, 93 (50.8%) were not eligible for the study, as they did not meet the inclusion criteria. Ninety infertile women who were diagnosed with mild endometriosis on laparoscopy were enrolled in the study. Women in group A (n=45) received GnRHa injections in the postoperative period. Four patients of group A and three patients of group B were lost to follow-up before the first cycle. Hence, 41 patients in group A and 42 patients in group B underwent SO and IUI cycles. A total of 156 treatment cycles were conducted. A maximum of three cycles was offered to the patients. The number of cycles varied from 1 to 3 in either group, with the majority of patients undergoing the first cycle (group A, 39% and group B, 43%).

Statistical Analysis

Statistical analysis was conducted using software Stata 11.0 (College Station, Texas, USA). Data were presented as number (percentage) or mean±SD/median (minimum, maximum) as appropriate. Baseline categorical variables were compared between the groups using chi-square test/Fischer's exact test, and continuous variables were compared using student's t-test

Table 1. Baseline characteristics

Variable	Group A (n=45)	Group B (n=45)	p
Age (years)	29.4+2.86	28.3+3.35	0.10
BMI (kg/m2)	25.3+3.66	25.5+2.31	0.83
Primary infertility	38 (84.4%)	28 (62.2%)	0.017
Secondary infertility	7 (15.6%)	17 (37.8%)	0.017
Duration of infertility (years)	4 (1–13)	4 (2–16)	0.78
Mild dysmenorrhea	10 (22.2%)	6 (13.3%)	0.27
Total count (million/mL)	78 (19–224)	75 (15–256)	0.92
Sperm motility (%)	67.9 (13.5)	61.1 (15.5)	0.02
Motile sperm count (million/mL)	53.2 (8.5–148)	46.8 (3.75–230.4)	0.39
Normal sperm morphology (%)	63.51 (13.9)	60.58 (17.7)	0.38
Surgical procedure performed			
• Fulguration of spots	34 (75.6%)	41 (91.1%)	0.08
• Excision+fulgration	11 (24.4%)	04 (9.9%)	

BMI: body mass index

Table 2. Secondary outcome parameters

Parameter	Group A (n=41)	Group B (n=42)	p
Dose of gonadotrophin (IU)	302.74 (17.5)	305.35 (24.2)	0.57
Duration of stimulation (days)	2 (0)	2.02 (0.11)	0.16
Number of follicles>18 mm in size	1.34 (0.36)	1.36 (0.42)	0.85
Endometrial thickness (mm)	9.7 (1.86)	9.1 (1.79)	0.13
Post-wash motile sperm count (million/mL)	46 (15–138)	40.5 (15–200)	0.42
Day of trigger	13.7 (0.92)	13.3 (1.22)	0.13
Cycle cancelation	None	None	

IU: international unit, mm: millimeter

Table 3. Primary outcome measures

Characteristic	Group A (n=41)	Group B (n=42)	p
Number of cycles	76	80	
Number of patients who conceived	9	10	
Pregnancy rate per cycle	11.8%	12.5%	0.90
Overall pregnancy rate	21.9%	23.8%	1.00
Cycle-wise distribution of pregnancies in the two groups			
Cycle 1	7/41 (17.1%)	8/42 (19.1%)	0.81
Cycle 2	1/25 (4%)	1/24 (4.2%)	1.00
Cycle 3	1/10 (10%)	1/14 (7.1%)	1.00
Live birth rate	21.9%	23.8%	1.00

for independent samples/Wilcoxon's rank-sum test, as the data were not following normal distribution. A P-value of<0.05 was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics, such as age and body mass index, were comparable in both groups as shown in Table 1. A significant difference was found in the distribution of patients between the two groups despite randomization, with more number of primary infertility patients in group A. The baseline hormone profile was also similar in both groups (Serum FSH: p=0.63, LH: p=0.28, prolactin: p=0.21, and TSH: p=0.66).

Semen analysis in the two groups was based on the WHO 2010 criteria [13]. Overall, the count, motility, and morphology were within normal limits. Sperm motility was significantly higher in group A than in group B, but the motile sperm count between the two groups was comparable (Table 1).

The major surgical procedure was fulguration of endometriotic spots in both the groups followed by endometriotic cyst excision with or without fulguration (Table 1).

Prior to surgery, menstrual cycle characteristics were comparable in both groups with respect to cycle frequency (p=0.11) and mild dysmenorrhea (p=0.27) as described in Table 1. Post-surgery, in group A, there was a variable cessation of menses after GnRHa injection. A majority (32 of 41, 78%) of women had amenorrhea lasting for 7–8 weeks, and the rest of the women had amenorrhea for 4–6 weeks. No amenorrhea was observed in group B. There were no symptoms of acute estrogen withdrawal such as hot flushes in group A. In group B, menstrual features did not change after surgery.

Cycle Outcome (Secondary Outcome)

The SO+IUI cycles were comparable between the two groups with regard to the secondary outcome parameters, which include dose and days of gonadotropin stimulation, number of dominant follicles>18 mm in diameter, and the day of ovulation trigger (Table 2).

None of the cycles was canceled in either group.

On an average, 1–2 follicles formed in each patient per cycle in both groups. All patients developed an ET of>7 mm. The mean ET in the first cycle was significantly higher in group A than in group B (10.2 vs. 9.1 mm, respectively, p=0.009). However, it was comparable in the remaining two cycles.

No significant difference was observed in the dose of hMG used and the duration of gonadotropin stimulation between the two groups. The post-wash motile sperm count between the two groups was also similar.

Primary Outcome Measures

The overall clinical pregnancy rate and LBR was similar in both groups as summarized in Table 3. We did not find any beneficial effect of GnRHa on fertility outcome.

When analyzed over the three cycles, the maximum number of pregnancies was seen in the first cycle in both groups. In our study, participation of the patients till the end of the third cycle was not compulsory, as the analysis of the effect of GnRHa can be assessed only at the end of the first cycle. Two more cycles were offered to the patients as a part of our unit protocol. However, the participation was seen to decline after the first cycle (Table 3).

All women who conceived after SO and IUI were booked with our antenatal unit and followed for their entire gestation in the unit. All the expecting women delivered at term gestation without any miscarriage or significant complications during pregnancy, with LBR being similar to the clinical pregnancy rate.

Discussion

Infertility associated with endometriosis has been treated empirically with assisted reproductive techniques. The role of GnRHa is well-established in cases of endometriosis-associated pain [9] and prior to IVF for long-term pituitary downregulation in women with endometriosis [10]. But its use before ovarian stimulation and IUI has not been explored. Advantages associated with depot GnRHa injection include its administration as a single monthly depot increasing patient acceptability. It has no major metabolic side effects except for reduction in bone mass on long-term use for which preventive strategies have been developed. However, side effects are associated with prolonged use of GnRHa, due to the profound hypoestrogenic state that includes hot flushes, headache, decreased libido, vaginal dryness, emotional lability, and insomnia.

Marcoux et al. [5] conducted a randomized controlled trial to determine whether laparoscopic surgery enhanced fecundity in infertile women with minimal or mild endometriosis and found the cumulative pregnancy rate to be 30.7% in women who underwent resection and ablation of endometriosis and 17.7% in women who underwent only diagnostic laparoscopy (p=0.006). The findings of this study are further supported by a meta-analysis published by Jacobson et al. [6], who demonstrated an advantage of operative laparoscopy (excision or ablation of endometriosis lesions) rather than diagnostic laparoscopy in terms of clinical pregnancy rates, with an OR of 1.66 (95% CI, 1.09–2.51) in infertile women with mild endometriosis.

On the contrary, a study by an Italian group showed a small negative effect. They reported higher pregnancy rate in women who underwent diagnostic laparoscopy than in those who underwent operative laparoscopy (29% and 24%, respectively, p>0.05) [14].

However, the results of Marcoux et al. [5] appear to be more reliable due to the higher power of their study. The conclusions of these studies suggest that when ectopic endometrial tissue is no longer present, the peritoneal environment becomes more favorable for pregnancy.

Milingos et al. [7] conducted a prospective cohort study on infertile women with minimal or mild endometriosis. Of the 151 women, operative laparoscopy was performed in 49 (group 1), diagnostic laparoscopy+GnRHa therapy was given in 59 (group 2), and diagnostic laparoscopy alone was performed in 43 patients (group 3). During a 24-month period, cumulative pregnancy rates were found to be 36.7%, 30.5%, and 20.9%, respectively. They concluded that laparoscopic surgery seems to be the milestone of treatment in such cases, increasing the fecundity and involving minimal risk. Pregnancy rates were comparable in groups 1 and 2 (p=0.19). However, both these groups had statistically significant higher pregnancy rates than group 3 (p=0.0001 and 0.014, respectively; group 1 and group 2 vs. group 3).

Similarly, in our study, the addition of GnRHa after laparoscopic treatment has not shown any significant difference in changing fertility outcome and does not have any added advantage in pregnancy rates.

Thus, it can be said that both surgical treatment (by ablation/resection) and treatment with GnRHa are equally effective in improving the hormonal milieu and that there is no added advantage of supplementing GnRHa over surgical treatment in patients with infertility. Fur-

thermore, patients can try for conception in the immediate cycle after surgical treatment, whereas GnRHa delays treatment by approximately 2 months due to the amenorrhea because of ovarian suppression. Also, there is an additional cost of therapy on administering GnRHa, which can be avoided if surgical treatment is done. However, GnRHa therapy might be a better option in cases wherein the focus of endometriosis is present in critical locations as in close proximity to the ureter; in such cases, attempting surgery can be risky for both patient as well as clinician. Postoperative GnRHa has a definite role in reducing pain and increasing time to recurrence of symptoms [15].

The next debatable issue is whether to go for SO and IUI or wait for spontaneous conception following surgical treatment and/or GnRHa therapy. We preferred to advise SO and IUI for these patients, as the best results are expected in the first few cycles. This theory is supported by several studies in the literature [8, 16, 17]. Tummon et al. [8] investigated the role of SO and IUI in improving fertility outcomes in infertile women with minimal or mild endometriosis. Live birth followed 11% of SO and IUI cycles and 2% of no-treatment cycles. They did not comment on the pregnancy rates. In addition, many of the patients (almost 50%) were not treated surgically during laparoscopy; therefore, the above pregnancy outcome cannot be compared with our results, as our patients underwent surgical treatment and subsequent SO and IUI. Fedele et al. [16] conducted a randomized controlled trial among 49 women with stage I/II endometriosis and infertility and compared three cycles of gonadotropin/IUI with 6 months of expectant management. They found significantly higher pregnancy rate per cycle in the gonadotropin/IUI group (15%) than in the untreated group (4.5%) ($p<0.05$). Another study by Kemmann et al. [17] reported higher pregnancy rate in women with infertility and minimal or mild endometriosis who received gonadotropin therapy or clomiphene citrate than those who did not receive any treatment (7.3%, 6.6%, and 2.8%, respectively). To emphasize, SO and IUI should be considered in infertile women with minimal and mild endometriosis.

To assess the role of GnRHa in various stages of endometriosis, Rickes et al. [12] conducted a prospective randomized controlled study among 110 infertile women with mild, moderate, or severe endometriosis. All women underwent operative laparoscopy. After that, 55 women received GnRHa therapy for 6 months followed by artificial reproductive technique (ART), and the remaining 55 women received ART immediately after surgery. In women with mild endometriosis, the pregnancy rate was higher with postoperative GnRHa therapy followed by IUI than surgery alone (86% vs. 58%), but this benefit was not statistically significant. Whereas in patients with mild endometriosis who opted for IVF or ICSI, the pregnancy rate was slightly lower in those who received GnRHa than in those who underwent only surgery (50% vs. 56%). In patients with moderate or severe endometriosis who underwent IVF or ICSI, GnRHa treatment significantly increased pregnancy rates compared with patients with surgery alone (82% vs. 40%; $p<0.05$). They concluded that postoperative GnRHa therapy is not useful for patients with mild endometriosis. It may be beneficial for women with advanced endometriosis, especially for patients undergoing IVF or ICSI.

Randomized prospective nature with pre-calculated sample size are the strengths of this study. Moreover we followed up all the women throughout the pregnancy, LBR was one of the primary outcome measures. Although the sample size was pre-calculated, a larger sample or a multicentric study to get a larger sample would have produced more robust results. This was perhaps one of the possible limitations of our study.

There is a clinical dilemma for the management of mild endometriosis, which clinicians usually face after surgical management, as to whether they should or should not give GnRH. In our study, both clinical pregnancy rate and LBR were comparable. We did not find any benefit of adding GnRHa after surgical management in women with mild endometriosis undergoing SO and IUI over surgical management alone.

After the analysis of our data, we conclude that postoperative GnRHa is not effective in women with mild endometriosis in improving fertility outcome. Although GnRHa may be equally effective as surgery, it delays resumption of menstrual cycles, impeding the chances of pregnancy, besides adding to the cost of therapy. Long-term follow-up studies with larger sample size are required to assess whether these patients do conceive spontaneously and whether the change in hormonal milieu leads to a better pregnancy outcome.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of All India Institute of Medical Sciences, New Delhi, India.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Effect of Nausea and Vomiting on Anxiety and Depression Levels in Early Pregnancy

Fatma Beyazit[1], Basak Sahin[2]

ABSTRACT

Objective: Nausea and vomiting of pregnancy (NVP) have been reported to be associated with distinct physiological responses to psychosocial stress. In this study, we aimed to evaluate the impact of nausea and vomiting on anxiety and depression during pregnancy.

Materials and Methods: Eighty-three pregnant women with nausea and vomiting and 83 healthy pregnant women were included. All participants completed the demography- and pregnancy-related questionnaire, including Rhodes Index of Nausea and Vomiting, Beck Anxiety Inventory (BAI), and Edinburgh Postnatal Depression Scale (EPDS).

Results: The median BAI and EPDS levels were 13 (min-max: 0–43) and 7 (min-max: 0–20) for the study group and 4 (min-max: 0–26) and 4 (min-max: 0–16) for control group, respectively. A univariate analysis revealed a statistically significant increase in terms of BAI levels ($p<0.001$) between the groups, but no significant difference was observed in terms of EPDS. In a logistic regression analysis, both anxiety ($p=0.018$) and depression ($p=0.022$) were found to be affected by NVP. The BAI levels of the NVP group correlated with the severity of NVP.

Conclusion: According to the results of the present study, women with severe NVP experienced a higher level of anxiety and depression, which necessitates an extra awareness from healthcare professionals in order to be able to contribute effectively.

Keywords: Pregnancy, nausea and vomiting, rhodes index, anxiety, depression

ORCID IDs of the authors:
F.B. 0000-0002-0667-6090;
B.S. 0000-0002-5943-4087.

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[1]Department of Obstetrics and Gynecology, Çanakkale Onsekiz Mart University School of Medicine, Çanakkale, Turkey
[2]Department of Psychiatry, Çanakkale Onsekiz Mart University School of Medicine, Çanakkale, Turkey

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Correspondence to: Fatma Beyazit
E-mail: fatmabeyazit@yahoo.com

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Introduction

Nausea and vomiting during the early stages of pregnancy usually occur between the fifth and eighteenth weeks of pregnancy, and more than 70% of pregnant women have reported the presence of these symptoms extending until parturition [1-4]. Pregnant women with severe nausea and vomiting may have hyperemesis gravidarum (HG), a separate entity from nausea and vomiting of pregnancy (NVP), which if left untreated may lead to increased maternal and fetal morbidity. HG is infrequent when compared with NVP and occurs in 0.3%–2% of all pregnancies [1, 4, 5]. The severity of complaints might vary from one pregnant woman to another and even between pregnancies of the same woman, which suggest the contribution of genetic, biological, and psychological factors.

In addition to the physical condition of pregnancy, NVP and HG also negatively affect the mental health, quality of life, and functional capacity of women [6]. In severe cases, fetal development might also be affected. Although there are still questions regarding the exact cause of both conditions, it does appear to be associated with various metabolic and endocrine factors. In this context, the most implicated factor is suggested to be the production of the human chorionic gonadotropin hormone. Moreover, there is evidence that links this condition to alternation in a variety of hormones, including estrogen, progesterone, placental prostaglandin E2, and thyroid-stimulating hormone [1]. In addition, studies have shown that NVP may also be linked with psychological disturbances, including eating disorders, neurotic tendencies, hysteria, and rejection of pregnancy, as well as anxiety and depression with psychological stress related to poverty and marital conflicts [6, 7]. From these psychological disturbances, anxiety and depression exert a special importance, because apart from being a cause, it can also be a consequence of NVP. Therefore, assessing the

presence and severity of anxiety and depression in patients with NVP may be relatively more important from the general population.

The relationship between NVP, HG, anxiety, and depression has been studied in some trials. Most of the studies focused on NVP and HG found conflicting results with respect to the development of anxiety and depression disorders [7-9]. In addition to these conflicting results, some studies have been criticized for having limitations, including small sample size, lack of control group, lack of objective diagnostic criteria, and inappropriate study design [5, 8, 10, 11]. Hence, the objective of this prospective case-control study was to determine the prevalence and severity of anxiety and depression disorders in patients with NVP using specifically designed and validated tools.

Materials and Methods

Characteristics of the Patients

This prospective case-control study was designed at the Gynecology and Obstetrics clinic of Canakkale Onsekiz Mart University and was approved by the ethics board of the same institution. The study was conducted with the guideline proposed by the World Medical Association of Helsinki, and written informed consent was obtained from all of the participating women.

For this study, 120 questionnaires were distributed to pregnant women with NVP in early pregnancy. However, 37 questionnaires were excluded because either they did not include enough details or were not eligible for inclusion (Figure 1). The final study group compromised 83 pregnant women with NVP followed up in the obstetrics and gynecology clinic of the same hospital. A control group consisted of 83 age, parity, and gestational age-matched healthy pregnant women without nausea and vomiting and admitted to the outpatient clinic for routine antenatal care. After inclusion, gestational age was determined according to the first day of last menstruation corrected by ultrasound finding when the discrepancy exceeded one week. A detailed sociodemographic data form was given to all subjects. Pregnancy characteristics, age, medication history, tobacco and alcohol use, and educational and familial status were recorded.

Inclusion criteria were a viable pregnancy of less than 14 weeks gestation, lack of fetal congenital malformations, lack of a systemic (gastrointestinal, renal, pulmonary, and cardiovascular system abnormalities) or hormonal disease that can cause nausea and vomiting, absence of diabetes mellitus, absence of previously known psychiatric disorders, and absence of multiple pregnancies and known obstetric complications. Pregnant women using medications (including antidepressant and antipsychotic drugs) that could alter the test results, history of current or past illegal drug abuse, and cognitive incompetence, which can make hard to score The Beck Anxiety Inventory (BAI) were excluded. render scoring challenging. The Beck Anxiety Inventory (BAI) were excluded.

Assessment

The Rhodes index of nausea and vomiting questionnaire was used to evaluate the presence and the severity of NVP. In order to evaluate NVP-associated psychological status two questionnaires, BAI and Edinburgh Postnatal Depression Scale (EPDS), were used.

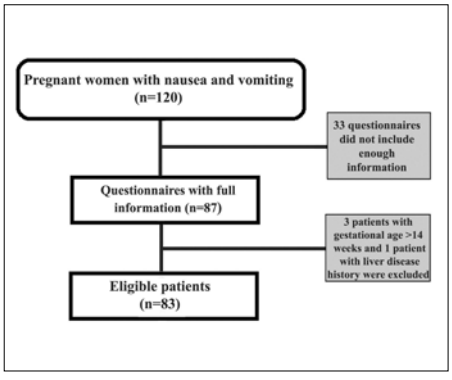

Figure 1. Flow chart of the recruited participants

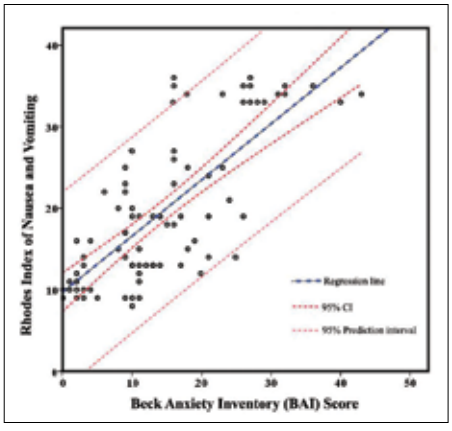

Figure 2. Correlation analysis between Rhodes Nausea and Vomiting index and Beck Anxiety Inventory (BAI) scores in NVP patients; lines representing the 95% confidence interval (CI) and the 95% prediction interval of the regression line

Table 1. Sociodemographic characteristics of study participants

	NVP patients (n=83)	Controls (n=83)	p
Age (years)	28.4±5.5	29.4±5.7	NS
Gestational age (weeks)	11.1±2.1	10.9±2.2	NS
BAI [median, (min-max)]	13 (0–43)	4 (0–26)	<0.001
EPDS [median, (min-max)]	7 (0–20)	4 (0–16)	NS
Gravida [median, (min-max)]	2 (1–7)	2 (1–5)	NS
Parity [median, (min-max)]	1 (0–4)	1 (0–3)	NS
Abortus [median, (min-max)]	0 (0–2)	0 (0–3)	NS
Occupation			NS
No (%)	65 (78.3)	59 (71.1)	
Yes (%)	18 (22.7)	24 (28.9)	
Education			NS
Illiterate (%)	5 (6.0)	4 (4.8)	
Primary (%)	22 (26.5)	13 (15.6)	
High (%)	32 (38.5)	36 (43.3)	
University (%)	24 (29.0)	30 (36.3)	
Housing			NS
Owned (%)	42 (50.6)	43 (51.8)	
Rented (%)	41 (49.4)	40 (48.2)	
Cigarette smoking			NS
No (%)	74 (89.1)	70 (84.3)	
Yes (%)	9 (10.9)	13 (15.7)	

BAI: Beck Anxiety Inventory; EPDS: Edinburgh Postnatal Depression Scale; NVP: nausea and vomiting of pregnancy; NS: not significant

Rhodes index of nausea and vomiting

The Rhodes index of nausea and vomiting questionnaire is a validated and objective form used to grade the presence and severity of nausea and vomiting and to follow the clinical progression of the disorder [12]. Historically, it was proposed by Rhodes and his colleagues in 1984 to evaluate nausea and vomiting in patients with tumoural disease receiving chemotherapy. This scoring system is based on a five-point scale and has a total of eight items capturing nausea, vomiting, and the components (duration, severity, and distress) of each symptom in the preceding 12 hours. A minimum score of eight and a maximum of 40 can be obtained with this scale. Scores below eight are recorded as no nausea and vomiting in the previous 12 hours, scores of 9–18 are recorded as mild, scores of 19–32 are recorded as medium, and scores 33–40 are recorded as severe NVP.

Beck Anxiety Inventory

The BAI is a 21-item self-report questionnaire that lists anxiety symptoms, such as "shakiness in legs," "scared," and "worry of losing control." Patients were asked to rate how much each of these symptoms concerned them in the previous week on a scale ranging from zero (not at all) to three. The total score can range from zero with a maximum of 63 [13]. Based on the total score, 8-15 points represent a mild level of anxiety, 16-25 indicates a medium level, and 26-63 points are an indication of severe anxiety level. The Turkish validity and reliability trial of BAI was performed by Ulusoy and colleagues. [14].

Edinburgh Postnatal Depression Scale

EPDS is a 10-item questionnaire developed to assist in identifying possible symptoms of depression in the postpartum period [15]. Moreover, it has adequate sensitivity and specificity to identify depression symptoms in the antenatal period and is useful in identifying symptoms of anxiety [16]. Although EPDS is not a diagnostic scoring tool, items of the scale refer to distinct clinical depression complaints, such as sleep disorders and weakness. The total evaluation was performed by adding the scores for each of the 10 items. A total score of 13 or more is considered a cut-off point for the possible depression diagnosis.

Statistical Analysis

The Statistical Package for Social Sciences (Version 19, SPSS Inc., Chicago, IL, USA) for Windows software was used to analyze data. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Student's t-test was used to compare the data that was normally distributed. Data non-normally distributed were compared using the Mann–Whitney U test. Comparison of more than two independent groups was performed by the Kruskal–Wallis test. A Spearman correlation analysis was used to analyze the correlation between the NVP and BAI scores of patients. A p value of<0.005 was used to indicate statistical significance. The factors that affect anxiety and depression status were evaluated using a logistic regression analysis. In both of the analysis, depression and anxiety were considered as dependent variables and age, occupation status, education level, gravidity, and emesis were considered as independent variables. Backward conditional logistic regression was performed for analysis.

Table 2. Logistic regression analysis of factors that effects anxiety levels

	B	OR	95% CI	p
Constant	−1.917	0.147		0.0001
Emesis (0)		1.0		
Emesis (1)	0.851	2.341	1.022–5361	0.018

OR: odds ratio; CI: confidence interval
Note: Backward conditional Logistic Regression analysis (step 5)
Dependent variable: Anxiety (No: 0; Yes: 1)
Independent variables: Age, Education (University: 0, high: 1, illiterate/primary: 2), Occupation (No: 0, Yes: 1), gravidity (>5:0, 3–4:1, 1-2:2); Emesis (No: 0, Yes: 1)

Table 3. Logistic regression analysis of factors that effects depression levels

	B	OR	95% CI	p
Constant	−2.317	0.099		0.0001
Emesis (0)		1.0		
Emesis (1)	1.096	2.993	1.172–7.644	0.022

OR: odds ratio; CI: confidence interval
Note: Backward conditional Logistic Regression analysis (step 5)
Dependent variable: Depression (No: 0; Yes: 1)
Independent variables: Age, Education (University: 0, high: 1, illiterate/primary: 2), Occupation (No: 0, Yes: 1), gravidity (>5:0, 3–4:1, 1-2:2); Emesis (No: 0, Yes: 1)

Results

In total, 83 women with NVP and 83 pregnant women without symptoms of nausea and vomiting were included in the study. The mean maternal age of study and control groups were 28.4±5.5 and 29.4±5.7 years, respectively. Median gestational age of study participants was 11.1±2.1 weeks and 10.9±2.2 weeks for controls. No statistically significant difference was observed between the study and control groups in terms of maternal and gestational age, gravidity, parity, abortus, occupation, housing, and education levels. Only nine women in the NVP group reported a history of cigarette smoking before pregnancy, which was statistically insignificant between groups. Median BAI and EPDS levels were 13 (0–43) and 7 (0–20) for the study group and 4 (0–26) and 4 (0–16) for the control group, respectively. Although a statistically significant increase in terms of BAI levels (p=<0.001) was observed between the two groups, no significant difference was observed between the groups in terms of EPDS (p=0.654). Table 1 shows sociodemographic characteristics of study participants.

The factors described in the univariate analysis were further examined using a logistic regression analysis, and our results indicated that the only emesis was an independent risk factor for anxiety (p=0.018) and depression (p=0.22; Table 2, 3).

According to the Rhodes scoring system, the study group was divided into three groups. Overall, 41 (49.3%) women were classified as mild, 24 (28.9%) as moderate, and 18 (21.8%) as severe NVP. The median BAI levels of mild, moderate, and severe NVP patients were 9 (0–25), 16 (6–26), and 27 (16–43) respectively. Median EPDS levels of mild, moderate, and severe NVP patients were 4 (0–20), 5 (2–20), and 11 (5–18) respectively. The BAI levels were significantly higher in severe NVP patients compared to mild (p<0.001) and moderate (p<0.001) NVP. Although a trend for increasing EPDS levels was found in moderate and severe NVP, this was not statistically significant (Table 4).

According to the BAI levels, pregnant women (study group and control group) were divided into four groups. In total, 77 women had no anxiety, 48 had mild, 29 had medium, and 12 (10.8%) had severe anxiety. Out of 18 women

with severe NVP, 11 (61.1%) had severe anxiety, 5 (27.8%) had medium, and 2 (11.1%) had mild levels of anxiety (Table 5). The correlation analysis revealed a significant correlation between NVP severity and BAI levels ($r=0.699$; $p<0.001$; Figure 2).

Discussion

In this study, we demonstrated that women experiencing NVP have elevated anxiety levels, which are correlated with the severity of NVP. Moreover, in the logistic regression analysis, emesis was observed to be an independent variable for anxiety and depression. No correlation was observed between depression scores and NVP grades according to the Rhodes scoring system.

Nausea and vomiting are common medical conditions seen in pregnancy, affecting 70%-80% of all pregnant women [17]. Although women who experience NVP have symptoms usually limited to the first trimester, some women experience these symptoms throughout the pregnancy. HG is a severe form of NVP and an important cause of maternal morbidity during pregnancy affecting 0.4%-3% of pregnancies [18]. HG may result in weight loss; nutritional deficiencies; ketosis; and abnormalities in fluids, electrolyte levels, and acid-base balance. We did not categorize our severe NVP patients as HG because of the lack of some referral criteria, which renders a definitive HG diagnosis difficult.

Psychosocial factors may play a significant role in the progression of psychiatric disorders and NVP progression. Although numerous studies have shown that psychiatric disorder diagnosis is elevated in NVP and HG, some contrary reports suggest that in the course of NVP and/or HG, no elevation exists in terms of psychiatric disorders. In a recent prospective case-control study by Aksoy et al. [19], the mean Beck depression inventory scores were found to be elevated compared with the control group. Authors speculated that psychological disturbances linked with HG were a direct effect rather than a cause of HG. Similarly, in a study by Kender et al. [20], the sociodemographic data showed no difference between HG and control groups, but depression and anxiety levels were found to be elevated in the HG patients. Contrary to these findings, Bozzo et al. [7] reported that there was no significant association between depressive symptoms and NVP probably due to the small size of their study population. Although in the present study, the univariate analysis did not demonstrate any relation between depression and severe NVP, anxiety levels of severe NVP patients were significantly elevated. Moreover, the logistic regression analysis showed that apart from multiple sociodemographic variables, the only independent variable that affected anxiety and depression levels was NVP.

Elevated stress levels, anxiety, or depression linked with pregnancy may be more marked in women suffering from NVP. In this study, we found that according to the Rhodes scoring system, symptoms of anxiety were more prominent among medium and severe NVP cases. Studies from Turkey have also suggested a significant correlation between HG and depression and anxiety. Şimşek et al. [21] demonstrated that women complicated with serious vomiting during their pregnancies had noticeably more anxiety and depression than a well-matched control group of healthy antenatal women. In an elegant article by Annagür and colleagues [22], it was reported that depression and anxiety scores were significantly higher in women with HG and HG appears to be associated with depression and anxiety symptoms rather than deterioration of eating attitudes and body image. In this context, no difference was noted in the present study between NVP grades and sociodemographic factors, including pregnancy characteristics, gestational age, patient age, educational status, smoking, and employment status. Moreover, these factors were not associated with psychiatric symptoms. In a recent article by Kamalak et al. [23], only education level of the pregnant women, monthly income, HG in the previous pregnancy, and short time intervals between pregnancies were found to be related to HG development. In a study by Roseboom et al. [24], it was reported that women with HG were slightly younger, had a lower income, and had more often conceived through assisted reproduction techniques. Contrary to these findings, Tsang et al. [25] reported results similar to the present study, demonstrating that women with HG had demographic characteristics that were comparable to the general obstetric population in terms of age, gravidity, race, and marital status.

This study has some limitations, and the recognition of these should help improve future research efforts. The major limitation of this study is the research design. Because our study was cross-sectional, we failed to display a clear causal relationship between NVP and psychiatric symptoms. Secondly, despite our findings, relatively moderate sample size limits the power of the present study. A significant difference in terms of sociodemographic variables could have been determined, if our study group had included larger numbers of subjects. Thirdly, it would be noteworthy if we had also used objective structured clinical evaluation tools as a method to assess anxiety and depression in early pregnancy.

In conclusion, the findings of our study demonstrated that anxiety levels of pregnant cases with NVP were more than those of healthy pregnant cases. No significant difference between the NVP group and healthy control group in terms of sociodemographic and gestational characteristics were found. It is important for clinicians to appropriately and promptly diagnose and follow-up pregnant women with NVP and NVP-associated anxiety and depression to reduce pregnancy-related complications.

Table 4. BAI and EPDS of the study group

	Nausea and vomiting of pregnancy			
	Mild (n=41)	Moderate (n=24)	Severe (n=18)	p
BAI [median, (min-max)]	9 (0–25)	16 (6–26)	27 (16–43)	<0.001*
EPDS [median, (min-max)]	6 (0–20)	7 (2–20)	9 (5–18)	NS

*mild vs. moderate p=0.002; mild vs. severe p<0.001; moderate vs. severe p=<0.001
NS: Not significant; BAI: Beck Anxiety Inventory; EPDS: Edinburgh Postnatal Depression Scale

Table 5. Anxiety levels of study participants according to Rhodes index of nausea and vomiting

	Anxiety levels				
	No anxiety	Mild	Medium	Severe	Total
Controls n (%)	59 (71.1)	17 (20.4)	7 (8.5)	0 (0)	83 (100)
Study Group n (%)					
Mild NVP	17 (41.5)	18 (43.9)	6 (14.6)	0 (0)	41 (100)
Moderate NVP	1 (4.2)	11 (45.8)	11 (45.8)	1 (4.2)	24 (100)
Severe NVP	0 (0)	2 (11.1)	5 (27.8)	11 (61.1)	18 (100)

NVP: nausea and vomiting of pregnancy

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çanakkale Onsekiz Mart University (KAEK-2016-08).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Effects of Nonsteroidal Anti-Inflammatory Drugs at the Molecular Level

Caner Gunaydin, S. Sirri Bilge

ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for their anti-inflammatory, analgesic, and antipyretic effects. NSAIDs generally work by blocking the production of prostaglandins (PGs) through the inhibition of two cyclooxygenase enzymes. PGs are key factors in many cellular processes, such as gastrointestinal cytoprotection, hemostasis and thrombosis, inflammation, renal hemodynamics, turnover of cartilage, and angiogenesis. Interest has grown in the various effects of NSAIDs during the last decade. Epidemiological studies have revealed the reduced risk of several cancer types and neurodegenerative diseases by prolonged use of NSAIDs. Recent advances in the understanding of the cellular and molecular mechanisms of NSAIDs will accelerate the processes of discovery and clinical implementation. This review summarizes the molecular mechanisms of NSAIDs on the body systems.

Keywords: Nonsteroidal anti-inflammatory drugs, mechanism, cyclooxygenase, molecular

ORCID IDs of the authors:
C.G. 0000-0002-8304-832X;
S.S.B. 0000-0003-2878-6968.

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Department of Pharmacology, Ondokuz Mayıs University School of Medicine, Samsun, Turkey

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Correspondence to: S. Sirri Bilge
E-mail: ssbilge@omu.edu.tr

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most prescribed drugs worldwide. It is estimated that 30 million people/day around the world take NSAIDs [1]. These drugs are used due to their potent analgesic, anti-inflammatory, and antipyretic effects. Inhibition of cyclooxygenase (COX) enzyme, which takes part in the biosynthesis of prostaglandins (PGs) and thromboxane (TX), is the mechanism of action of NSAIDs [2]. PGs and TXs are important mediators of fever, pain, and inflammation. Inflammation has a major role in the pathophysiology of various diseases. NSAIDs affect the synthesis and action of inflammatory mediators including PGs, coagulation cascade-derived peptides, interleukin (IL)-2, IL-6, and tumor necrosis factor (TNF). The synthesis of prostanoids that are produced from arachidonic acid causes inflammatory pain [3]. Arachidonic acid mainly exists as esterified phosphatidylcholine and phosphatidylethanolamine phospholipid forms in the membranes. It is released from the cell membrane by phospholipase A_2 (PLA_2), which is the overall rate-limiting step for eicosanoids. There are two isoforms of PLA_2 classified as secretory and cytoplasmic. This multiple isoform existence allows for various biological responses for different tissues. PLA_2 isoforms can be stimulated by TNF-α, granulocyte-macrophage colony-stimulating factor, interferon (IFN), and various growth factors, such as mitogen-activated protein kinase (MAPK) and phosphokinase C. COX enzymes convert arachidonic acid to PGs, prostacyclins, and TXs. The first member of this cascade starts with the formation of PGG_2 then PGH_2. PGH_2 is converted into various PG isoforms, such as PGE_2, PGD_2, PGF_{2alpha}, PGI_2, or TXA_2 via tissue-specific isomerases. In another pathway, arachidonic acid is converted into leukotrienes by three forms of lipoxygenases (5-LOX, 12-LOX, and 15-LOX) (Figure 1). Various types of cells produce leukotrienes including mast cells, white blood cells (leukocytes, which give the compounds their names), brain, lung, spleen, and heart. 12-LOX and 15-LOX play roles in the production of lipoxins.

There are three isoforms of COX enzyme, namely COX-1, COX-2, and COX-3. Human chromosome 9 (loci 9q32–33.3 and 1q25.2–25.3) contains COX-1 coding gene, and chromosome 1 has COX-2 coding gene [4]. COX-3 is the product of the same gene, such as COX-1, which is expressed in the spinal cord and cerebral cortex and is found in the endothelial cells, monocytes, and heart in smaller quantities. It may play a role in the perception of pain, but its function is

not fully understood yet. COX-1 and COX-2 are also called PGG/H synthase 1 and PGG/H synthase 2. COX-1 is found in the platelets, blood vessels, mesothelial cells, stomach, kidneys, and other tissues [5]. It is a constitutive enzyme and participates in the production of prostanoids that adjust physiologic processes (e.g., hemostasis). Generally, it has non-inducible capacity, but human chorionic gonadotropin can upregulate COX-1 expression in amniotic fluid. COX-2, an inducible form of COX, is present in inflamed tissues through stimulation by cytokines, lipopolysaccharide (LPS), and TNF-α, and protein expression increases up to 80% upon induction. It can also be found in healthy organs in smaller quantities, including the kidneys [6].

NSAIDs act in many different events in the cells. In addition, some NSAIDs participate in calcium-mediated intracellular response, suppression of free radicals and superoxide, downregulation of the production of IL-1, and inhibition of chemotaxis [7]. Arachidonic acid metabolism that is inhibited by NSAIDs also regulates Rho/Rho kinase pathway directly [8]. Consequently, Rho/Rho kinase pathway regulatory pathway of survival, cytoskeleton, and actin–myosin interaction could be intervened with NSAIDs that can explain more mechanism of intercellular responses. Certain NSAIDs can bind to members of the peroxisome proliferator-activated receptor (PPAR) family and other intracellular receptors and activate them. Activation of PPAR is believed to moderate anti-inflammatory activities. More accordingly, a study about nimesulide, which is also a COX-2 inhibitor, showed that PPAR-δ activity that mediated through COX-2 and further 15d-PGJ_2 suppresses hepatic inflammation [9]. NSAIDs have also been shown to increase heat shock protein (HSP) response [10]. Although NSAIDs exert their effects on COX pathways, there are many studies about their effects on more complicated mechanisms. The first evidence about these mechanisms emanating from acetylsalicylic acid reported nuclear factor-kappa beta (NF-κB) inhibition [11, 12]. Studies also showed that indomethacin, aspirin, and phenylbutazone enhance TNF-α release induced by LPS [13]. Moreover, in their study, they also showed that phenylbutazone, sulindac, and acetylsalicylic acid significantly increase nitric oxide (NO) release.

Effects of NSAIDs on Systems

Central nervous system

PGs have been found in many regions of the brain. NSAIDs have anti-pyretic and analgesic effects in humans and animals. These activities are thought to be the result of the inhibition of PG formation in the central nervous system (CNS). Most of the COX-1 is in the microglia, though it has been found in the hippocampal and cerebral cortical neurons as well. Although it is clear that COX-3 is expressed abundantly in the cerebral cortex, its enzymatic activity has not yet been elucidated. In contrast to most tissues, inducible COX-2 is also constitutively expressed in the cervical lumbar sections of the spinal cord and several brain regions, such as the cerebral cortex, hippocampus, and amygdala in discrete populations of neurons and but not in glia. COX-1 expression at the spinal level is not wide-ranging and is localized in the cytoplasm of glial cells [14, 15].

NSAIDs are thought to delay the onset of Alzheimer's disease. COX-2 inhibition interferes with β-amyloid cascade that mediates the suppression of memory and synaptic plasticity. According to data, selective COX-2 inhibitors may have protective effects against Alzheimer's disease by reducing PGE_2 response at synapses due to COX-2 inhibition [15]. PPAR-γ activation that mediated through 15-deoxy PGJ_2 also inhibits LPS-stimulated inducible nitric oxide synthase expression and TNF-α production as well as IFN-γ-induced expression of major histocompatibility complex class II antigens, by preventing the activation of the transcription factors signal transducer and activator of transcription 1 and NF-κB, which is also a regulator of microglial inflammation and functions. In animal models, treatment with ibuprofen or indomethacin reduced microglial activation, with a concomitant reduction in amyloid β (Aβ) plaques and inflammatory markers. Activation of PPAR-γ inhibits the Aβ-stimulated activation of the microglia and monocytes and their neurotoxic products. PPAR-γ agonists act to inhibit the Aβ-stimulated expression of IL-6 and TNF-α [16].

On the other hand, NSAIDs inhibit gamma secretase activity, reducing the formation and accumulation of Aβ in animal models and neurodegeneration [17]. In addition, they modulate microglial phagocytosis, contribute to plaque and debris removal and to lower plaque burden and gliosis, and had seen long-term NSAID treatment [18, 19]. *In vitro* study evaluating the effects on microglial activation of opsonization of Aβ deposits with anti-Aβ IgG (immunoglobulin G), as a strategy to enhance microglial clearance of Aβ deposits, indomethacin had negligible effects on microglial migration and phagocytosis of Aβ, but it did significantly inhibit microglial secretion of IL-6 following opsonization [20]. Another possible mechanism about PGs in Alzheimer's disease, PGE_2 production elevated in the early stages of pathology. This also indicates PGE production of several inflammation molecules, such as IL-6 and chemokines [16].

Two meta-analyses have been published about the useful effects of COX-2 inhibitors in schizophrenia. NSAIDs are thought to have beneficial effects in the prevention of Parkinson's disease since neuroinflammation can have

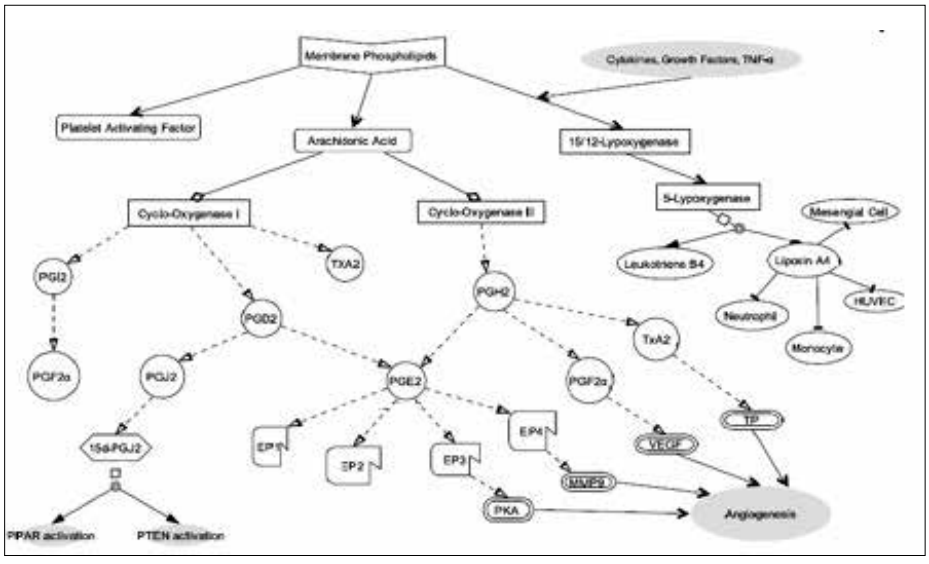

Figure 1. Schematic presentation of cyclooxygenase and lipoxygenase pathway
PGH_2: prostaglandin H_2; PGF_2: prostaglandin F_2; PGD_2: prostaglandin D_2; PGE_2: prostaglandin E_2; PGI: prostacyclin; TXA_2: thromboxane A_2; PHJ_2: prostaglandin J_2; $PGF_2\alpha$: prostaglandin $F_2\alpha$; MMP_9: matrix metalloproteinase 9; VEGF: vascular endothelial growth factor; TP: thromboxane receptor; EP1, 2, 3, and 4: prostaglandin E receptors; HUVEC: human umbilical vein endothelial cell; PPAR: peroxisome proliferator-activated receptor; PTEN: phosphatase and tensin homolog

important an role in the neurodegeneration associated with Parkinson's disease [21].

Fever is a complex response triggered by inflammatory and infectious diseases. It generally occurs when peripheral endogenous pyrogens come into contact with the hypothalamus. Having a cytokine structure, these pyrogens are generally synthesized by leukocytes and other cells, the most well-known of which are TNF-α, IL-1 β, and IL-6. They can be synthesized in the CNS as well. The preoptic area is near the rostral hypothalamus and is important in controlling thermoregulation. Specialized cells, called temperature-sensitive neurons, regulate thermoneutral set point temperature [22]. Pyrogens cause an increase in set point temperatures, and fever occurs [23]. In febrile response, these pyrogens are not the final mediators. These cytokines induce COX-2 production that increases the synthesis of PGs. These prostanoids adjust hypothalamic temperature control by increasing heat production. The mechanism of action of antipyretics is based on reducing PG production. Alleviation of discomfort, prevention of febrile seizures, reduction of cognitive impairment, and reduction of morbidity and mortality are among the reasons why antipyretics are used [24].

Gastrointestinal system

PGI_2 and PGE_2 inhibit gastric acid secretion and have vasodilator effects on the vessels of the gastric mucosa. PGs also stimulate mucus secretion. On the other hand, NSAIDs could inhibit PG-mediated effects on the gastrointestinal tract. This effect includes the inhibition of mucin production, HCO_3 secretion, and mucosal proliferation. NSAIDs can cause gastrointestinal damage due to the deterioration of this mechanism [25]. This injurious effects can be caused by PG or non-PG-mediated mechanisms. Several studies suggested that increased endothelin-converting enzyme, NO hydrogen sulfide, IL-1β, and calcitonin gene-related peptide (CGRP) and decreased constitutive nitric oxide synthase and polyamines support NSAID-mediated non-PG-dependent injurious mechanism [26]. However, this effect can be seen in supratheurapeutic concentrations of NSAIDs.

COX-1 inhibition by the use of NSAIDs causes gastric hypermotility. This mechanism is unclear but could assume restricted blood flow with high amplitude, resulting in tissue hypoxia and microvascular damage. Gastric lesion that formed eventually because of increased mucosal permeability and myeloperoxidase activity comes up with this enhanced gastric hypermotility [26]. NSAIDs have been shown to upregulate various stress proteins in in vitro and in vivo studies including heat shock protein 72 (HSP-72), glucose-regulated protein 78 (GRP-78), and HO-1 (Heme oxygenase-1, also known as HSP-32) [27]. Stress proteins protect the gastric mucosa from NSAID-induced apoptosis and may therefore play an important role in NSAID-induced cytoprotection and adaptive gastroprotection when PGs are suppressed [26].

Urinary system

NSAIDs can inhibit both constitutive COX-1 in the kidney and intravascular volume-dependent inducible COX-2. Apart from glomerular filtration rate and renal hemodynamics dependence on COX-1, salt and water excretion is mainly under control of COX-2. PGE_2, which is the product of COX-induced reaction, controls NaCl transport in the loop of Henle and modulates water transport. PGI_2, which is also the product of the same reaction, modulates glomerular filtration rate and renin release. It is already known that COX-2 activates the renin system, but increased activity of the renin system inhibits COX-2. Additionally, PGI_2 and PGE_2 increase potassium secretion, sensing NaCl concentration at the distal end of the loop of Henle serves tubuloglomerular feedback, thus both of these effects are modulated by PG, which is derived from the macula densa. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists that interfere with the angiotensin cascade increase the expression of COX-2 in the kidney [28]. In addition, MAPK and p38 regulate the COX-2 expression in the renal cortex [29]. Consequently, partial mechanism of NSAID on sodium and water retention is mediated through PGE_2 and PGI_2.

Several studies have investigated the role of COX enzymes and the relationship with glomerular diseases. Monocyte chemoattractant protein-1 (MCP-1) is expressed in animals and humans with glomerulonephritis. Endogenous PGs can reduce MCP-1 expression, which is primarily involved in monocyte/macrophage infiltration, suggesting a role for COX-1 and COX-2 enzymes in renal inflammation. In addition, it has been shown that NSAIDs, especially indomethacin, have a potential in different types of glomerulonephritis and nephrotic syndrome [30]. A study about indomethacin in podocytes also showed that inhibition of inflammatory response, which is dependent on TNF-α, triggers the activation of NF-κB [31].

COXs are locally produced in numerous sites in the kidney. It is already known that COX-1, which assumes PGE_2, is primarily synthesized in the tubules, whereas the glomeruli synthesize both PGE_2 and PGI_2. PGE_2 plays a role in modulating vasopressin effects on the reabsorption of water in the collecting duct system of the kidneys. PGs play essential roles in the regulation of renal hemodynamic, renin release, as well as water and salt balance [32]. Renal PGs predominantly have vasodilator effects on the kidneys. On the other hand, PGs are increased to maintain renal perfusion and reduce ischemia in case of hypotension and reduced renal perfusion due to vasoconstriction stimulated by norepinephrine, angiotensin II, vasopressin, or endothelin [33]. The most common renal effect of NSAIDs is increased sodium reabsorption that causes peripheral edema through the inhibition of PGE_2. NSAID-caused electrolyte imbalance is not fed to sodium though; inhibition of PG biosynthesis in the kidneys causes hyperkalemia as well. The decrease in renal blood flow due to NSAID may result in kidney failure [34]. Long-term NSAID consumption can induce analgesic nephropathy, which is identified by chronic nephritis and renal papillary necrosis.

Cardiovascular system

PGs and TXs are essential in vascular function. In normal conditions, COX-dependent vasodilators, such as PGI_2, regulate vascular tone. Nonetheless, COX-dependent vasoconstriction (triggered by TX and/or its precursor, PGH_2) takes part in some vascular pathologies including cerebral ischemia, diabetes, systemic hypertension, and aging [35].

The fact that NSAIDs inhibit PGs may affect cardiovascular regulation. PGE_2 and PGI_2 are shown to have glomerular vasodilatory effects in the kidney. PGE_2 has direct natriuretic effects. Inhibition of the synthesis of PGs by NSAIDs may cause sodium and water retention and worsen hypertension [36]. Selective COX inhibitors can induce thrombosis risk due to decreased synthesis of PGI_2, which plays a critical role in vasodilation and platelet inhibition in endothelial cells. Consequently, imbalance can occur between PGI_2 and TXA_2 that is a vasoconstrictive substance and contribute to platelet aggregation and thrombus formation. TXA_2 is released from platelets and plays a role in aggregation, whereas PGI_2 is released from the endothelium and plays a role in the inhibition of aggregation.

Aspirin inhibits platelet aggregation by blocking not only COX enzyme but also synthesis of TXA_2 and PGI_2. Although aspirin inhibits TXA_2 synthesis in low doses (100 mg), it inhibits both TXA_2 and PGI_2 in high doses. Moreover, the inhibition of

platelet aggregation by aspirin may inhibit the release of certain platelet-associated substances in the venous circulation, including fibrinogen, platelet factors III and IV, von Willebrand factor, factors V and XIII, thrombospondin, serotonin, and calcium ions among other substances that aid with the improvement of venous thrombosis, and COX-2 selective NSAIDs have little or no role on platelet function.

Bone metabolism

PGs take part in the control of osteoblast and osteoclast functions, and the inhibition of PG synthesis restrains bone formation [37]. They directly affect osteoclasts that lead to increased bone resorption by a mitogenic effect and increase their functional activity. They exert this range of action through a variety of receptors expressed. These receptors belong to the G protein-coupled receptor family and have four subtypes (EP1, EP2, EP3, and EP4) [38]. Although the role of each receptor is not fully explored, studies suggested that the PGE_2 binding to EP4 can stimulate osteoclastogenesis and osteoblastic differentiation, and animal models lacking the EP2 and EP4 receptors had defects in bone metabolism [39] Although all NSAIDs have similar effects, certain NSAIDs can modulate the behavior of osteoblasts, such as proliferation, differentiation, adhesion, and migration.

However, PGs may increase the multiplication and differentiation of osteoblasts and reveal anabolic effects on the bone (Ippokratis Pountos et al. [40]). In bone tissue, local regulation of PGs is conducted through COX-2 activation [41]. On the contrary, PG's exact mechanism on bone cells is considered intricate but, it was found that PGE_2 regulates bone morphogenetic protein-2 (BMP-2), BMP-7, and receptor activator of nuclear factor-kappa B ligand expression [42], [38]. It can also increase cell numbers through suppression of apoptosis without direct effect on proliferation. There is also a theory about the inhibition of COX-2 deviating from the arachidonic acid cascade from lipoxygenase pathway that negatively affects bone healing [43]. This pathway negatively influences osteoblast proliferation and stimulation of osteoclast activity [43] COX-2 selective inhibitors also showed an increase in aggrecan and type II collagen mRNA levels that indicate chondrocyte differentiation and, consequently, failed to hypertrophy, which impeded the healing process of another mechanism [43]

Studies about NSAIDs, well known as immunoregulators, on lymphocytes, potent immune elements, also showed a different regulation of cytokine production in human IFN-δ and IL-2. A randomized open label trial about cytokine concentration and signal transduction pathways in the synovial fluid also showed increased vascular endothelial growth factor, IL-6, and TNF-α concentrations. They also evaluated the effects of NSAIDs on MAPK, extracellular signal-regulated kinase (ERK), Jun kinase (JNK), p38, and RAS phosphorylation signal transduction pathways on the synovial membrane. However, they only tested NSAIDs on the highest doses and showed that NSAID treatment significantly inhibits ERK, JNK, p38, and RAS phosphorylation along with caspase-3 activation [44]. Studies with chemical-induced animal models of inflammation and open label trial on patients showed different cytokine modulation with NSAIDs. It should be noted that NSAIDs exert different effects, thus these cellular signal pathways need more research and clinical-based evidences.

Respiratory system

Inhibition of COX-1 causes a decrease in some PGs, which exert important regulatory effects on respiratory epithelial cells. Decreased PG production can induce leukotriene pathway, causing bronchoconstriction. When used in high doses, salicylates damage the process of oxidative phosphorylation, causing an increase in plasma carbon dioxide levels (COX-independent effects) followed by hyperventilation. Higher doses can result in depression of respiration.

A special case about COX inhibition on the respiratory system, which was named aspirin-exacerbated respiratory disease consisting of asthma, aspirin sensitivity, and nasal polyps, came to be known as Samter's triad. It is also known as NSAID-exacerbated disease, and the mechanism of this pathology is not clearly understood. Reduction of PGE_2, a potent inhibitor of leukotriene pathway, by COX is considered as the mechanism responsible for the progression of the disease.

Cancer

In the research of various mechanisms about cancer progression and metastasis, anti-inflammatory drugs are also investigated. Epidemiological studies have showed that the use of NSAID is inversely related to the incidence of some cancer types [45]. Long-term NSAID users who have colorectal cancer have showed lower mortality rates than non-NSAID users [46]. In addition, sulindac, ibuprofen, piroxicam, and aspirin have been shown to decrease the recurrence, incidence, mortality rate, and number of cancer cells in a significant manner. [47] , [28]. Some clinical trials for several malignancies have showed that selective COX-2 inhibitors, particularly celecoxib have potential cancer chemopreventive effect [48].

The effects of NSAIDs on tumor inhibitions and prevention of metastasis have not been fully understood yet [49]. It is widely accepted that an extreme amount of the production of PGs and cytokines by tumors is associated with their metabolism, proliferation, angiogenesis, invasion ability, resistance to apoptosis, and suppression of antitumor immunity.

In tumorigenesis, transcriptional upregulation of the COX-2 gene in colorectal adenomas and carcinomas has been observed, although COX-1 is not affected [50] Upregulated COX-2 in colorectal carcinoma and, consequently, enhanced PGE_2 signaling via PGE-EP receptors is 3–4-fold higher than that in healthy tissue. It has been shown in other studies that PGE_2 inhibits apoptosis and stimulates tumor growth and angiogenesis via the activation of β-catenin/T-cell factor dependent transcription [51]. On the other hand, PPAR-δ, which inhibits tumorigenesis, is inhibited with sulindac and indomethacin.

The known inhibitory effects of cyclooxygenase pathways prompted the investigation on NSAIDs through COX-2 specific and non-COX pathway for cancer research. From these studies, the NF-κB pathway initially emerges. NF-κB activation is inhibited with acetylsalicylic acid without interfering gene transcription [52]. In addition, sulindac inhibits NF-κB pathway [53]. Another family of intercellular pathways, WNT pathway, which is associated with carcinogenesis, most notably that of colorectal cancer, can also be inhibited by sulindac [54].

Generally, NSAIDs are used prevalently for their analgesic effects. Although cyclooxygenase inhibition is the main NSAIDs in use today, they are also associated with safety and tolerability concerns. However, further investigation of NSAID's mechanism of action disclosed complicated molecular pathways. It is important to understand which pathological pathways they are able to modulate and how these pathways interact with multiple targets. Molecular approaches may further enhance our understanding of the pathological pathways, improve the identification of risks, and aid in the design of novel treatment strategies. Several mechanisms are determined, but the remainder needs to be clarified. How can NSAIDs counter inflammation in other cellular pathways? Are NSAIDs the new research area for diseases with high mortality such as Alzheimer's disease and cancer? Although this answers far away from our knowledge, the

exact cellular pathways will aid us to learn more about their mechanisms. Results of recent studies suggested that both Cox-dependent and Cox-independent mechanisms are involved in various pharmacological activities of NSAIDs.

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Suture Granuloma 14 Years Following Partial Thyroidectomy Masquerading as Tuberculosis af The Sinus Tract

Mohamed Faisal Abdul Hamid, Andrea Ban Yu-Lin, Tidi Maharani Hassan

ABSTRACT

Suture granuloma rarely occurs after thyroid surgery using non-absorbable sutures. We report the case of a 63-year-old female with a chronic discharging sinus in the anterior neck region. She had a history of subtotal thyroidectomy at the age of 45. The sinus had been excised and was reported as granulomatous lesions suggestive of tuberculosis. She was treated with anti-tuberculous medications, but unfortunately, she developed side effects. Histopathological slides were re-evaluated, which showed evidence of foreign material under polarized light; hence, the diagnosis was revised to suture granuloma. In conclusion, although sinus tract discharges are commonly attributed to tuberculosis, physicians should consider suture granuloma if they encounter a patient who has undergone a surgical procedure in the past.

Keywords: Suture granuloma, thyroidectomy, tuberculosis

Introduction

Suture granuloma is a rare complication that occurs following the use of a non-absorbable suture. It can complicate several different types of surgical procedures and has been reported to occur post brain surgery, post appendicectomy, post lung segmentectomy and post thyroidectomy. Suture granuloma following subtotal thyroidectomy has not been commonly documented in the literature. The present case highlights the dilemma that we faced before making a diagnosis of suture granuloma.

Case Presentation

A 63-year-old female presented with a 12-month history of intermittent discharge from a sinus on the right anterior aspect of the neck. There was no history of chronic cough or constitutional symptoms. She was diagnosed with thyrotoxicosis at the age of 42, for which she underwent subtotal thyroidectomy 3 years later followed by radioiodine therapy.

Four years ago, she developed discharging clear serous fluid from a sinus in the right anterior neck region. The remaining scar was well healed. A computed tomography sinogram showed a well-formed fibrous sinus tract in the subcutaneous tissue in the right anterior neck region with no evidence of fistula. The sinus tract was excised. Histopathological examination (HPE) revealed granulomatous lesion secondary to a foreign body (Figure 1-3).

The patient was well until 3 years later when she developed a small sub-centimeter nodule in the right anterior neck region 4 cm away from the scar. An ultrasound (Figure 4) revealed a well-defined heterogeneous lesion measuring 0.4×0.9 cm in size in the subcutaneous tissue, representing a well-formed fibrous tissue. The sinus tract was re-excised. HPE (Figure 5-6) showed granulomatous inflammation with no central caseation or foreign body.

The serous discharge from the lesion continued, and the patient was subsequently referred to the respiratory team with a possible diagnosis of tuberculosis of the sinus tract/tuberculous lymphadenitis. Upon review, a small sinus in the anterior aspect of the neck with a healed thyroidectomy scar was found. The sinus was located 2 cm away from the healed scar. The rest of the physical examination findings were normal. Chest x-ray findings were also normal.

ORCID IDs of the authors:
M.F.A.H. 0000-0002-7526-361X;
T.M.H. 0000-0001-6392-3273;
A.Y.L.B. 0000-0003-3788-4789.

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Respiratory Unit, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

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Correspondence to: Mohamed Faisal Abdul Hamid
E-mail: arabinose@hotmail.com

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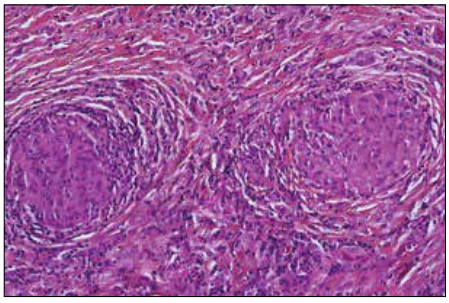

Figure 1. Histopathological examination of sinus tract under the magnification of 20 showing the presence of granuloma with no central caseation (arrow)

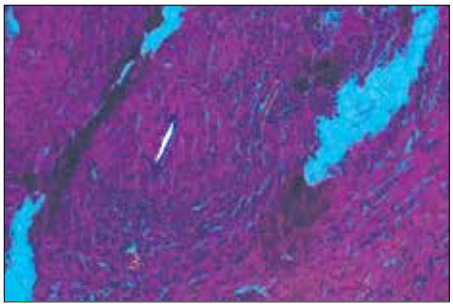

Figure 2. Histopathological examination under polarized light showing the presence of refractile materials (arrow)

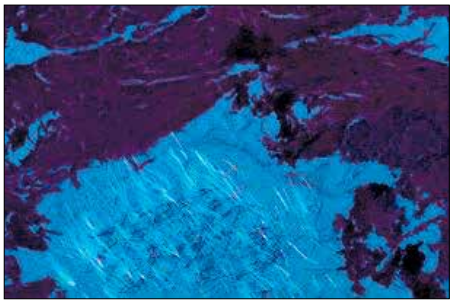

Figure 3. Histopathological examination under polarized light showing the presence of suture material within the granuloma (arrow)

The patient was empirically treated for tuberculosis of the sinus tract in view of HPE findings and the history of chronic discharging sinus. Further investigations for the evidence of active tuberculosis showed negative results; the Mantoux test result was negative (0 mm), and acid-fast bacilli direct stain as well as culture was negative.

Unfortunately, the patient had developed nausea and mild hepatitis due to anti-tuberculous (anti-TB) medication. Tissue slides were reviewed again, and deeper sections were made. Refractile body was found under polarized light microscopy. On periodic acid-Schiff, Ziehl–Nielsen, and Grocott stainings, no fungal organisms or acid-fast bacilli were detected. Thus, a diagnosis of suture granuloma was made. The patient had been receiving anti-TB medications for about a month before they were stopped, and fortunately, the discharge from the sinus tract stopped.

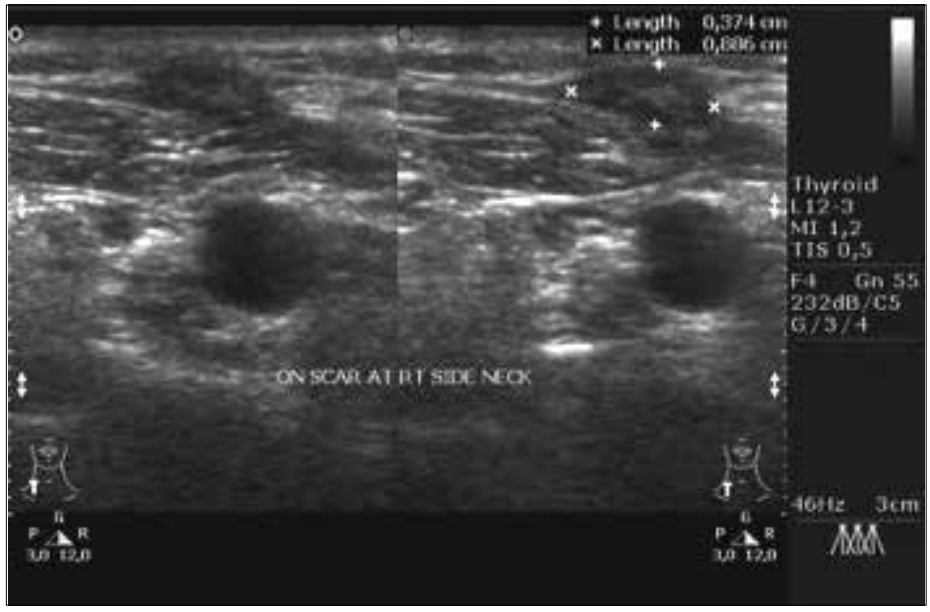

Figure 4. Ultrasound of the neck showing a well-defined heterogeneous lesion in the subcutaneous tissue measuring 0.4×0.9 cm (arrow)

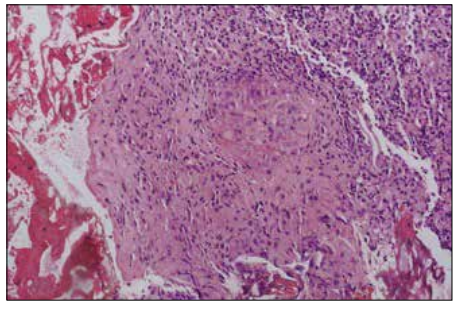

Figure 5. Histopathological examination showing poorly formed granuloma without central necrosis (arrow). Underlying stroma is composed of granulation tissue, which is heavily infiltrated by neutrophils, lymphocytes, and histiocytes

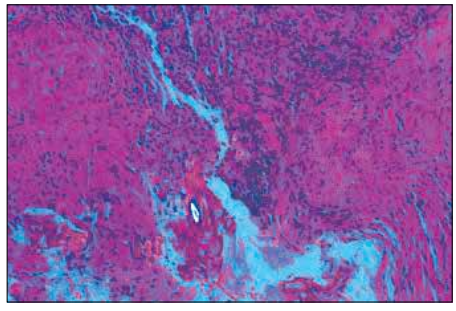

Figure 6. Histopathological examination under deeper sections with polarized light showing the presence of a refractile body (arrow)

Discussion

Suture granuloma is the development of a granulomatous lesion following reaction to suture material. It can develop up to 56 months post thyroidectomy [1]; however, in our patient, the symptoms appeared 14 years after the surgery.

Suture granuloma occurs more commonly in association with non-absorbable sutures [2-3]. It can occur anywhere in the body and after a variety of surgeries. Shauffer et al. [4] reported the case of a patient with colonic carcinoma who developed suture granuloma resembling recurrent carcinoma at the anastomotic site of the colon. Fink et al. [5] reported suture granuloma simulating lung neoplasm occurring after segmentectomy. Epstein et al. [6] reported suture granuloma as an unusual cause of ring-enhancing lesion postoperatively in the brain.

Suture granuloma as in our patient is a rare complication post thyroidectomy. Langer et al. [1] reported foreign body granuloma resembling a suture in 4 out of 156 patients who developed palpable neck mass following thyroidectomy for thyroid cancer. The duration of development of granuloma in these patients ranged between 6 and 56 months. Augustin et al. [7] reported suture granuloma in the abdominal wall with intra-abdominal extension 12 years after open appendicectomy. In our patient, granuloma was detected 14 years postoperatively.

Suture granuloma is treated by removing the sutures. Hocwald et al. [8] reported two cases with severe reaction to silk sutures after thyroid surgery; removal of the sutures along with granulomatous masses cured both the patients.

Suture granuloma can mimic tuberculous lymphadenitis. The initial decision to initiate anti-TB medication was based on the histopathological finding of a granuloma. In our

country, the commonest cause of extra-pulmonary tuberculosis is tuberculous lymphadenitis, and tuberculosis may have atypical presentations [9-13]. However, in our patient, culture was not positive for tuberculosis, and she did not have any constitutional symptoms. She also developed side effects to anti-TB medication. Retrospectively, her negative Mantoux test results and the absence of constitutional symptoms indicated that granuloma was indeed not tuberculosis related.

Further assessments were made on the tissue slides upon our request; deeper section cuts were investigated, and a refractile body, which we assumed to be suture material, was found. We have discontinued her anti-TB medications after 1 month of intensive treatment with these. She remained well after that.

Suture granuloma is not commonly seen in the respiratory clinic and can be misdiagnosed as tuberculous lymphadenitis. This case highlights the importance of considering suture granuloma as a differential diagnosis in post thyroidectomy patients who present with a lump in the neck.

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Exogenous Lipoid Pneumonia due to Chronic Inhalation of Oily Product Used as a Lubricant of Tracheotomy Cannula

Antonio Tancredi[1,2], Paolo Graziano[3], Roberto Scaramuzzi[1,4], Gerardo Scaramuzzi[1], Illuminato Carosi[3], Vito Attino[3], Antonello Cuttitta[1], Marco Taurchini[1]

ABSTRACT

Exogenous lipoid pneumonia (ELP) is caused by the inhalation of vaporized oily products. Long-term exposure can result in chronic disease, whereas acute form usually results from massive aspiration of fatty substances. It has an incidence of 1.0%–2.5%.

In case of symptomatic patients, the clinical presentation mainly includes acute or chronic respiratory symptoms such as dyspnea, fever, cough and less frequently chest pain, hemoptysis, or weight loss. Radiological findings are often aspecific or misinterpreted, and ELP is sometimes misdiagnosed as a malignancy of the lungs.

Patient history and radiological findings can lead to a suspicion of ELP, but histological microscopic findings of intra-alveolar lipid and lipid-laden macrophages are required to confirm the diagnosis The mainstay of treatment consists of avoiding ongoing exposure and providing supportive care as repeated whole-lung lavage, corticosteroids, and/or immunoglobulins. Surgery is reserved for cases of high suspicion of cancer or serious clinical impact (as recurrent infections).

Prognosis is benign, even if it has been reported cases of progression to severe respiratory failure, cor pulmonale, superinfection, and association with lung cancer. Here, we describe a case of ELP due to chronic inhalation of oily product (Vaseline) used as a lubricant of tracheotomy cannula.

Keywords: Lipoid pneumonia, tracheotomy, fatty lubricant

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[1]Unit of General Surgery 2nd and Thoracic Surgery, IRCCS " Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Foggia, Italy
[2]Department of Emergency Medicine, IRCCS " Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Foggia, Italy
[3]Unit of Pathology, IRCCS " Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Foggia, Italy
[4]Unit of Thoracic Surgery, Second University of Naples, Naples, NA, Italy

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Correspondence to: Antonio Tancredi
E-mail: antoniotancredi@virgilio.it

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Introduction

In 1925, Laughlen [1] first described four cases of a rare form of pneumonia caused by inhalation of fatty substances and named it exogenous lipoid pneumonia (ELP).

In 1949, McDonald et al. [2] reported an endogenous form of lipoid pneumonia that presented similar clinical, histological, and radiological findings of the exogenous form but with different pathogenesis related to chronic bronchial obstruction from chronic bronchitis, neoplasms, or other endogenous factors (as lipid storage disorder).

Since then, lipoid pneumonia, both as exogenous and as endogenous forms, has been widely studied, and an incidence of 1.0%–2.5% has been reported [2].

Recently, we treated a patient with ELP due to chronic inhalation of an oily product (Vaseline), which was used as a lubricant of tracheotomy cannula.

Because it was a very peculiar case, we consulted the medical literature to deeply understand the topic, and till date, we have found only 14 cases [3-5]; therefore, we believed it important to share our anecdotal experience which, to our knowledge, is the 15th reported case.

Case Presentation

An asymptomatic 59-year-old man, who was tracheotomized after total laryngectomy for laryngeal squamous cell carcinoma 3 years earlier, presented to our unit because chest computed tomography (CT) revealed a mass in the middle lobe of his right lung during his oncologic follow-up (Figure 1).

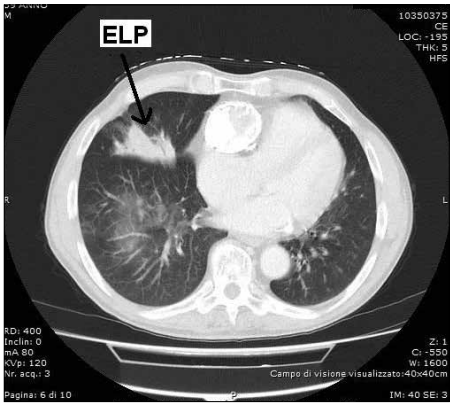

Figure 1. Chest computed tomography shows a consolidation area presenting ground glass opacity in the middle lobe of the right lung

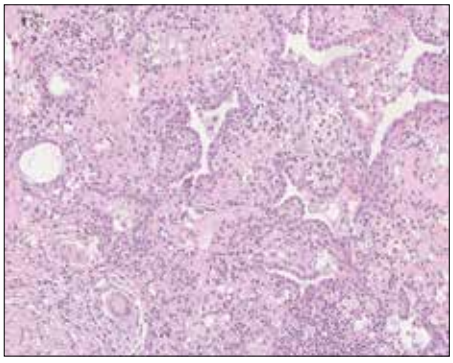

Figure 2. Pulmonary lymphoplasmacytic infiltrates associated with multinucleated giant cells containing fat clefts and intra-alveolar lipid-laden macrophages (H&E ×20)

Total-body positron emission tomography–CT confirmed the mass, and malignancy (metastatic or primitive) was suspected. Bronchoscopy, bronchoalveolar lavage (BAL) fluid analysis, skeletal scintigraphy, and tumor markers were negative.

Bronchoscopic biopsy was not feasible either endoscopically or under ultrasound guidance. Therefore, the patient consented to surgery and a thoracoscopic lung biopsy was performed, followed by a middle right lobectomy through a minithoracotomy because the middle lobe had a global malacic appearance.

Definitive histology showed characteristic features of lipoid pneumonia (Figure 2). When questioned about his habits, the patient reported the daily use of an oily product (Vaseline) to lubricate his tracheotomy cannula during changing or positioning.

Therefore, ELP was diagnosed. The patient had a normal postoperative course, but he died 6 months later because of other natural causes.

Discussion

ELP is caused by the inhalation of vaporized oily products and can be chronic when associated with long-term exposure or acute when resulting from massive aspiration of fatty substances [4].

It has been reported in all age groups and may be due to anatomical or functioning abnormality in deglutition, such as Zenker's diverticulum, cleft palate, hiatal hernia, achalasia, or other neuromuscular diseases, affecting pharyngeal motility or the cough reflex [2, 6].

In healthy individuals, it may be due to professional exposure (e.g., siphoning of mineral oils worker) or daily habits such as use of oil-based laxatives, lip balm, or flavored lip gloss [2, 6].

Among other reported curious cases, we would like to mention that of long-term exposure to vaporized paraffin from burning candles in a shrine, that of a chef specialized in tabletop "Teppanyaki/Hibachi" cooking, and the cases of fire-eaters [2-9]. The main pathological mechanism is the vaporized fat entry into the tracheobronchial tree without stimulating the cough reflex. Once in the alveoli, macrophages take up the fat after emulsification, but they cannot metabolize fatty substance and it is repeatedly released into the alveoli after the death of the macrophages. This released fat activates a giant-cell granulomatous reaction (also called lipid granulomatosis), chronic inflammation, and alveolar and interstitial fibrosis.

Histologically, ELP is characterized by the presence of intra-alveolar lipid and lipid-laden macrophages and a chronic foreign body-type reaction with inhaled exogenous lipid droplets [1, 2].

Clinically, except the cases of asymptomatic patients, ELP can have acute or chronic presentation. The former case, which is rarer, is typically due to massive aspiration of vaporized fats and may simulate infectious pneumonia with fever and/or cough. The chronic form, which is more common, is a result of long-term exposure to irritant agents and usually presents with dyspnea, restrictive pattern, chronic hypoxia, and/or cough. Some authors have described symptoms of chest pain, hemoptysis, and weight loss [2].

There are no diagnostic radiological features on chest radiography. The most common findings on chest CT are consolidations and areas of peribronchial ground glass opacities, mainly in the lung bases. Other less common radiological findings include "crazy paving" pattern in the lung parenchyma; endobronchial secretions; or unspecific areas of post-obstructive pneumonitis, pneumatoceles, pneumomediastinum, pneumothorax, and pleural effusions [3-5].

Chest magnetic resonance imaging can be useful because it shows the fat content of lesions in T1-weighted sequences and signal suppression in fat suppression sequences [4, 5].

A definitive diagnosis of ELP is obtained by detecting intra-alveolar lipid and lipid-laden macrophages in respiratory specimens. Various specimens that may be used for the confirmation of the diagnosis include sputum, BAL, transthoracic fine-needle aspiration cytology, or biopsy from the lesion [2]. Some authors are of the opinion that radiological testing may be sufficient and invasive testing procedures can be avoided [4].

The mainstay of the treatment consists of avoiding ongoing exposure and providing supportive care.

Corticosteroids are a therapeutic option only in case of severe and ongoing lung injury; other treatment options are immunoglobulins and repeated whole-lung lavage. Surgery may be performed only in cases highly suspected of cancer [2].

Usually, ELP has a benign prognosis even if it has been reported in cases of progression to severe respiratory failure, cor pulmonale, superinfection, and association with lung cancer [4].

In conclusion, some observations can be made about our experience and ELP case:

- We reported that, in this 15th case, ELP was caused by chronic inhalation of an oily product (Vaseline), which was used as a lubricant of tracheotomy cannula, and perhaps many other iatrogenic cases remain unknown and could be prevented if ELP knowledge were more widespread in medical community
- Diagnosis of ELP is very difficult because:
  - » It is not routinely suspected at the time of presentation.
  - » There are no typical clinical signs or symptoms.
  - » Imaging studies can often be inconclusive or misinterpreted.
- Preoperative diagnosis is very important to avoid unnecessary surgery.
- Definitive diagnosis is only histological.

Informed Consent: Written informed consent was obtained from patient who participated in this study

Peer-review: Externally peer-reviewed.

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Myasthenia Gravis Attack after Oral Risperidone Treatment: A Case Report

Hakan Ogutlu[1], Ali Karayagmurlu[2], Ibrahim Selcuk Esin[1], Onur Burak Dursun[1]

ORCID IDs of the authors:
H.O. 0000-0002-1325-446X;
A.K. 0000-0001-5464-2891;
I.S.E. 0000-0001-5598-2097;
O.B.D. 0000-0001-5598-2097.

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[1]Department of Child and Adolescent Psychiatry, Ataturk University School of Medicine Erzurum, Turkey
[2]Department of Child and Adolescent Psychiatry, Gaziantep Maternity and Child Health Hospital, Gaziantep, Turkey

Received: September 28, 2017
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Correspondence to: Ibrahim Selcuk Esin
E-mail: esinibrahimselcuk@gmail.com

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune disease, which can be triggered by anticholinergic agents. The 6-year-old female patient was admitted to the outpatient clinic. She was had been previously diagnosed with comorbid attention deficit hyperactivity disorder and conduct disorder and was receiving short-acting methylphenidate and risperidone, as recommended by a child psychiatrist. However, after using the drugs, she stated that she was overly tired during the day and that her eyelids drooped. Hence, the current treatment was stopped. She was hospitalized with a prediagnosis of ocular type MG and pyridostigmine (90 mg/day) treatment was started. The patient recovered and subsequently the treatment was stopped. Since psychiatric symptoms of the patient resurfaced, long-acting methylphenidate treatment was initiated. During this treatment, the symptoms of MG did not return. The Naranjo's scale of adverse drug reaction probability was completed. Consequently, there may be an association between risperidone and MG.

Keywords: Myasthenia gravis, risperidone, adverse effect

Introduction

Myasthenia Gravis (MG) is a disease characterized by time-varying muscular weakness and fatigue resulting from an autoimmune response to acetylcholine receptors (AChR) in the postsynaptic neuromuscular region, generally due to the parasympathetic nervous system effect [1]. MG is a neuromuscular disorder that can be triggered by anticholinergic agents [2]. In addition to the trigger by anticholinergic agents, it was found that antipsychotics used during schizophrenia treatment worsen MG [3]. However, to the best of our knowledge, there has been no report in literature for the worsening of MG due to oral risperidone treatment. This patient is the first case of an MG attack followed by oral risperidone treatment. Written informed consent was obtained from the patient and her family.

Case Presentation

A 6-year-old female patient was admitted to our clinic by her foster family with symptoms of inattention, distraction, hyperactivity, and impulsivity. She was insisting on her wills, and the family had problems with setting rules. According to the information received from her teacher, she would not pay attention to what the teacher said. Moreover, she extensively moved around in class, disturbed the order of the class, and talked a lot. A psychiatric assessment revealed that she had concentration problems, hyperactivity, and impulsivity. At the age of 5 years, she was beaten up by her biological family and was sent to an orphanage. With regard to her biological family, her mother had been diagnosed with MG, schizophrenia, and tonic-clonic type epilepsy, and her father had been diagnosed with epilepsy. The patient was diagnosed with attention deficit hyperactivity disorder (ADHD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and was recommended behavioral interventions. Although a follow-up was suggested, the patient did not attend the follow-up visit.

One year later, it was reported that the patient was admitted to another clinic and was diagnosed with ADHD and conduct disorder and was prescribed methylphenidate (10 mg/day) and risperidone (0.25 mg/day). The symptoms benefited from the medication. After using the medications, the movements of the patient began to decrease considerably. The patient stated

that she started to feel extremely tired to move during the day and that her eyelids drooped. Subsequently, her gaze became stunned. Hence, the current treatment of the patient was discontinued, and she was directed to a neurology clinic and was hospitalized with a prediagnosis of ocular type MG. A neurological examination revealed that the eyelid ptosis was present and ptosis increased due to a challenged upward gaze. A thymoma-compatible lesion was detected in a thorax–neck computed tomography (CT) scan. In a blood analysis, the AChR antibody was established as positive (10 mg/dL).

Pyridostigmine bromide (90 mg/day) treatment was started for the patient. After the patient recovered, she was discharged and pyridostigmine was discontinued. Since the psychiatric symptoms of the patient returned to the initial severity, long-acting methylphenidate (10 mg/day) was restarted. Methylphenidate was gradually increased to 20 mg/day. She benefited from the drug at that dose and continued her follow-up regularly for 1.5 years. The Naranjo's scale score of adverse drug reaction probability was 5. Consequently, we hypothesized that risperidone has a probable association with MG.

Discussion

MG is a complex disease caused by antibody-mediated damage to the neuromuscular junction. The frequency of MG is reported to be 20 in 100,000 [4]. MG is rare in childhood since it is primarily an adult-specific disease.. Only 10%–15% of myasthenia patients are in the childhood group. This rate is detected as 4.2% in children under 10 years of age [5, 6]. Muscular weakness and fatigue that gradually increase during the course of activity and decrease during rest are characteristics of MG. In many patients, eyelid droop described as blepharoptosis is the first known symptom. The onset of the disease may be immediate, and the symptoms are usually transient and periodic [7]. In the present case, the patient had a rapid-onset eyelid droop as the first symptom of an early-onset MG.

In patients with MG, the usage of antipsychotics, mood stabilizers, and antidepressants are risk factors for potentially exacerbating symptoms. Antipsychotic agents are highly selective for muscarinic receptors. Additionally, acetylcholine (Ach) blockade in nicotinic receptors is also minimal with antipsychotic agents. Nicotinic receptors directly affect MG. Thus, anticholinergic effects of antipsychotics have the potential to worsen the symptoms of MG. Antipsychotics with a high severity of these effects include chlorpromazine, thioridazine, clozapine, olanzapine, and haloperidol [3, 8].

Risperidone is a second-generation antipsychotic that has been shown to be effective with Dopamine D2 and Serotonin 5-HT2A receptor antagonistic mechanism. Reportedly, anticholinergic side effects of risperidone were very low compared to clozapine and olanzapine [9]. However, in a recently published case report, MG symptoms in a 29-year-old woman with MG and schizophrenia, who had no myasthenic crisis for 7 years, were found to worsen after the first, second, and third Risperidone Consta injection for antipsychotic treatment. In this case report, depending on the patient's use of fluoxetine, which increases the blood plasma level of risperidone by 2.5-fold, myasthenic symptoms might be caused by the increase of risperidone blood level [10].

Our case is the first to demonstrate that the use of oral risperidone may trigger MG symptoms. The AChR antibody was positive during the attack leading to a diagnosis of risperidone-induced MG. With regard to the use of methylphenidate, there is no literature stating its worsening effect on MG. Stimulants increase ACh levels by inhibiting acetylcholinesterase, and hypothetically, may improve MG symptoms instead of worsening [11]. Although the patient continued to use methylphenidate in follow-ups, MG symptoms did not occur. Hence, we hypothesized that methylphenidate may not trigger MG. The probable relationship defined at Naranjo adverse drug reaction scale explained that the main reason for the attack is risperidone. Therefore, it should be considered that oral risperidone may trigger and worsen MG and that it should be used with caution in MG patients.

Informed Consent: Written informed consent was obtained from patients and the parents of the patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Selective Arterial Embolization of Giant Renal Angiomyolipoma Associated with Tuberous Sclerosis Complex Using Particular and Liquid Embolic Agents

Deniz Ozturk Kocakgol[1], Erdem Cayli[2], Sukru Oguz[1], Hasan Dinc[1]

ABSTRACT

Renal angiomyolipoma (AML) is a benign hamartomatous tumor that is sometimes associated with the tuberous sclerosis complex. We report a 23-year-old man who presented with acute abdominal pain and hematuria. Computed tomography (CT) revealed large heterogeneous right renal mass of 17×13×13-cm diameter, consistent with AML, and acute and subacute hemorrhages. Digital subtraction angiography revealed massive tumor vascularization and multiple aneurysms associated with right renal artery branches. First, polyvinyl alcohol particles were used for the selective embolization of AML. Then, N-butyl cyanoacrylate (glue) mixed with lipiodol in a 1:3 ratio was injected for the permanent embolization of AML. CT scan revealed 59% reduction in size at 5 months after embolization. This case illustrates the selective embolization of giant renal AML with the combination of particular and liquid embolic agents with a significant reduction in size during the follow-up period.

Keywords: Angiomyolipoma, renal, treatment, selective arterial embolization

Introduction

Renal angiomyolipoma (AML) is a benign hamartomatous tumor comprising variable amounts of adipose tissue, smooth muscle, and abnormal blood vessels. Approximately 20% of AMLs are associated with the tuberous sclerosis (TS) complex [1, 2]. Because AMLs are usually asymptomatic, tumors of >4-cm diameter are usually symptomatic and present with retroperitoneal and/or urinary bleeding, which can be life threatening [1, 3, 4]. The standard treatment option in symptomatic patients with AML is nephron-sparing surgery [1, 2, 5]. However, in the past two decades, selective arterial embolization (SAE) has been used as the first-line treatment option in patients presenting with acute bleeding as well as prophylactically to prevent future bleeding complications [3, 6]. This case represents a successful embolization of giant renal AML with the combination of particular and liquid embolic agents.

Case Presentation

A 23-year-old male patient was admitted to the emergency department with acute abdominal pain and hematuria. On laboratory analysis, hemoglobin (Hb; 8.1 mg/dL) and hematocrit (HTC; 36%) values were decreased. Blood pressure was stable at approximately 100/70 mmHg with a mean heart rate of 76 bpm. Patient's history revealed the diagnosis of TS with right kidney AML, which was under follow-up. Non-enhanced computed tomography (CT) scan revealed bilateral subependymal calcific nodules around the foramen of Monro and lateral ventricles consistent with TS (Figure 1). Contrast-enhanced CT scan of the upper and lower abdomen showed well-defined right renal mass of 17×13×13-cm diameter containing adipose [−40 Hounsfield units (HU)] and heterogeneous soft-tissue structures consisted with AML. Hyperdense and isodense collections within the mass and in pelvis were also observed consistent with acute and subacute hemorrhages that occurred at different times (Figure 2). Selective digital subtraction angiography (DSA) of the middle and lower branches of the right renal artery revealed multiple pseudoaneurysms and tumor vascularization (Figure 3). According to angiographic findings, we intended to embolize the AML. After placing a 5-F cobra catheter within the lower branch of the right renal artery, the first part of embolization was performed using 355- to 500-µm non-calibrated polyvinyl alcohol (PVA) particles (Contour; Boston Scientific, Marlborough, Massachusetts). Following particular embolization, *N*-butyl cyanoacrylate (NBCA) glue

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[1]Department of Radiology, Karadeniz Technical University School of Medicine, Trabzon, Turkey
[2]Private Practice, Ankara, Turkey

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Correspondence to: Erdem Cayli
E-mail: erdemcayli@yahoo.com

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(Histoacryl, B. Braun) mixed with ethiodized oil (Lipiodol® Ultra-Fluid, Guerbet, France) in a 1:3 ratio was injected for permanent embolization. After embolization, the hypervascularization of AML and pseudoaneurysms completely disappeared with the preservation of the viable upper pole of renal parenchyma. The patient was stable and discharged without any complication. Abdomen CT scan showed modest reduction in the size of the mass [59% reduction; 10×10×12 cm) at 5 months after embolization.

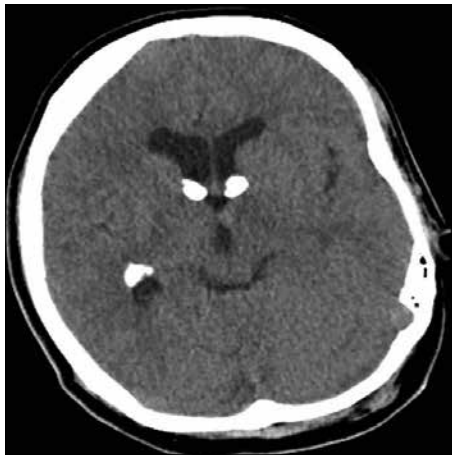

Figure 1. Axial non-contrast CT scan revealed bilateral subependymal calcific nodules around the foramen of Monro and lateral ventricles

Discussion

Renal AML is an uncommon benign tumor, and approximately 20% cases are associated with the TS complex [1-4]. Because it is benign in nature, asymptomatic cases can be managed by active surveillance [1, 2]. Approximately 60% of patients with large AMLs present with a combination of acute bleeding, flank pain, hematuria, and palpable mass. Tumors over 4 cm often experience hemorrhage and internal tumaro growth. The main indications for treatment are abdominal pain, internal tumor growth, retroperitoneal hemorrhage, and gross hematuria [2, 3, 7].

AML can be easily diagnosed by ultrasound (US), CT, and MRI findings. On US, AMLs almost always appear as a hyperechoic mass due to the fat component of the tumor, an area of negative attenuation value (<−20 HU), and high signal intensity on T1-weighted on CT MR images. However, not all AMLs demonstrate these classic imaging findings; RCC also appears hyperechoic on US in approximately one third of the cases [1-3, 8]. Histopathological examinations should be performed in case of suspicious lesions [2]. In our patient, CT revealed a low-attenuation renal mass compatible with fat (−40 HU), which was consistent with AML.

The treatment options for renal AML include SAE, nephron-sparing surgery, radiofrequency and cryoablation of the tumor, and nephrectomy [1-3]. Symptomatic patients with AMLs over 4 cm require surgical intervention. Selective nephron-sparing surgery is the gold standard if radiological diagnosis is certain. However, radical nephrectomy should be the procedure of choice if malignancy is suspected [1, 3, 7]. Surgery allows the complete resection of the tumor and pathologic confirmation. Surgery can

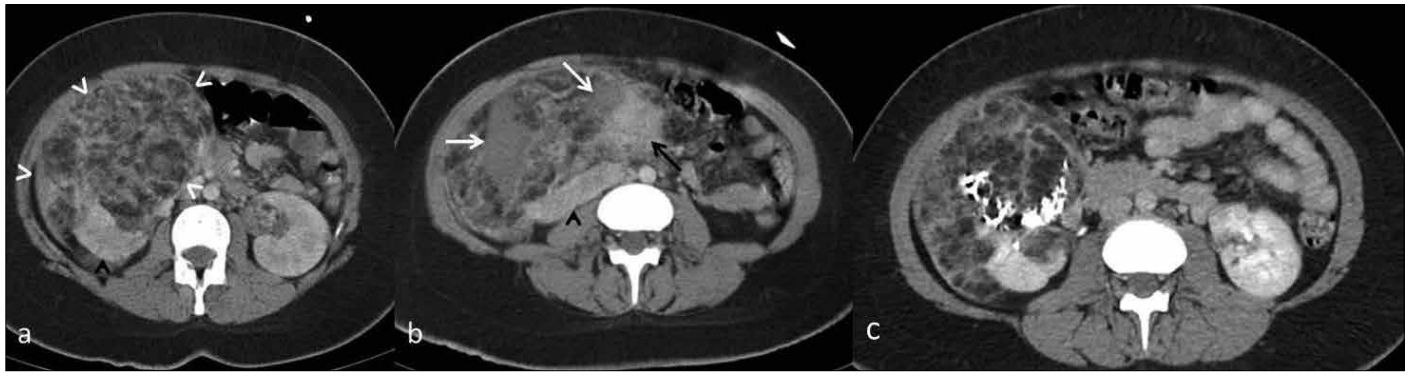

Figure 2 a-c. Axial contrast-enhanced CT images show huge angiomyolipoma (white arrowheads) with large fatty components (a), hyperdense acute (white arrows) and isodense former (black arrow) hemorrhagic areas and the right kidney parenchyma (black arrowheads) displaced inferior and medial by mass (b), and significant reduction (59%) in size of mass 5 months after embolization (c)

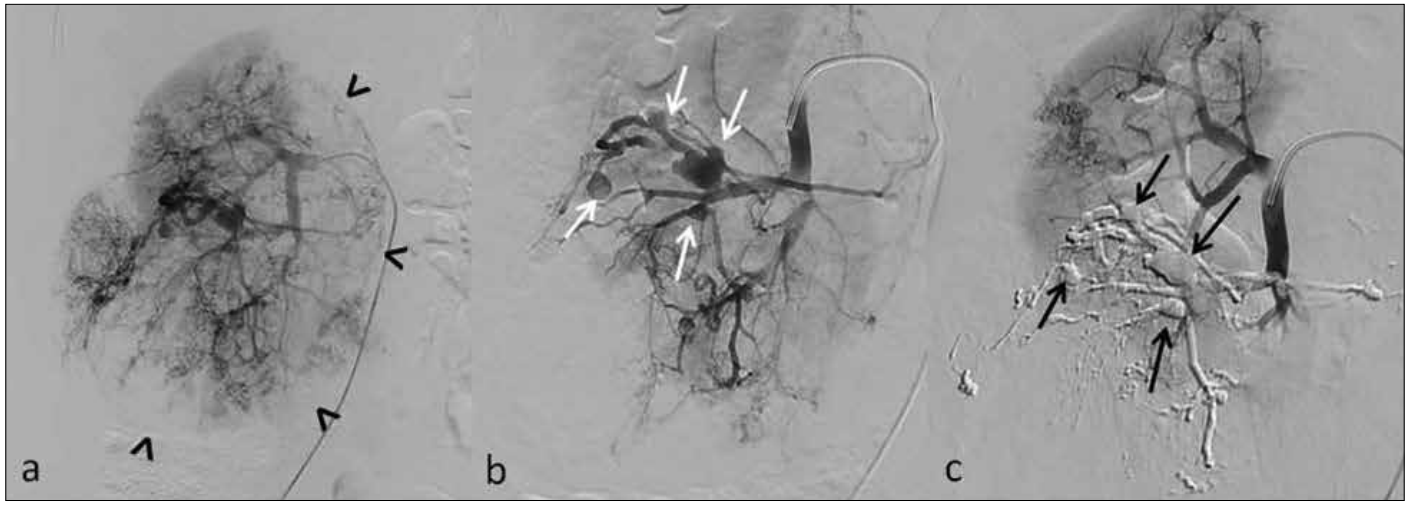

Figure 3 a-c. Pre-embolization (a, b) arterial phase DSA images show huge mass lesion (arrowheads) of the right kidney supplying multiple renal segmentary arteries and multiple aneurysms (white arrows) originating from the feeding arterial branches of the mass. Post-embolization image (c) revealed the complete disappearance of tumor vascularization and aneurysms (black arrows)

be quite difficult in cases with a complex vascular anatomy, hilar location, or multiplicity of lesions [8].

SAE has been used as the first-line management option for AML because >50% of tumors over 4 cm present with hemorrhage and one third of the patients with acute hemorrhage exhibit shock [3, 6].

Blood vessels within AMLs are abnormal and have no internal elastic lamina and form aneurysms and rupture [7]. Therefore, the selective embolization of AML is aimed at occluding these abnormal vessels and the optimal sparing of the normal renal parenchyma to maintain the maximal renal function [2, 3, 6]. Another aim of the embolization of AML is to decrease the tumor size. Because AMLs comprise varying amounts of adipose, smooth muscle, and vascular tissue, the effects of embolization are variable. Because the adipose tissue is hypovascular, it is resistant to embolization; therefore, some adipose tissues may not be adequately affected by embolization. In contrast to adipose tissues, the angiomyogenic components of AML respond to embolization to a greater extent; therefore, decrease in tumor size is more prominent in these components [6, 9]. In our patient, embolization was decided because of angiographic findings indicating abnormal tumor vascularization and aneurysms related to tumor vessels. An additional indication for embolization was the presence of acute and subacute hemorrhage within the tumor and pelvis.

Some researchers have advocated prophylactic embolization because embolization has proven to be a safe and effective procedure in experienced patients, and prophylactic embolization could be used in hypervascular AML to prevent acute hemorrhagic conditions [6].

Numerous agents can be used for the embolization of AML including particles, coils, vascular plugs, absolute ethanol, and glue. Several types of agents are available, including non-calibrated PVA particles (Contour; Boston Scientific, Marlborough, Massachusetts), acrylic polymer microspheres impregnated with gelatin (Embosphere Microspheres, Biosphere Medical, Rockland, MA) and calibrated PVA microspheres (Beadblock, Terumo, Leuven, Belgium), liquid embolic agents including NBCA (Histoacryl, B. Braun) mixed with ethiodized oil (Lipiodol® Ultra-Fluid, Guerbet, France), and Onyx® 18 (Covidien, Mansfield, MA, USA). Several microciols are also available, including Micrus (Micrus Corporation/Codman), Microvention, (Terumo), Axium (eV3), Target (Boston Scientific/Stryker), Penumbra coils 400 (Penumbra), and Barricade koiller (Balt) [3, 6, 10].

Thus far, no study has demonstrated the superiority of an embolic agent over another with regard to treating actively hemorrhaging AMLs, preventing hemorrhage, and treating symptoms [2]. Particular agents, such as PVA or embosphere, are the most commonly used in the embolization of AML. Particular embolization was commonly performed with a combination of 350- to 500-mm PVA particles to occlude the distal vascular bed followed by coils to block the arterial inflow and prevent the retrograde filling of the aneurysm and abnormal tumor vessels reference [7]. Coils should be avoided because they only provide proximal vessel occlusion, which may form collaterals around or at the distal level of occlusion, further making embolization difficult or impossible [3-6].

Another liquid embolic agent is the NBCA which is a product that polymerizes upon contact with an ionic medium and particularly when in contact with blood. The peripheral dissolution and speed of polymerization depend on the degree of dilution in an oily contrast agent lipiodol [11]. In experienced hands, glue provides a very fast and effective distal embolization with a high dilution of lipiodol (glue:lipiodol ratio, 1:3–1:6). Glue is a very effective embolic agent for the management of acute hemorrhages, aneurysms, arteriovenous malformations, and fistulas [5, 12]. In the present case, initially non-calibrated 355- to 500-mm PVA particles were used to occlude the distal vascular bed. Following PVA, we used NBCA mixed with lipiodol in 1:3 ratios. Because PVA has the risk of recanalization within 7 d, using PVA particles alone in SAE may cause re-bleeding. Therefore, we consider that the combined use of liquid embolic agent with PVA particles in embolization significantly reduces the risk of re-bleeding because the NBCA permanently occludes the tumor vascularity and aneurysms.

No studies have described the use of glue alone or in combination with other embolic agents. Because glue is a permanent embolic agent, its use in embolization needs a high level of experience. Accidental embolization or reflux of glue into non-targeted arteries may result in catastrophic complications [5].

Ethanol is a liquid embolic agent that provides permanent occlusion at the arteriolar and capillary level distal to the level of collateral inflow and causes tumor tissue necrosis. The major risk with the use of ethanol is non-target embolization resulting from the reflux out of tumor-feeding vessels, which can result in devastating consequences [6, 11].

Complications of SAE include pain, post-embolization syndrome, vascular injury, hematuria, renal infarction with abscess formation, renal failure, infections, accidental embolization, and intraprocedural rupture. Post-embolization syndrome occurs as a result of renal tissue necrosis and is characterized by nausea, vomiting, fever, abdominal pain, and leukocytosis. The syndrome has been reported to occur in up to 80% of cases and is conservatively treated [2, 11]. In our case, no complication was encountered during embolization and postoperatively.

Ramon et al. [3] in their study evaluated 41 patients (48 kidneys) with AML who were treated by SAE using a mixture of 96% ethanol and PVA particles with a minor complication rate of 11%. The mean tumor size was 10.3 cm. Retroperitoneal hemorrhage did not occur during the follow-up. The freedom from surgery at 5-year follow-up was 94% for SAE [3]. Bardin et al. [5] have recently reported 23 symptomatic patients with AML treated by SAE using various embolization agents including particles, coils, and liquid agents; six of these patients were treated because of acute retroperitoneal hemorrhage and the remaining 17 patients were treated prophylactically. Major complications occurred in three patients (renal abscess in two and femoral psodoaneurysms in one) and minor complications in 14 patients as a post-embolization syndrome. The mean AML size reduction was 26.2% after mean 20.5 months of follow-up. Lee et al. [12] also have recently showed that the mean AML size reduction was between 33% and 43% within and after 6 months follow-up, respectively. In the present case, mean 59% tumor size reduction was observed within 5 months follow-up.

In conclusion, renal AML is a benign hamartomatous tumor. AMLs >4 cm in diameter are usually symptomatic and present with retroperitoneal hemorrhage, which can be life threatening. Our case represents the successful embolization of giant renal AML with the combination of particular and liquid embolic agents with 59% tumor size reduction in 5 months follow-up.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Farabi Hospital School of Medicine.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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A Rare Presentation of Anterior Mediastinal Teratoma Mimicking Valvular Heart Disease with A Systolic Murmur

Henry Tan Chor Lip[1-3], Tan Jih Huei[1-3], Adrena Abdul Wahid[4], Simon Jerome Vendargon[3]

ORCID IDs of the authors:
H.T.C.L. 0000-0003-0621-9276;
T.J.H. 0000-0001-9833-5164;
S.J.V. 0000-0003-4480-2825;
A.A.W. 0000-0001-7377-9025.

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[1]Department of General Surgery, School of Medicine, National University of Malaysia Medical Centre, Kuala Lumpur, Malaysia
[2]Department of General Surgery, Hospital Sultanah Aminah, Johor Bahru, Malaysia
[3]Department of Cardiothoracic Surgery, Hospital Sultanah Aminah, Johor Bahru, Malaysia
[4]Department of Pathology, Hospital Sultanah Aminah, Johor Bahru, Malaysia

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Correspondence to: Henry Tan Chor Lip
E-mail: relos1402@gmail.com

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ABSTRACT

Extrinsic pulmonary artery stenosis caused by anterior mediastinum teratoma presenting with an ejection systolic murmur is a rare phenomenon. Till date, 15 cases have been reported (inclusive of this case) in the English literatures. Herein we report a 20 year old female with extrinsic pulmonary artery stenosis because of compression by an anterior mediastinal teratoma with a loud ejection systolic murmur. The case report aims to highlight the awareness of such rare presentation of anterior mediastinal teratomas that may mimic congenital valvular heart diseases among clinicians.

Keywords: Teratoma, benign, systolic murmurs, pulmonary artery

Introduction

Pulmonary stenosis caused by extrinsic compression of an anterior mediastinal teratoma is a rare phenomenon [1]. The first case was described by Maier et al. [2] in 1948. In this case, a 4-year-old girl presented with a harsh systolic murmur because of extrinsic compression of the pulmonary artery by a teratoma in the anterior mediastinum [2]. To our knowledge, till date, only 15 cases (including our case) of teratoma within the anterior mediastinum causing extrinsic pulmonary stenosis have been reported in the English literatures [1-7]. Herein, we report on a 20-year-old female with an anterior mediastinal teratoma mimicking a valvular heart disease with a loud ejection systolic murmur. This case report aims to increase the awareness of such rare presentations of anterior mediastinal teratomas that may mimic congenital valvular heart diseases.

Case Presentation

A 20-year-old female previously healthy, presented with symptoms of reduced effort tolerance and chest discomfort for four months without orthopnea or paroxysmal nocturnal dyspnea. The electrocardiogram and blood investigations were within normal limits. Physical examination by the primary care health team revealed that the ejection systolic murmur was loudest over the pulmonary area. There were no other constitutional signs of heart failure. Based on the findings of a heart murmur, she was referred to the cardiology department with a primary suspicion of congenital valvular heart disease. However, transthoracic echocardiography revealed extrinsic compression of the main pulmonary artery causing turbulent blood flow. The peak pressure gradient was 35 mmHg which led to the presence of an ejection systolic murmur. No other structural abnormalities in the heart were detected on the transthoracic echocardiography. A chest roenterogram disclosed a round, smooth

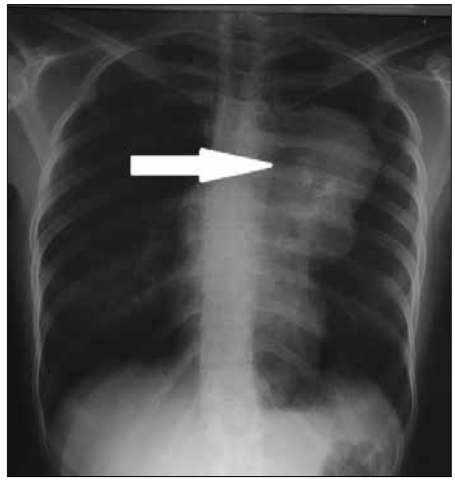

Figure 1. Chest roenterogram showing a suspicious mass over the left upper thorax (green arrow) with clear lung fields

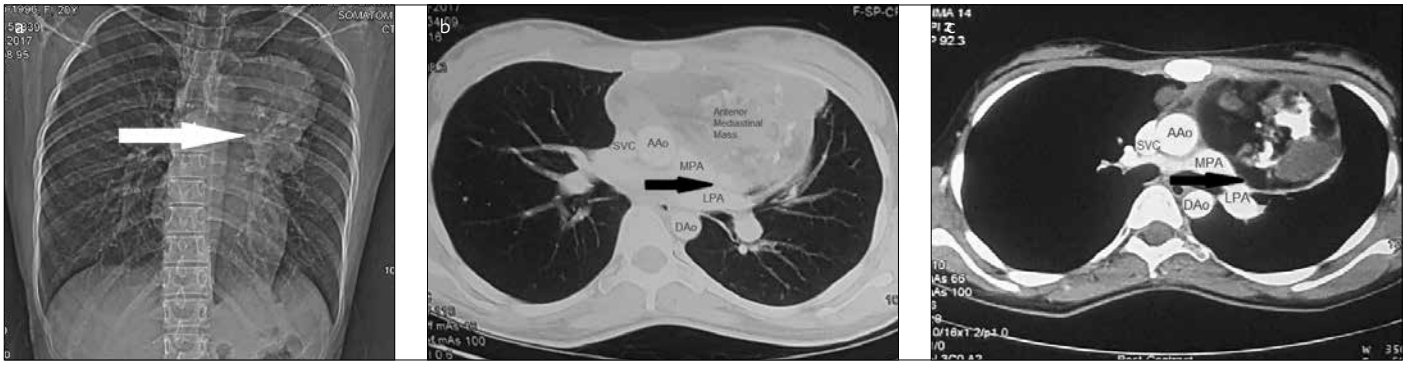

Figure 2. a-c. Coronal view of thorax on CT scan showing anterior mediastinal mass in the left upper thorax (green arrow) (a), Lung window view showing anterior mediastinal mass compressing over the pulmonary artery (green arrow) (b), Mediastinal window view showing anterior mediastinal mass compressing the pumonary artery (green arrow) (c)
SVC: superior vena cava; AAo: ascending aorta; MPA: main pulmonary artery; LPA: left pulmonary artery; DAo - descending aorta

mass in the left upper border of the mediastinum (Figure 1). Computed tomography (CT) of the thorax shows a large anterior mediastinal mass measuring 5.6cm × 10.7cm × 9.5cm causing compression to the pulmonary trunk and left atrium (Figure 2 a-c). There were no enlarged mediastinal lymph nodes and the lung fields were clear. Through a primary median sternotomy, a well encapsulated cystic tumor measuring 15 cm in diameter was found within the anterior mediastinum causing compression to the main pulmonary artery (Figure 3a). Excision was meticulously performed to dissect the tumor from the pericardium. Sectioning of the specimen revealed a yellowish solid multicystic mass containing hair, sebaceous material, cartilage, and bone (Figure 3b). Microscopic examination revealed that the cystic structures were lined by keratinizing stratified squamous epithelium (skin) and ciliated bronchial epithelium (Figure 4b, c). The solid area contained fat, smooth muscles, hair follicles, sebaceous glands, eccrine glands, exocrine pancreas, cartilage, bone, and sero-mucinous salivary glands arranged in haphazard pattern (Figure 4a). The histology of the resected specimen had no immature cells and this led to a diagnosis of a mature teratoma of the mediastinum. Post-operative recovery was uneventful and the murmur disappeared following excision of the mass. Patient was discharged on post-operative day six and was well on subsequent clinical follow-up. Informed consent was taken from the patient prior publication and the consent form is available with the authors and publisher.

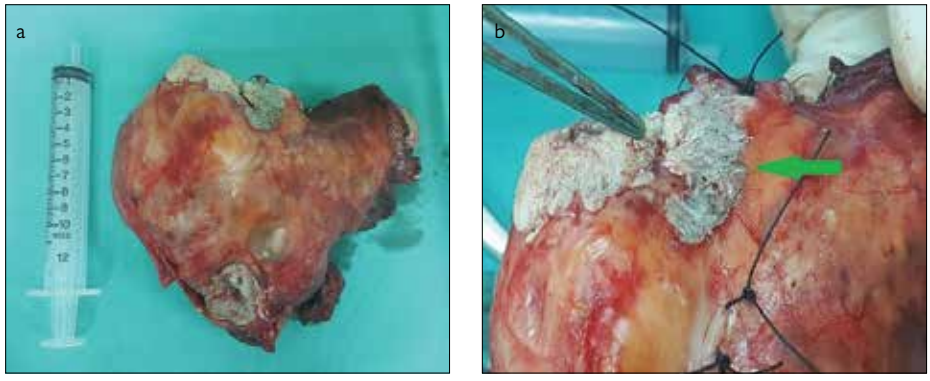

Figure 3. a, b. Gross specimen after excision of a cystic mass with presence of sebum, and hair (a), Close up view showing sebum and hair over the surfaces of the tumor (green arrow) (b)

Discussion

Pulmonary stenosis is defined as the constriction of the right ventricular outflow tract below, above, or at the pulmonary annulus which leads to an increase in right ventricular pressure [3]. The causes may be broadly divided into intrinsic (congenital) or extrinsic compression. Several known causes of extrinsic pulmonary stenosis are Hodgkin's disease, lymphoma, teratoma, lung carcinoma, pericardial sarcoma, thymoma, and chondrosarcoma of the sternum [4]. Including our case, only 15 cases of pulmonary stenosis because of extrinsic compression by a teratoma in the anterior mediastinum have been reported. All of the 15 cases reported in the literatures demonstrated a loud systolic murmur on presentation. Extrinsic compression of the pulmonary artery invariably leads to acute symptoms which differs from pulmonary stenosis due to congenital causes which may have a more prolong and chronic symptoms prior seeking medical attention. Other associated symptoms are exertional dyspnea, pleuritic chest pain with cough, and palpitations [1-7]. In the evaluation of such cases, chest roenterogram may be of great benefit. The presence of a mass on a chest roenterogram may aid the clinician in diagnosis and making necessary referrals to a cardiology center with cardiothoracic surgery backup. Transthoracic echocardiography is equally important to ascertain extrinsic pulmonary stenosis and identify any other related structural heart abnormalities [5]. CT of the thorax gives essential information for pre-operative planning, possibility of benign or malignant tumor, and any suspicious lymph node or invasion in the surrounding organs. Teratoma is a germ cell tumor composed of somatic tissue derived from two or three of the germ cell layers. Teratoma can be further classified as mature teratoma (adult-type tissue) and immature teratoma [8]. Microscopic examination of mature teratoma may demonstrate squamous epithelium, hair follicles, sebaceous sweat glands, smooth and striated muscle, respiratory epithelium, thymus, thyroid, intestines, bone, or cartilage tissue [1]. Patients with anterior mediastinal teratomas of the mature type, generally carries a good prognosis after complete resection of tumour. The majority of the systolic murmurs which occur due to the extrinsic compression disappears after complete excision of the teratoma [3]. Anterior mediastinal teratoma masquerading as valvular heart disease is of particular interest to clinicians, cardiologist, and surgeons alike because of its nature to mimic congenital valvular heart disease. This leads to frequent difficulty and errors in interpretation of physical signs and chest roenterograms of such cases [5]. Delay due to misinterpretation may lead to death in some cases of malignant disease as reported by Fry et al. [7]. Therefore it is of utmost

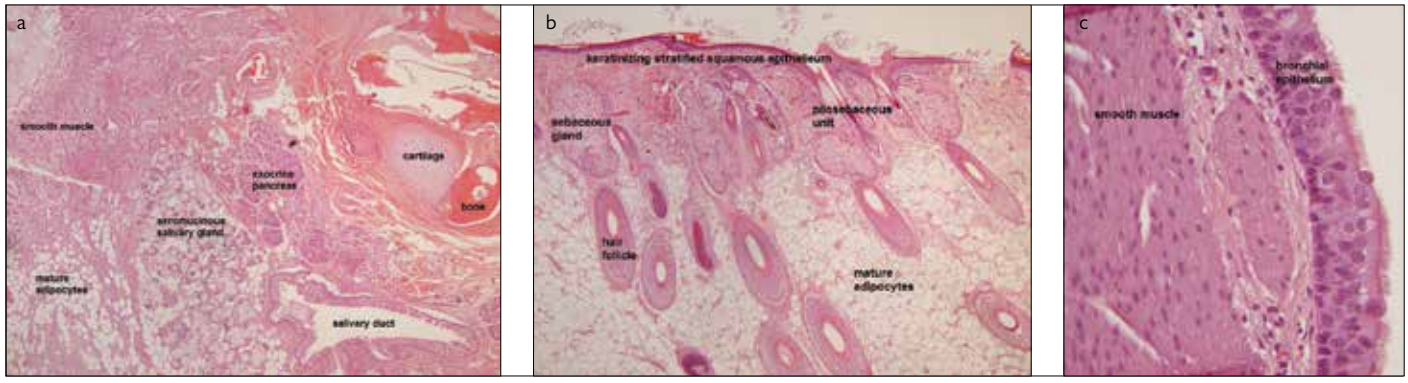

Figure 4. a-c. Microscopic examination showing mature components of smooth muscle, mature adipocytes, seromucinous salivary gland, salivary duct, exocrine pancreas, cartilage, and bone (a), Keratinizing stratified squamous epithelium, hair follicle, and sebacaeous gland (b), Bronchial epithelium (c)

importance to highlight such cases to increase the awareness among medical practitioners. In conclusion, extrinsic pulmonary artery stenosis due to anterior mediastinal teratoma is a rare phenomenon with only 15 cases reported till date. This case report highlights the awareness of anterior mediastinal teratoma which may mimic valvular heart disease with the presence of a systolic murmur. A simple chest roentero-gram revealing a suspicious mediastinal mass may aid in the diagnosis of such cases.

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Hydronephrosis due to a Migrated Intrauterine Device into the Ureter: A Very Rare Case

Ibrahim Halil Bozkurt, Ismail Basmaci, Tarik Yonguc, Ozgu Aydogdu, Mehmet Erhan Aydin, Ertugrul Sefik, Tansu Degirmenci

ABSTRACT

Intrauterine device (IUD) insertion is a long-acting and one of the most effective modes of reversible contraception. Complications that most commonly arise following IUD insertion are failed insertion, pain, vasovagal reactions, infection, menstrual abnormalities, and expulsion. In this paper, we present the case of a woman who experienced hydronephrosis due to the migration of IUD into the ureter after 30 years of insertion. To the best of our knowledge, this is the third such case reported in the literature.

Keywords: Intrauterine device, hydronephrosis, ureter migration

Introduction

Intrauterine device (IUD) insertion is a long-acting and one of the most effective modes of reversible contraception [1].

The most common complications of IUD insertion are failed placement, infection, pain, menstrual abnormalities, expulsion, and vasovagal reactions [2]. Rare complications of IUD insertion are embedment in the myometrium and perforation beyond the uterine serosa, with an incidence rate of 0.01% [2, 3].

Risk factors for uterine perforation are postpartum amenorrhea, breastfeeding, postpartum period less than 6 months, and inexperienced practitioners [3, 4]. Symptoms of IUD misplacement are abnormal vaginal bleeding and abdominal pain; however, at times, this complication may be asymptomatic [4, 5]. Intra-abdominal migration occurs very rarely and may result in injury to various structures [6].

We present a case of hydronephrosis due to the migration of IUD into the ureter after 30 years of insertion. To the best of our knowledge, this is the third such case reported in the literature.

Case Report

A 54-year-old woman presented with left-side flank pain, hematuria, and dysuria. IUD had been inserted 30 years prior to the presentation. Obstetric history (Gravida, Para 2 and Abortion 0) revealed that all labors were normal vaginal deliveries, and 6 months after the second delivery, an IUD was inserted for contraception.

The patient presented to our clinic with left-flank pain that had initiated 15 days prior to the presentation. She had no previous history of stone disease. A non-contrast-enhanced computed tomography (CT) scan was performed. CT imaging revealed left hydronephrosis due to intraluminal extension of a part of foreign material that looked like an IUD in the distal 1/3rd of the ureter (Figure 1).

Under general anesthesia, left ureteroscopy was performed. The ureteral mucosa was severely edematous and obstructive, and no foreign material could be seen in the lumen. Subsequently, open surgery with left inguinal incision was performed. The left ureter was isolated and IUD was

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Department of Urology, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey

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Correspondence to: Mehmet Erhan Aydin

E-mail: merhanaydin@gmail.com

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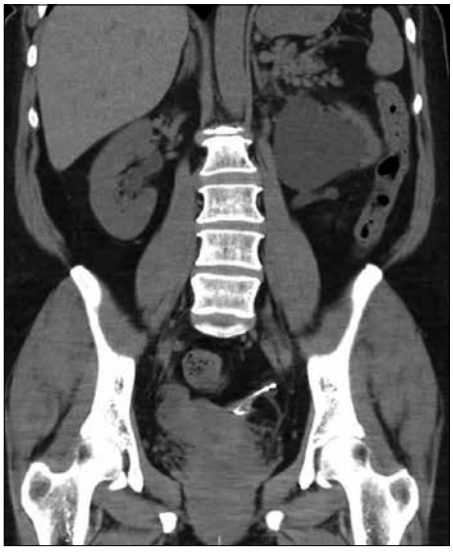

Figure 1. Intrauterine device migrated to the left ureter

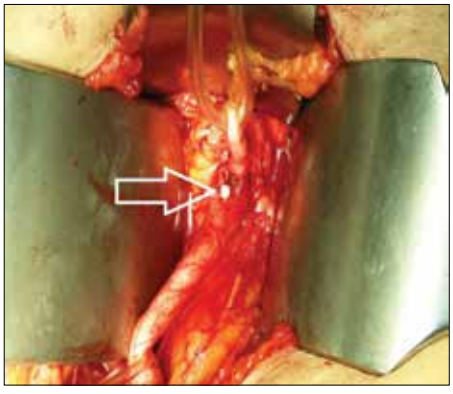

Figure 2. Intrauterine device (arrow)

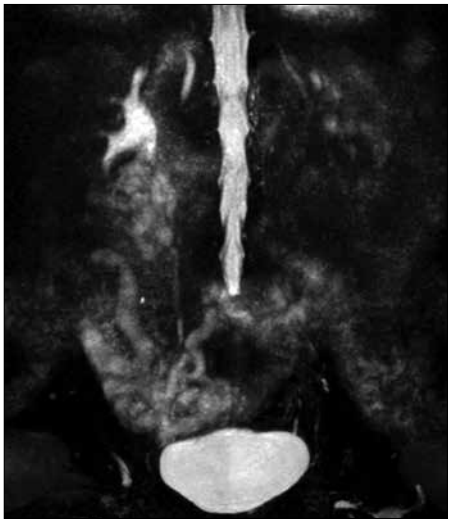

Figure 3. MR urography

palpated in the lumen. The ureteric wall was incised and IUD was extracted (Figure 2).

A JJ stent (Biorad Medisys, Bangalore, India) was inserted at the end of the operation. The postoperative period was uneventful. The patient was discharged at postoperative day 2. The JJ stent was extracted 6 weeks later. At the 1-year follow-up, the patient was evaluated with magnetic resonance urography (Figure 3). Hydronephrosis had disappeared, and no stricture was observed in the ureter.

Informed consent was obtained from the patient for the publication of this case report.

Discussion

Intrauterine device perforation mechanism has not been explained yet, and various theories pertaining to it exist [7].

The first theory states that perforation occurs when the device is placed and IUD is released beyond the uterine serosa. The second theory states that although IUD is placed correctly, transmural migration of IUD causes perforation. Finally, embedment may occur during placement and result in transmural migration and perforation.

Other rare complicationswere trans-tubal migration and trans-cervical perforation [8]. Symptoms of IUD misplacement are abnormal vaginal bleeding and abdominal pain; however, at times, this complication may be asymptomatic [4, 5]. Intra-abdominal migration very rarely occurs and may result in injury to various structures [6].

Complications resulting from uterine perforation include infection, abscess formation, bleeding, or perforation of other intraperitoneal organs, most often involving the bowel or bladder [9, 10]. Our patient presented with left-side flank pain that had initiated 15 days before admission to our clinic. A CT scan showed the migration of IUD into the ureter as the cause of hydronephrosis.

In conclusion, this case presents a very rare cause of hydronephrosis that should be kept in mind in the absence of other factors in women having undergone IUD insertion. The treatment should include surgery for the extraction of the device, and the patient should be followed up for a possible formation of ureteric stricture over the long term.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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Author Contributions: Concept - I.H.B., I.B.; Design - I.B., T.Y.; Supervision - I.B., T.D.; Resources - O.A., T.Y.; Materials - I.H.B., T.Y.; Data Collection and/or Processing - O.A., M.E.A., E.S.; Analysis and/or Interpretation - O.A., T.D., E.S.; Literature Search - M.E.A., I.H.B.; Writing Manuscript - M.E.A., I.B., T.D.; Critical Review - O.A., T.D., E.S.

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An Unusual Headache: Red Ear Syndrome

Ignazio La Mantia I[1], Claudio Andaloro[2]

A 4-year-old boy presented with a 2-year history of unilateral recurrent ear erythema (generally on the left ear) that was associated with episodic ear swelling, discomfort, and a burning sensation (Figure 1). These episodes occurred up to three times every month; each episode lasted for approximately 1 h and spontaneously resolved. Initially, the episodes were isolated, but during the last 6 months, they began to be associated with a migraine without aura simultaneous to ear redness. In the interval between two episodes, the patient had no problem. His perinatal history and childhood development were reportedly normal. Visual inspection results of the pinna and otoscopic examination results were bilaterally normal. The head and neck examination and allergological assessment were within normal limits as well as laboratory tests and a magnetic resonance imaging (MRI) of the brain. A neurological visit led to a diagnosis of idiopathic red ear syndrome (RES) being made. The patient started treatment with cetirizine for 2 weeks and showed a slight reduction in the frequency of attacks.

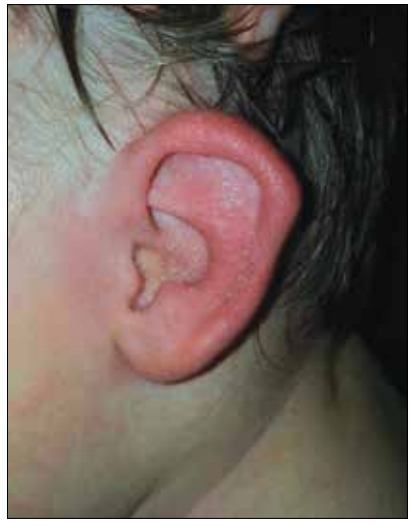

Figure 1. Red and slightly swollen left ear during an episode

Red ear syndrome is a rare entity characterized by paroxysmal unilateral or bilateral painful attacks to the external ear that are accompanied by ear redness, burning, or warmth. Swelling is rare [1]. RES episodes are generally isolated, but they can also occur with primary headaches as migraine among young patients or with trigeminal autonomic headaches among the elderly. Currently, there are no medications with approved efficacy. A study has proposed the use of gabapentin, amitriptyline, or non-steroidal anti-inflammatory drugs, but with poor results [2]. Familiarization with RES presentation symptoms is important to recognize this relatively new disease, thus avoiding delayed diagnosis and mistreatment.

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[1]Department of Medical Sciences, Surgical and Advanced Technologies, GF Ingrassia, University of Catania, Catania, Italy
[2]ENT Unit, Santa Marta e Santa Venera Hospital, Acireale, Catania, Italy

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Correspondence to: Claudio Andaloro

E-mail: cla.anda@gmail.com

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"Malignant" Chronic Constrictive Pericarditis

Ali Ayaon Albarrán, José Antonio Blázquez González, José María Mesa García

A 32-year-old woman who suffered from acute myopericarditis after an upper respiratory infection when she was 15 years old was diagnosed 4 years later with restrictive cardiomyopathy. Ten years later, she became symptomatic, with episodes of right-sided heart failure, lower extremity edema, hepatosplenomegaly, and mild ascites. Echocardiography revealed normal right and left ventricular function without tricuspid regurgitation but with severe dilation of both atrial chambers. Cardiac catheterization revealed the presence of the square root sign with equalization of right and left ventricular end-diastolic pressures, together with modest elevation in right ventricular systolic pressure (40 mmHg) and absence of respiratory variations. Finally, contrast-enhanced thoracic computed tomography revealed severe concentric pericardial calcification with partial infiltration of the myocardial free wall of the right ventricle with a maximum width of 10 mm (Figure 1, 2). The patient was finally diagnosed with constrictive pericarditis. Our multidisciplinary team decided to inform the patient to undergo cardiac transplantation.

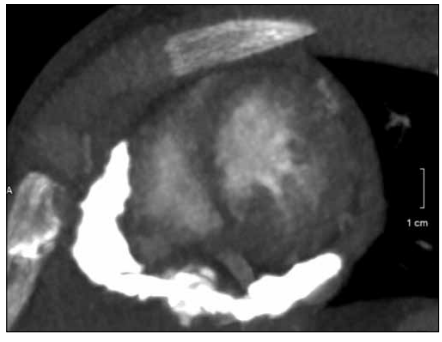

Figure 1. Sagittal contrast-enhanced thoracic computed tomography scan showing severe concentric pericardial calcification with partial infiltration of the myocardial free wall of the right ventricle with a maximum width of 10 mm

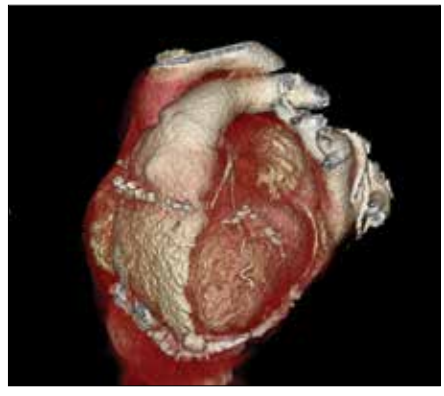

Figure 2. Volume rendering of the contrast-enhanced thoracic computed tomography scan. The red arrow shows the severe calcification of the myocardial free wall

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ORCID IDs of the authors:
A.A.A. 0000-0003-4879-077X;
J.A.B.G. 0000-0002-8502-660X;
J.M.M.G. 0000-0002-1785-7313.
Department of Adult Cardiac Surgery, La Paz University Hospital, Madrid, Spain

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Correspondence to: Ali Ayaon Albarrán

E-mail: ali.ayaon@salud.madrid.org

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