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RQ
Rheumatology Quarterly

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galenos yayınevi

AIMS AND SCOPE

The Rheumatology Quarterly is a peer-reviewed periodical journal that publishes quarterly (March, June, September, December) in English electronically. The journal publishes original contributions in the form of experimental and clinical research articles, case reports and litrerature review, reviews, news, letters to the editor and authors, as well as announcements related to all topics of rheumatology.

The Rheumatology Quarterly aims to constitute a current scientific discussion platform and archive in rheumatology with the contribution of the disciplines related to rheumatology together. The journal intends to share its experiences with the international scientific community in a prestigious way and provide an academic contribution to the development of rheumatology science.

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.

Title: The Rheumatology Quarterly

Journal abbreviation: Rheumatol Q

E-ISSN: 2980-1559

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INSTRUCTIONS TO AUTHORS

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Peer Review Process

The Rheumatology Quarterly uses an independent, unbiased, double-blind peer review process. Manuscripts are received and reviewed by the editor-in-chief, who directs them to the appropriate section editor. The section editor sends the manuscript to three independent referees. Referees are selected by the editorial board from among national and international experts in the area relevant to the study. The referees accept or reject the invitation to review the manuscript within two weeks. If they accept, they are expected to return their decision within 21 days. The associate editor reviews the referees' decisions, adds their own feedback, and returns the manuscript to the editor-in-chief, who makes the final decision. In case of disagreement among referees, the editor can assign a new referee.

The editor-in-chief, associate editors, biostatistics consultant, and English language editor may make minor changes to accepted manuscripts before publication, provided they do not fundamentally change the text.

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.

All submissions must be accompanied by a signed statement of scientific contributions and responsibilities of all authors and a statement declaring the absence of conflict of interests. Any institution, organization, pharmaceutical or medical company providing any financial or material support, in whole or in part, must be disclosed in a footnote (ICMJE Disclosure Form for Potential Conflict of Interest(s)).

The manuscript format must comply with the ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2018).

The presentation of the article types must be designed in accordance with trial reporting guidelines:

Human research: Helsinki Declaration as revised in 2013

Systematic reviews and meta-analyses: PRISMA guidelines

Case reports and litrerature review: The CARE case report guidelines

Clinical trials: CONSORT

Animal studies: ARRIVE and Guide for the Care and Use of Laboratory Animals

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GENERAL RULES

SUBMISSION REQUIREMENTS

- Cover Letter,
- "ICMJE Conflict of Interest Statement Form" (http://www.icmje.org/conflicts-of-interest/) for all contributing authors,
- A separate title page (Title Page should be submitted with all manuscripts and should include the title of the manuscript, name(s), affiliation(s), major degree(s) and ORCID ID of the author(s). The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be clearly listed. Grant information and other sources of support should also be included. Individuals who contributed to the preparation of the manuscript but did not fulfil the authorship criteria should also be acknowledged in the title page),
- Abstract divided into appropriate sections,
- Keywords (For indexing purposes, a list of 4–8 key words in English is essential),
- Article divided into appropriate sections,
- List of references styled according to "journal requirements",
- A blinded main text (Please exclude all information that may indicate an individual or institution from the main document to ensure a blinded review process),
- The Copyright Agreement and Acknowledgement of Authorship form (Please submit a wet-signed and scanned copy of the Copyright Transfer Form with your submission),
- Upload your title page and forms in the system to Potential Conflict of Interest category to ensure a blinded review process,
- Figures (Figures should be submitted as standalone images through the submission system in .JPG or .TIFF format),
- Ethics Committee Approval Statement (with decision/file no, date and name of the institution, for original articles).

Abstract

The research articles should consist of Objectives, Methods, Results and Conclusion sections and should not exceed 250 words. At least 3, a maximum of 6 keywords should be determined on the Abstract page, and the title of the article should be added.

Main Text

The introduction should consist of the Patients / Materials and Methods, Results, Discussion and References sections. Abbreviations should be standard and should be explained in parentheses when they are used first. Internationally accepted units should be used in the measurements.

Tables, Figures and Images

It should be numbered in the order of use in the text, and unnecessary use should be avoided. In the photographs used in the cases, permission should be obtained, and necessary measures should be applied to prevent recognition. Attention should be paid to the quality of photographs and drawings, if any. Editorial Board may request correction or renewal in tables, figures and pictures on the grounds that it is not of sufficient quality. Figures and pictures must be original. For the pictures, figures and graphics used in another publication to be published in our journal, the necessary permissions must be obtained by the authors and before applying for an article. A copy of the document indicating that the permit has been obtained must be sent to the journal with the article.

References

References should be selected from the ones that are up to date and necessary for the article. References in the text should be indicated in parentheses and numbered

according to the order of use. The name of the journals should be abbreviated in accordance with PubMed rules, and abbreviations should not be used in the names of journals which are not included here. Citation of proceedings should be avoided. Manuscripts accepted by a journal but not yet published can be documented as required and used as a source. Information other than this, including unaccepted articles, can be used by stating "unpublished observation" in the article. References should be written according to the examples below, and all the authors should be presented in references up to 6 authors, references which have more authors should be arranged in a way that "et al." abbreviation will be placed at the end of the first three authors. The responsibility for the accuracy of the references belongs to the authors.

Examples:

Periodical publication example:

Wolfe F, Hawley DJ, Cathey MA. Termination of slow-acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.

Example of periodical publication published in an online journal:

Yurdakul S. Is there a higher risk of infection with anti-TNF-alpha agents, or is there a selection bias? Lett Ed Rheumatol 1(1):e110006. doi:10.2399/ler.11.0006

Example of book section:

Buchanan WW, Dequeker J. History of rheumatic diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Edinburgh: Mosby; 2003:3-

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,

• Name(s), affiliations and major degree(s) of the author(s)

• Grant information and detailed information on the other sources of support,

• The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author,

• Acknowledgement of the individuals who contributed to the preparation of the manuscript but do not fulfil 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 (Aim, Materials and Method, Results and Conclusion).

Keywords: Each submission must be accompanied by a minimum of three and a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations.

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 (with subheadings), Results, Discussion, Study Limitations, Conclusion subheadings.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with the 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 statistical software that was used the process must certainly be specified. Data must be expressed as mean±standard deviation when parametric tests are used to compare continuous variables. Data

INSTRUCTIONS TO AUTHORS

must be expressed as median (minimum-maximum) and percentiles (25th and 75th percentiles) when non-parametric tests are used. In advanced and complicated statistical analyses, relative risk (RR), odds ratio (OR) and hazard ratio (HR) must be supported by confidence intervals (CI) and p values.

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

Review Articles: Reviews which are prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into high volume of publication and higher citation potential are taken under review. The authors may be invited by the journal. Reviews should be describing, discussing and evaluating the current level of knowledge or topic used in the clinical practice and should guide future studies. Please check Table 1 for limitations for Review Articles.

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

Letters to the Editor: This type of manuscripts can discuss important parts, overlooked aspects or lacking parts of a previously published article. Articles on the subjects within the scope of the journal that might attract the readers' attention, particularly educative cases can also be submitted in the form of "Letter to the Editor". Readers can also present their comments on the published manuscripts in the form of "Letter to the Editor". Abstract, Keywords, Tables, Figures, Images and other media are not included. The text should be unstructured. The manuscript that is being commented on must be properly cited within the manuscript.

Images: Authors can submit for consideration an illustration and photos that is interesting, instructive, and visually attractive, along with a few lines of explanatory text. Images can include no more than 200 words of text. No abstract, discussion or conclusion are required but please include a brief title.

Table 1: Limitations for each manuscript type.

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	200 (Structured)	50	6	7 or total of 15 images
Review Article	5000	200	50	6	10 or total of 20 images
Case reports and litrerature review	1500	200	10	No tables	10 or total of 20 images
Letter to the Editor	500	N/A	5	No tables	No media
Scientific letter	900	N/A	10	No tables	2 or total of 4 images
Clinical Imaging/Visual Diagnosis	400	N/A	5	No tables	3 or total of 6 images
History	900	N/A	10	No tables	3 or total of 6 images

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REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author, and their publication approval is requested within two days of their receipt of the proof.

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Out of respect to the reviewers, journal staff and the Editorial Board, authors are asked to submit a withdrawal request only if the reasons are compelling and unavoidable. Withdrawal requests should be submitted in written form, signed by all contributing authors of the manuscript. Reasons for withdrawal should be stated clearly. Each request will be subject to the Editorial Board's review and manuscripts will only be assumed withdrawn upon Editorial Board's approval. Cases of plagiarism, authorship disputes or fraudulent use of data will be handled in accordance with COPE guidelines.

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INSTRUCTIONS FOR REVIEWERS

Please structure your review using the following headings:

A brief summary of manuscript:

• What is the intent of the study?

• What conclusions do the authors reach?

• Do you believe this study has previously been published in whole or in part?

The Title

• Does the title adequately reflect the content of the manuscript?

Keywords

• Are the keywords appropriate?

The Abstract

• Is it structured?

• Does the Abstract adequately summarize the manuscript?

• Can the Abstract be understood without reading the manuscript?

• Does it specify outcome measures, and provide salient statistics?

• Do any discrepancies exist between the Abstract and the rest of the paper?

The Introduction

• Is the Introduction brief?

• Is the rationale for conducting the study explained based on a review of the medical literature?

• Is the purpose of the study clearly defined? Is there a well-described hypothesis?

Materials and Methods

• Is the design of the methods appropriate to allow the hypothesis to be tested?

• Could another investigator reproduce the study using the Methods as outlined?

• Is the sample or participant recruitment described in detail with the inclusion and exclusion criteria?

• Have the authors obtained Informed Consent and Ethical Committee Approval (if relevant)?

• Do the authors specify the data acquisition and evaluation (e.g., the index test, the reference standard)?

• Are the statistical methods described? Are they appropriate?

Results

• Are the Results clearly explained?

• Is the order of presentation of the Results parallel the order of presentation of the Methods?

• Are the Results convincing and reasonable?

• Are there any Results given that are not preceded by an appropriate discussion in the Methods?

Discussion

• Is the Discussion concise?

• Does it begin with the most important finding and summarize key results?

• Does it relate exclusively to the results of the study?

• Does it compare the results with the relevant literature?

• Are the conclusions justified by the results found in the study?

• Are the unexpected results explained sufficiently?

• Is the clinical applicability of the study findings discussed?

• Are the limitations of the study clearly stated?

Figures and Graphs

• Are all figures referred to in the text?

• Are the figures and graphs correct and appropriately labeled?

• Is the number of Figures within the limitations of the Journal?

(Please check out Table 1 on the Instructions to Authors page)

• Do the figures and graphs adequately show the important results?

INSTRUCTIONS FOR REVIEWERS

• Do arrows need to be added to depict important or subtle findings?

• Are the figure legends self-sufficient and understood without making reference to the remainder of the manuscript?

Tables

• Do the tables appropriately describe the Results?

• Are the abbreviations used in the tables explained at the bottom?

References

• Does the reference list follow the style for the Journal?

• Is the number of references within the limitations of the Journal? (Please check out Table 1 on the Instructions to Authors page)

• Does the reference list contain obvious mistakes?

• Do any important references need to be added?

Final appraisal and decision

• Please summarize the Major strengths and Major weaknesses of the manuscript, and make your decision according to your answer to the following questions;

1. Does the article provide novel information (data, techniques, or idea) that is not already available in the literature?

If **yes,** please describe what you believe is new.

If **no,** ask the authors to explain what they consider new in their work. Otherwise, unless the paper has something else extremely important to present, the manuscript should likely be rejected.

2. Do the authors provide a solid rationale for conducting this study? If no, then the manuscript should likely be rejected.

3. Has the data analysis been performed appropriately?

If no, then the manuscript should likely be rejected, or major revisions should be requested.

4. Have the results been clearly and accurately presented? If no, then a major revision should likely be requested.

5. If the article is scientifically acceptable, but the text is poorly written, then a minor revision should likely be requested.

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- A 'biology-first' approach to drug discovery[2]

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Reference: 1. AMGEN Fact Sheet. C2020. Accessed 25/3/2020. Available from https://www.amgen.com/about/quick-facts/ **2.** AMGEN Our Strategy. C2017. Accessed 6/4/2020. Available from https://www.theamgendifference.com/our-strategy.html

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*Efficacy was shown in disease symptoms that are important for patients with AS or nr-axSpA with VERXANT.
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AS=Ankylosing spondylitis; nr-axSpA=Axial spondyloarthritis without radiographic evidence.

References:
1. Verxant® (secukinumab) Summary of Product Characteristics. 2. Marzo-Ortega H, et al. Lancet Rheumatol. 2020;2: e339-48. 3. Deodhar A et al. Arthritis Rheumatol. 2021;73(1):110-120. 4. Baraliakos X, et al. RMD Open. 2019;5(2):e001005. 5. Deodhar A, et al. Arthritis Res Ther. 2019;21(1):111. 6. Schreiber S, et al. Ann Rheum Dis. 2019;78(4):473-479. 7. Marzo-Ortega H, et al. The Lancet Rheumatology. 2020 June;2(6):e339-e348. 8. Novartis data on file. Arsiv 2021.

▼This medicinal product is subject to additional monitoring. This triangle will ensure that new safety information is quickly identified. Reporting ensures continuous follow-up of risk-benefit ratio of this medicine. Healthcare professionals are expected to report the suspected adverse reactions to Turkish Pharmacovigilance Center (TUFAM www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0312 218 30 00, 0800 314 00 08; fax: 0312 218 35 99) and/or related pharmaceutical company officials.

Verxant® (Secukinumab) Basic Succinct Statement (BSS) Important note: Before prescribing, consult full prescribing information. Presentation: Lyophilised powder for solution for subcutaneous injection in a vial containing 150 mg of secukinumab. Indications: Plaque psoriasis: Verxant is indicated for the treatment of moderate to severe plaque psoriasis in adults who fail to respond to, or who have a contraindication to, or are intolerant to conventional systemic therapies including ciclosporin, methotrexate and PUVA. Psoriatic arthritis: Verxant, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease modifying anti rheumatic drug therapy has been inadequate. Ankylosing spondylitis: Verxant is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. Axial spondyloarthritis without radiographic evidence (nr-axSpA): VERXANT is indicated for the treatment of adult patients with axial spondyloarthritis who respond inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), have high C-reactive protein (CRP) levels and/or objective signs of inflammation evidenced by magnetic resonance imaging (MRI) without active radiographic evidence. Dosage and administration: Plaque psoriasis: The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg. For some patients, a dose of 150 mg may be acceptable. Psoriatic arthritis: For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg. For other patients, the recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg. Ankylosing spondylitis: The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. In patients with inadequate response (in patients with ongoing active ankylosing spondylitis), the dose can be increased to 300 mg. Each 300 mg dose is given as two subcutaneous injections of 150 mg. Axial spondyloarthritis without radiographic evidence (nr-axSpA): The recommended dose is 150 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Contraindications: Verxant is contraindicated in patients who have/had severe hypersensitivity reactions to the active substance or to any of the excipients and in patients who have clinically important, active infection (e.g. active tuberculosis). Warnings and precautions: Infections: Caution should be exercised when considering the use of Verxant in patients with a chronic infection or a history of recurrent infection. If a patient develops a serious infection, the patient should be closely monitored and Verxant should not be administered until the infection resolves. Anti-tuberculosis therapy should be considered prior to initiation of Verxant in patients with latent tuberculosis. Verxant should not be given to patients with active tuberculosis. Inflammatory bowel disease: Caution should be exercised when prescribing Verxant to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis. Patients should be closely monitored. Hypersensitivity reactions: Rare cases of anaphylactic reactions have been observed during clinical trials. Administration of Verxant should be discontinued immediately and appropriate therapy initiated if an anaphylactic or other serious allergic reaction occurs. Vaccinations: Verxant should not be given concurrently with live vaccines. Pregnancy: Category C Breast-feeding: Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Verxant must be made taking into account the benefit of breast-feeding to the child and the benefit of Verxant therapy to the woman. Adverse drug reactions: Very common (≥1/10): Upper respiratory tract infections. Common (≥1/100 to <1/10): Oral herpes, rhinorrhea, diarrhoea. Uncommon (≥1/1,000 to <1/100): Oral candidiasis, tinea pedis, otitis externa, neutropenia, conjunctivitis, urticaria. Rare: Anaphylactic reactions Interactions: Live vaccines should not be given concurrently with Verxant. Overdose: In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately. Contents of container: Verxant is supplied in a colourless glass vial with a grey coated rubber stopper and aluminium cap with a white flip-off component containing 150 mg of secukinumab. Storage: Store in a refrigerator (2°C - 8°C). Shelf Life: 3 years. After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. 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▼ This medicinal product is subject to additional monitoring. This triangle will allow quick identification of new safety information. Healthcare professionals are encouraged to report suspected adverse reactions to TÜFAM (Turkish Pharmacovigilance Center).

ACR20 = American College of Rheumatology 20% improvement criteria; cDMARD = conventional disease-modifying antirheumatic drug; DAS28-hsCRP = Disease Activity Score for 28 joints with high sensitivity C-reactive protein; IR = inadequate responder; JAK = janus kinase; LTE = long-term extension; MTX = methotrexate; RA = rheumatoid arthritis; SDAI = Simplified Disease Activity Index.

References: 1. Taylor PC et al. N Engl J Med 2017;376:652–62 (including supplementary appendix). 2. UNAMITY®, SmPC 2022. 3. Smolen JS et al. Rheumatology (Oxford) 2021;60:2256–66. 4. Taylor PC et al. Ann Rheum Dis 2021 Oct 27;annrheumdis-2021-221276. doi: 10.1136/annrheumdis-2021-221276.

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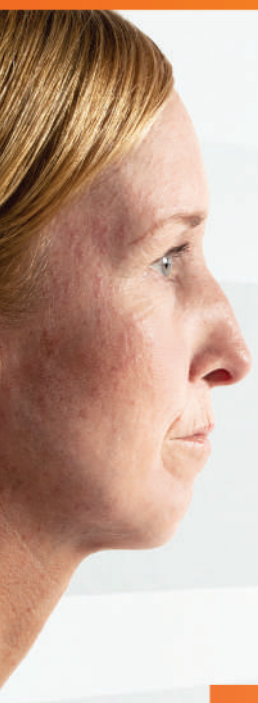

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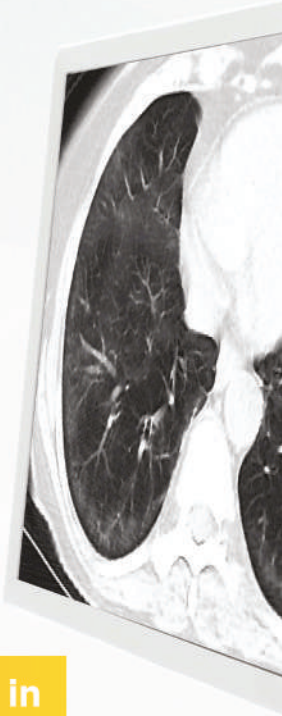

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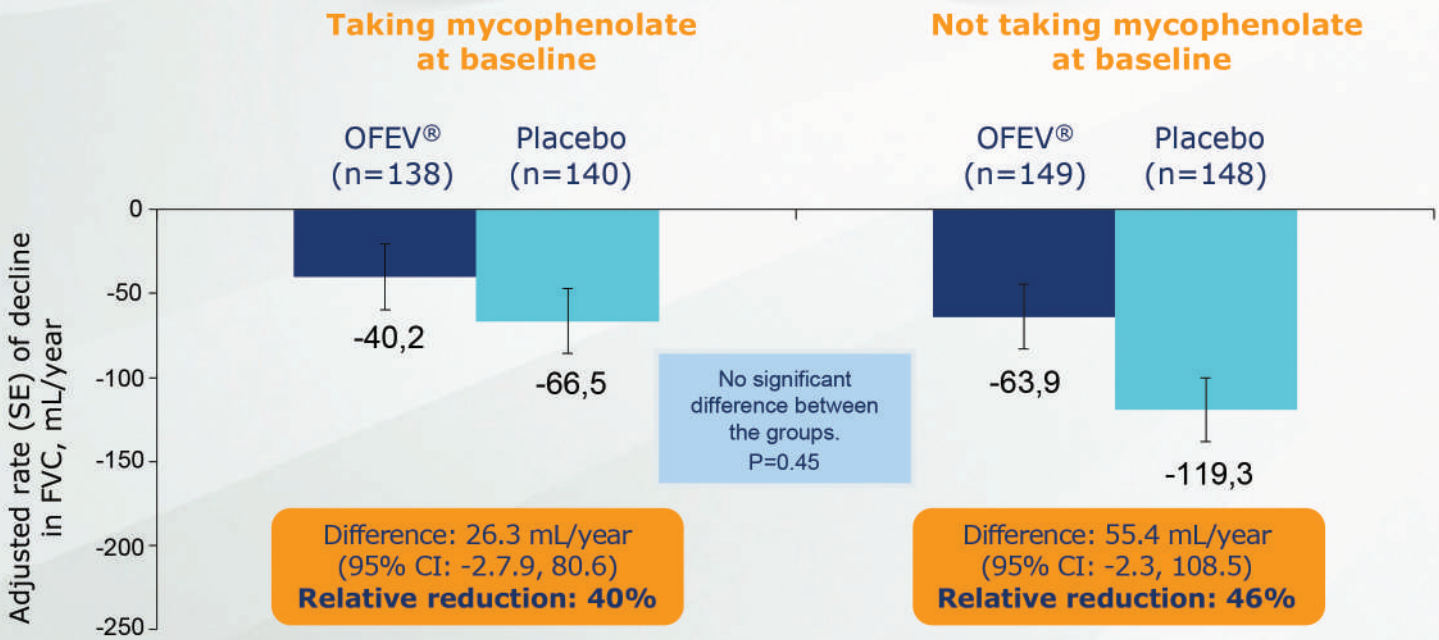

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References: 1. Strand V ve ark. Arthritis Res Ther. 2020 Oct 15;22(1):243. 2. Cohen SB ve ark. RMD Open 2020;6:e001395. 3. Xeljanz® XR Kısa Ürün Bilgisi.

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REVIEW

Rheumatology Quarterly

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Rheumatology Quarterly 2023;1(2):33-8

SCLERODERMA RENAL CRISIS

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Abstract

Systemic sclerosis (SSc), also known as scleroderma, is a disease that can affect many tissue and organ systems. Contrary to expectations, SSc can also frequently affect the kidneys. Most renal involvements are in the form of asymptomatic proteinuria and elevated creatinine levels. Scleroderma renal crisis (SRC), which is one of the mortal clinical findings of SSc, is rarely seen. The diffuse skin involvement subtype of SSc, early stage of the disease (first 4 years), anti-RNA-polymerase III antibody positivity, and corticosteroid use are risk factors for SRC. Angiotensin-converting enzyme inhibitor (ACEi) is used for treating SRC. For this reason, a close follow-up of patients with high risk of SRC is recommended because early initiation of treatment increases the chance of success. In the prophylactic use of ACEi, the prognosis may be worse since the clinical manifestations of SRC are suppressed, and the diagnosis of SRC is delayed, and thus SRC treatment is delayed (ACEi are used in higher doses in treatment). Angiotensin receptor blockers and iloprost are alternatives to ACEi in SRC treatment. The decision for renal transplantation should not be rushed in patients treated for SRC, as renal function may return late.

Keywords: Systemic sclerosis, renal involvements, scleroderma renal crisis

INTRODUCTION

Systemic sclerosis (scleroderma, SSc) is a chronic autoimmune/inflammatory disease characterized by fibrosis the skin and internal organs. Although the prevalence of SSc may show significant differences in relation to ethnic and regional factors, it varies between 30 and 240 per million. The disease is most commonly seen between the ages of 30 and 50 and the female/male ratio is 8-9/1 (1-3). In a study conducted in the Edirne region, the prevalence of SSc was determined to be 110 per million in our country (4). Immune activation, vasculopathy, oxidative stress, and subsequent increased fibroblastic activation are considered to be the basic steps in the pathogenesis of SSc. Activated fibroblasts (myofibroblasts) produce many pro-fibrotic cytokines and growth factors, along with the production of extracellular matrix main structures. Episodic vasospasm in the vascular bed and fibrointimal proliferation that occur in the later stages contributes to tissuing damage by causing ischemia/hypoxia in the tissues. Because of these events, structural and functional problems occur in the skin and visceral organs (lung, kidney, gastrointestinal system, and heart) with diffuse fibrosis (5,6). Although the clinic of the patients is shaped according to the severity of the skin and internal organ involvement, the first complaints and findings often nonspecific. Weakness, fatigue, joint pain, and morning stiffness is common nonspecific complaints. The Raynaud phenomenon (RF) is the earliest manifestation of SSc and may occur years before the disease develops. RF is characterized by triphasic color changes consisting of pallor, cyanosis, and erythema triggered by cold and emotional stress in the extremities of the body, especially in the hands and feet. The first specific finding in SSc is swelling and hardening

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of the skin of the hands and fingers. The clinical course after this stage is highly variable. Patients may present with dyspnea, cough, arthralgia/arthritis, dental problems, gastroesophageal reflux, dysphagia, or sexual problems depending on the organ involved and the severity of involvement, as well as skin findings such as RF, digital ulcer/gangrene, itching, and dryness (5,6).

According to the clinical findings of scleroderma, it is divided into two subgroups: localized and systemic. In localized forms, unlike SSc, there is no RF, autoimmune markers, or visceral involvement. SSc with diffuse cutaneous involvement (dcSSc) and SSc with limited cutaneous involvement (lcSSc), which are the most common systemic forms encountered in the clinic, are mainly differentiated according to the localization and extent of skin involvement and differ from each other in many aspects (3,7). In lcSSc, skin involvement is present on the face and distal parts of the knees and elbows, whereas the proximal trunk and extremities are not involved. In lcSSc, internal organ involvement is less common than dcSSc or occurs latter. Common clinical findings of lcSSc are calcinosis, RF, esophageal dysmotility, sclerodactyly, and telangiectasia, and these findings are also called calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome. In addition, pulmonary arterial hypertension (PAH) without interstitial lung disease (ILD) is an important complication of lcSSc. Anti-centromere antibody positivity is frequently found in lcSSc and its prognosis is better than dcSSc (5,6). In dcSSc, skin involvement progresses to the proximal extremities and trunk. Unlike lcSSc, the time between the RF and the onset of the skin involvement is shorter. In these patients, anti-centromere antibody was negative and anti-topoisomerase-I (anti-Scl-70) antibody was positive. In dcSSc, internal organ involvement is more common and the prognosis is worse. It may lead to ILD and/or PAH in the lung. In addition to these, scleroderma renal crisis (SRC), gastrointestinal findings, and digital vasculopathies constitute serious problems (5,6). Skin findings play a key role in the diagnosis of SSc. The patient has a typical facial appearance. Facial mimic lines disappear, radial lines appear around the mouth, mouth opening decreases (tapir mouth appearance), the nose becomes sharper, and teeth due to atrophy in the gums become visible. In addition, hypo- and hyperpigmented areas of the skin, telangiectasias, calcinoses, and ulcerated areas on bone protrusions may occur in the later stages. The diagnosis of SSc can be made easily in patients with typical skin and visceral organ involvement. American College of Rheumatology diagnosis/classification criteria are used in diagnosis. However, these criteria are insufficient in diagnosing patients presenting with early RF, edematous skin involvement, and mild skin hardness. In such cases, autoantibodies (anti-nuclear antibody, anti-centromere, and anti-Scl-70 antibodies) and typical nail bed capillaroscopy findings (giant capillaries, microhemorrhages, avascular areas, “droup out” sign and neovascularization) guide us and enable us to make an early diagnosis (2).

RENAL INVOLVEMENT IN SCLERODERMA

It is stated that more than half of SSc patients have asymptomatic renal involvement (such as proteinuria, elevated creatinine level and hypertension). In the autopsy series, 60-80% of SSc patients have renal pathologies. On the other hand, the presence of renal involvement is one of the indicators of poor prognosis in SSc patients (8-10). SRC is a well-known and rare form of renal involvement of SSc. Mild proteinuria and renal failure are more common examples of renal involvement in SSc. In addition, membranous glomerulonephritis and renal failure associated with anti-neutrophil cytoplasmic antibody (ANCA) positivity (crescentic glomerulonephritis) are other rare examples of renal involvement that can be seen in SSc. Proteinuria is one of the mortality risk factors in SSc patients. In patients with overt proteinuria, lupus serology should be studied. Systemic lupus erythematosus (SLE) may anti-dsDNA positive without clinical signs and may be associated with proteinuria in SSc. In SSc, we rarely encounter patients with proteinuria more than 1 g/day. However, it should be known that 17.5% of the patients have proteinuria and 25% have albuminuria (10). Albuminuria is associated with long disease duration and high blood pressure in SSc. Angiotensin-converting enzyme inhibitor (ACEi) therapy in proteinuria seen in SSc can reduce the amount of proteinuria, as in other proteinuria-causing diseases. ANCA positivity can be rarely seen (9%) in SSc patients. Slow-progressing renal failure and glomerulonephritis symptoms can be seen in ANCA-positive SSc patients, and unlike SRC, blood pressure does not elevate. ANCA positivity is seen more frequently in the lcSSc subtype, and clinical findings that may be associated with ANCA positivity occur in the late stages of the disease. On the other hand, SRC occurs in the dcSSc subtype and in the early years of the disease (8,11,12).

SCLERODERMA RENAL CRISIS

SRC is a mortal complication of SSc. Although its frequency has decreased recently, it is seen at a rate of 4% in dcSSc and 1% in sSSc (7). SRC usually occurs within the first 4 years of the onset of the disease. SRC manifests itself with sudden elevation of blood pressure and deterioration in kidney function (Table 1). In these patients, findings such as hyperreninemia, microangiopathic hemolytic anemia, thrombocytopenia, heart failure, pulmonary edema, hypertensive encephalopathy, and retinopathy can be

Table 1. Diagnostic criteria and supporting evidence were determined in the set of classification criteria for scleroderma renal crisis UKSSG 2016 (13)

Diagnostic criteria (essential)	Supportive evidence (desirable)
1. High blood pressure a. New onset BP >150/85 mmHg b. Increase ≥20 mmHg from usual systolic BP **2. Acute kidney failure** a. >50% increase in serum creatinine from stable baseline b. Increase of 0.3 mg/dL in serum creatinine level	- Microangiopathic hemolytic anemia, thrombocytopenia, and biochemical findings of hemolysis. - Accelerated hypertension on retinal examination microscopic hematuria. - Oliguria or anuria pulmonary oedema. - Renal biopsy: onion skin proliferation within the walls of intrarenal arteries and arterioles, fibrinoid necrosis, glomerular shrinkage.

BP: Blood pressure, UKSSG: UK Scleroderma Study Group

seen (8,13). Blood pressure usually high in SRC. However, at a rate of 10%, blood pressure can be found to be normal due to previous antihypertensive drug use or myocardial involvement. This situation is called normotensive renal crisis (14). It is thought that excessively elevated renin in patients with SRC changes perfusion in the juxtaglomerular apparatus, leading to renin-mediated hypertension, which may be a factor in the development of SRC. In renal histopathology, ischemic changes in glomeruli and proliferative occlusive vessel pathologies in arterioles (nested "onion membrane" appearance) can be observed in renal histopathology in SRC (10).

DIAGNOSIS

For the diagnosis of SRC, new-onset blood pressure (arterial blood pressure >160/100 mmHg), presence of fragmented erythrocytes in peripheral blood, elevated creatinine, and presence of proteinuria are sought. The major risk factors for developing SRC are the early stage of the disease, dcSSc subtype, and the history of corticosteroid use. Roughly 80% of SRC is observed within the first 4 years of the disease (8,15). Similarly, using ≥15 mg/day prednisone in the last 6 months increases the risk of SRC from 12% to 36% (13). Therefore, the blood pressure and renal functions of SSc patients who need to use corticosteroids should be closely monitored (16). In addition, anti-RNA polymerase III antibody positivity (8,17), high serum CD147 (18), high skin score, joint contracture, tendon friction sound, *HLA-DRB1*0407*, and **1304* presence are other risk factors for SRC in SSc patients (19) (Table 2).

Table 2. Risk factors for scleroderma renal crisis

1. Subtype with diffuse skin involvement
2. Rapid progression of skin involvement
3. Disease duration <4 years
4. New cardiac event: pericarditis and left ventricular failure
5. New-onset anemia
6. Anti-RNA-polymerase III antibody positivity
7. Using corticosteroids (>15 mg/day) in the last 3 months
8. Using cyclosporine in the last 3 months

DIFFERENTIAL DIAGNOSIS

SRC causes rapidly progressive renal failure and high blood pressure. Diseases such as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, renal artery stenosis, and toxic nephropathy should be kept in mind in the differential diagnosis of SRC (Table 3). SSc patients may have anti-dsDNA antibody positivity without SLE and ANCA test positivity without vasculitis findings. However, the possibility of renal involvement is high in patients with SSc positive for these antibodies. It is necessary to pay attention to the distinction between renal involvement and SRC in an ANCA positive SSc patient (Table 4). ANCA positivity occurs in the lcSSc subtype after many years of SSc diagnosis. However, SRC is common in the dcSSc subtype and in the first years of SSc diagnosis. While corticosteroids are used for treating renal involvement associated with ANCA positivity, ACEi is ineffective. In contrast, ACEi is used in the treatment of SRC and corticosteroid is one of the risk factors of SRC (10,20).

Table 3. Diseases to be considered in the differential diagnosis of scleroderma renal crisis

1. Renal artery stenosis
2. Thrombotic thrombocytopenic purpura (TTP)
3. Atypical hemolytic uremic syndrome (aHUS)
4. Rapidly progressive (crescentic) glomerulonephritis (RPGN)
5. ANCA-associated vasculitis
6. Toxic nephropathy
7. Transplant rejection

ANCA: Anti-neutrophil cytoplasmic antibody

TREATMENT

SRC is an emergency that requires hospitalization and close monitoring and treatment (Figure 1). Treatment of SRC should be carried out in specific centers because mortality due to SRC is still quite high in centers that do not specialize in this disease (8). ACEi

Table 4. Comparison of scleroderma renal crisis and ANCA-associated vasculitis

Scleroderma renal crisis	ANCA-associated vasculitis
Occurs mainly in dcSSc and only rarely (1-2%) in lcSSc	Occurs mainly in lcSSc
Patients develop SRC within 7.5 months to 4 years of SSc onset	Typically occurs several years after SSc onset
Malignant hypertension (seen in less than 10% of normotensive SRC)	Mild hypertension
Anti-RNA polymerase III positive	ANCA positive
Acute renal failure and severe hypertension	The subacute presentation with progressive renal failure (crescentic glomerulonephritis)
Steroids (≥15 mg/day) are one of the major risk factors	Responsive to steroids
ACEi as the first-line treatment in SRC	Does not respond to ACEi. Cyclophosphamide (or rituximab) and corticosteroids are used in the treatment

ANCA: Anti-neutrophil cytoplasmic antibody, dcSSc: Diffuse cutaneous systemic sclerosis, SSc: Systemic sclerosis, lcSSc: limited cutaneous systemic sclerosis, SRC: Scleroderma renal crisis, RNA: Ribonucleic acid, ACEi: Angiotensin-converting enzyme inhibitors

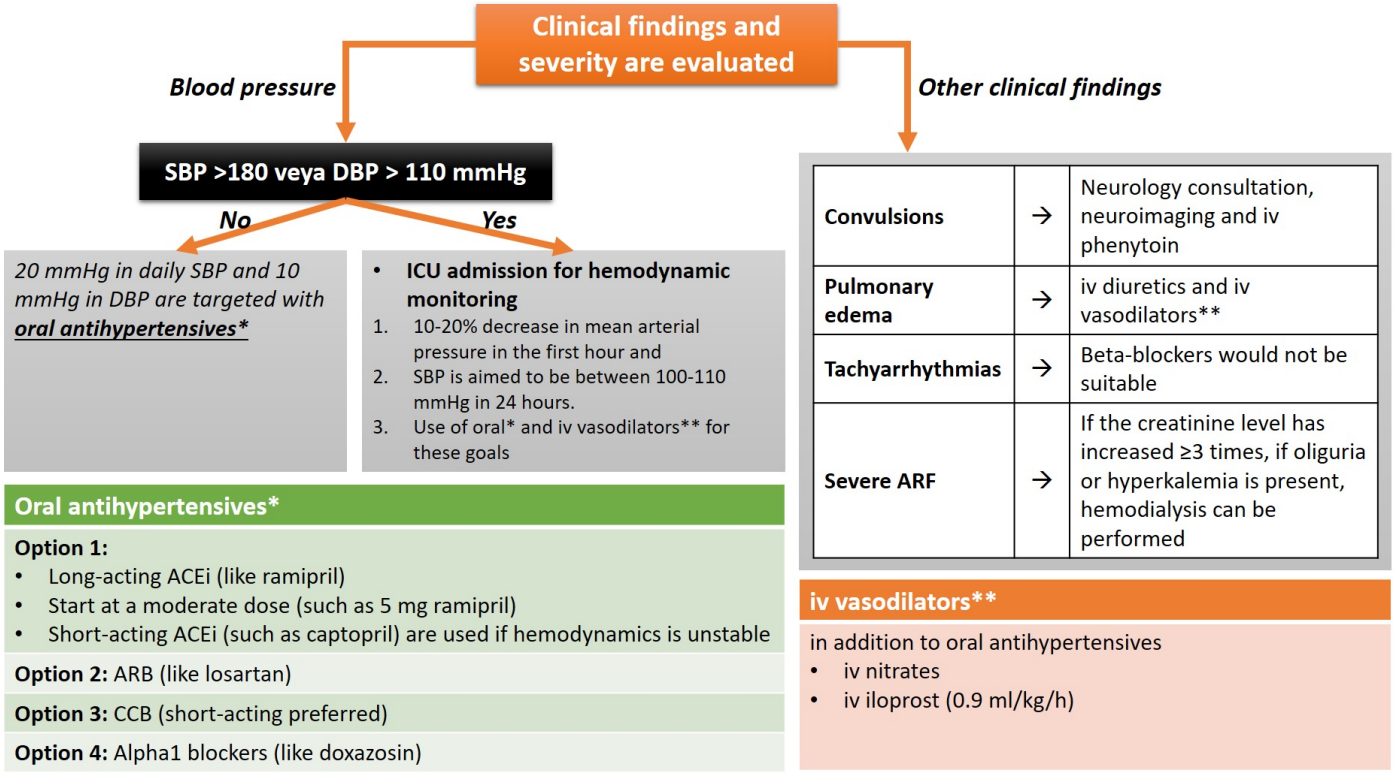

Figure 1. Scleroderma renal crisis treatment recommendations created by the UK Scleroderma Study Group (UKSSG) (13)
ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin 2 receptor blocker, CCB: Calcium channel blocker, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

are the first choice for treating SRC. With the use of ACEi, there was a significant decrease in the mortality of SRC, and the 5-year survival increased from 10% to 68-90%. Also, ACEi have severely reduced the need for continuous dialysis (10). Even in patients on dialysis, 30% improvement in renal function has been reported with ACEi treatment. The efficacy of ACEi is related to the baseline renal injury. If ACEi is started while the serum creatinine value is below 4 mg/dL, renal functions can be improved to a great extent (8). If blood pressure remains high despite treatment with the maximum dose of ACEi, angiotensin 2 receptor blockers (ARBs) can be added to the treatment. However, ARB therapy alone is insufficient without ACEi (8,21). If these treatments fail, calcium channel blockers (CCBs) or alpha blockers may be added to the treatment (15,16). If a drug belonging to the ACEi group needs to be discontinued due to its side effects, another ACEi should be tried first (switched). The systolic

blood pressure should be reduced by 20 mmHg daily and the diastolic blood pressure by around 10 mmHg daily until the blood pressure returns to normal limits. Hypotension should be avoided; for this purpose, blood pressure should be titrated with close monitoring (8). Pregnancy is not recommended in SRC. If 5 years after SRC, the skin score is low and the patient feels well, ACEi can be discontinued, and pregnancy may be permitted in selected cases. During pregnancy, blood pressure and renal functions should be closely monitored by starting a drug that is not contraindicated in pregnancy, such as CCB, or before any medication is started (13). Despite the positive developments, SRC is still an important cause of mortality and morbidity. Knowing the risky patients in advance and the precautions to be taken are more effective than the treatment given after SRC development. The use of ground-breaking ACEi for treating SRC for prophylaxis is discussed. The reason for this confusion is that in a previously published case series, it was suggested that the clinical course was more severe in patients who developed SRC while using ACEi for any reason, and more patients needed dialysis (22). ACEi are used at high doses for treating SRC; ACEi that are not effective when used in low doses may delay the diagnosis by masking the initial findings of SRC. In SRC patients who need dialysis, at least 2 years should be waited for kidney transplantation because kidney functions may improve in the future. Re-occurrence of SRC in the same patient is extremely rare (23,24).

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.R.A., S.S.K., Concept: F.A., A.K., Design: M.R.A., S.S.K., Data Collection or Processing: F.A., A.K., Literature Search: M.R.A., S.S.K., Writing: M.R.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL ARTICLE

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THE RELATIONSHIP OF BODY MASS INDEX WITH SERUM TGF-BETA LEVEL AND CLINICAL FINDINGS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Abstract

Aim: Systemic sclerosis (SSc) is an inflammatory disease characterized by a widespread fibrosis of affected tissue. Obesity is characterized as a chronic inflammatory state and affects the production of cytokines. The aim of the present study was to evaluate whether obesity alters clinical characteristics and serum were transforming growth factor-beta (TGF-β) levels in patients with SSc.
Material and Methods: Eighty-six patients with SSc were enrolled in this study. Body mass indexes (BMI) were calculated and the cases were divided into 3 groups (normal, overweight and obese). In each group, the extent of skin involvement was determined by modified Rodnan skin score, pulmonary function test, and carbon monoxide diffusing capacity were measured. TGF-β levels were measured by the enzyme-linked immunosorbent assay.

Results: Thirty-eight patients were of normal weight (BMI: ≤25 kg/m^2), 27 patients were overweight (BMI: 25-30 kg/m^2) and 21 patients were obese (BMI >30 kg/m^2). Their clinical and laboratory findings were similar. However, serum TGF-β level was significantly lower in obese SSc patients compared with those with normal weight.

Conclusion: These results suggest that obesity does not affect the severity of SSc. The cause of decreased serum TGF-β level in obese patients may be increased by fat tissue instead of SSc. Despite decreased TGF-β level, the severity of SSc is not different between obese and non-obese patients. These differences apart from TGF-β may be responsible for the SSc severity in obese SSc patients.

Keywords: Systemic sclerosis, obesity, body mass index, transforming growth factor-beta

INTRODUCTION

Systemic sclerosis (SSc) is a chronic inflammatory autoimmune disease characterized by fibrosis of the skin and internal organs. Although SSc is a rare disease, it has high morbidity and mortality due to difficulties in treatment (1). Although the etiology of SSc has not been fully elucidated, it is thought that its pathogenesis consists of several steps that result in vasculopathy and immune activation-triggered fibrosis (2). It is thought that some cytokines secreted because of immune activation trigger fibrosis. At the beginning of these cytokines, transforming growth factor-beta (TGF-β) appears first. It has been shown that TGF-β levels are increased in fibrotic (skin and lung) tissues taken from patients

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with SSc and are associated with disease activity (3). All these suggest that TGF-β cytokine plays a central role in the pathogenesis of SSc. However, there is also a study showing that there is an inverse correlation between TGF-β level and modified Rodnan skin scores (mRSS) (4). This can be explained by the fact that TGF-β has both anti-and pro-inflammatory effects (5) and that SSc has different subtypes and different clinical stages. Moreover, both overexpression and insufficient expression of TGF-β are thought to cause vascular pathology (3). According to data from the World Health Organization in 2016, more than 1.9 billion adults aged 18 years and older were overweight, and more than 650 million of these were obese (6). In recent years, it has been shown by many studies that obesity is closely associated with chronic systemic inflammation. In obesity, it is thought that pro-inflammatory cytokines secreted from increased subcutaneous adipose tissue play an important role in triggering the systemic acute phase response (7,8). The role of obesity and thus adipose tissue in the pathogenesis and disease activity of inflammatory rheumatic diseases has been the subject of research. There is increasing evidence that adipose tissue contributes significantly to the pathogenesis of SSc. It has been shown that in SSc, adipose tissue fat cells transform into myofibroblasts and contribute to fibrosis (9). In this study, we investigated the effect of obesity on clinical findings and serum TGF-β levels in SSc patients.

MATERIAL AND METHODS

Newly diagnosed or followed scleroderma patients who met the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 Scleroderma Classification Criteria and who applied to the Rheumatology outpatient clinic of Fırat University Faculty of Medicine, Department of Internal Medicine between 2013 and 2014 were included in the study. Before starting the study, the approval of the Fırat University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee was obtained with the decision number 97521439-8b dated 02.05.2013.

Inclusion criteria;

- Being between the ages of 18 and 65,
- To establish cooperation,
- To be diagnosed according to the 2013 ACR/EULAR SSc Classification Criteria.

Exclusion criteria;

- Having Overlap syndrome
- Having additional systemic disease that can affect TGF-β levels
- Patients with a diagnosis of malignancy
- Patients who did not accept participation in the study.

Written informed consent was obtained from all subjects included in the study regarding the purpose of the study and the issues related to blood sampling. Demographic characteristics, clinical findings, organ involvement, and other follow-up parameters of the patients were evaluated in terms of SSc. 8-10 mL of venous blood samples taken into biochemistry tubes from the patients and control groups included in the study were centrifuged at 4000 rpm for 5 min, and serum samples were stored in a deep freezer at -80 °C until they were studied. Complete blood count, sedimentation, C-reactive protein (CRP), anti-nuclear antibody (ANA), anti-topoisomerase I (anti-Scl-70), and anti-centromere antibody (ACA) were recorded simultaneously. The severity of skin involvement of all patients was calculated and noted with mRSS, and pulmonary function test was performed. High-resolution lung computed tomography was performed in patients with abnormal findings on posteroanterior chest X-ray. Pulmonary arterial pressure (PAP) was measured using transthoracic echocardiography, and systolic PAP above 40 mmHg were considered pulmonary arterial hypertension. Body mass index (BMI) of patients was calculated as weight/height (2). They were divided into 3 groups according to their BMI. Those with a BMI of ≤25 kg/m^2 were considered "normal", those with a BMI of 25-30 kg/m^2 as "overweight", and those with a BMI >30 kg/m^2 as "obese" (10). Serum TGF-β levels were measured using the ELISA method using an appropriate commercial kit (Boster Biological Technology Co., Ltd., Pleasanton, USA). Results were expressed as pg/mL.

Statistical Analysis

IBM SPSS 22.0 for Windows statistical package program was used for the statistical evaluation of our research data. Measured variables were presented as mean ± standard deviations, while categorical variables were presented as numbers and percentages (%). It was checked whether the data fit the normal distribution or not. Showing a normal distribution; Independent samples t-test was used to compare the two groups. The Mann-Whitney U test was used to compare the two-choice groupings that did not show a normal distribution. Normally distributed; one-way analysis of variance in the comparison of groupings with more than two options; non-normal distribution; Kruskal-Wallis H test was used to compare groupings with more than two options. Correlation analysis was performed by choosing either Pearson or Spearman correlation analysis depending on whether the parametric test conditions were met or not. Chi-square (χ^2) test was used for the comparison of qualitative variables. The hypotheses will be taken in two directions; a p value of <0.05 was considered statistically significant.

RESULTS

Eighty-six patients with a diagnosis of SSc were included in the study. Thirty-eight (44.2%) patients were of normal weight, 27 (31.4%) patients were overweight, and 21 (24.4%) patients were obese. Demographic, clinical, imaging, and laboratory characteristics are shown in Table 1. No statistically significant difference was observed between the groups in terms of age and gender (p value 0.158 and 0.808, respectively). While limited SSc was common in overweight and obese patients, diffuse SSc was more common in patients with normal BMI, but this difference was not statistically significant (p=0.585). There was no statistically significant difference between the groups in terms of ANA, ACA, and anti-Scl-70 antibody positivity (p value 0.178, 0.920, 0.931, respectively). No statistically significant findings were observed in terms of forced vital capacity, diffusing capacity of the lungs for carbon monoxide, systolic PAP, or pulmonary fibrosis findings. When laboratory findings were evaluated, there was no statistically significant difference in terms of CRP, erythrocyte sedimentation rate, hemoglobin level, and leukocyte level (p values 0.478, 0.228, 0.708 and 0.285, respectively).

When the level of TGF-β1 was evaluated, it was measured as 65.1±163.7 pg/mL in those with normal weight, 28.1±24.1 pg/mL in those with overweight, and 16.7±14.7 in those who were obese. Although TGF-β1 levels were significantly higher in normal-weight individuals, no statistically significant difference was observed (Kruskal-Wallis p=0.124). However, when TGF-β1 levels were evaluated in post hoc analyses, there was a statistically significant difference between those with normal weight and those with obesity (Mann-Whitney U p=0.045, Figure 1).

DISCUSSION

Systemic sclerosis is a chronic, multisystemic, autoimmune disease. Due to the difficulties in its treatment, it can cause serious morbidity and mortality. The clues to be discovered regarding the pathogenesis and the factors affecting the clinical course may guide new treatment searches. Among the multiple cytokines associated with SSc, TGF-β is considered to be the main regulator of physiological and pathological fibrogenesis (11). In a study examining the effect of TGF-β on the differentiation of human adipocyte precursor cells, it was found that TGF-β had

Table 1. Clinical and laboratory characteristics in SSc patients with different BMI

BMI (kg/m^2)	≤25 (Normal) (n=38)	25-30 (Overweight) (n=27)	>30 (Obese) (n=21)	p
Age, years	48.4±15.1	54.4±10.1	52.5±10.8	0.158
Disease duration, years	6.5±5.7	6.2±4.8	5.6±4.1	0.808
mRSS	11.6±7.1	10.3±5.9	10.9±4.9	0.589
Limited SSc, %	40.3	34.3	25.4	0.585
Diffuse SSc, %	58.3	25.3	16.7	0.585
ANA positive, %	81.6	96.3	90.5	0.178
ACA positive, %	15.8	18.5	14.3	0.920
ATA positive, %	47.4	51.9	47.6	0.931
DL_{co}, %	86.8±30.1	87.6±25.9	88.1±21.9	0.985
FVC, %	72.1±16.2	76.1±15.2	78.3±115.6	0.319
sPAP, mm/Hg	37.7±12.9	34.6±10.7	37.5±7.5	0.495
Pulmonary fibrosis, %	55.3	63.0	42.9	0.380
PAH, %	26.3	11.1	33.3	0.163
Hemoglobin, g/dL	12.7±2.1	12.4±1.1	12.8±1.1	0.708
Leukocyte, 10^3/μL	7.1±2.8	9.9±1.2	8.3±2.6	0.285
ESR, mm/h	28.5±18.9	31.1±15.8	22.8±13.2	0.228
CRP, mg/dL	1.2±2.3	1.8±4.1	2.5±5.6	0.478
TGF-β1, pg/mL	65.1±163.7	28.1±24.1	16.7±14.7	0.124

BMI: Body mass index, SSc: Systemic sclerosis, ANA: Anti-nuclear antibody, ACA: Anti-centromere antibody, ATA: Anti-topo antibody, FVC: Forced vital capacity, PAH: Pulmonary arterial hypertension, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TGF-β: Transforming growth factor-beta, DL_{co}: Diffusing capacity of the lungs for carbon monoxide, mRSS: Modified Rodnan skin scores, sPAP: Systolic pulmonary arterial pressure

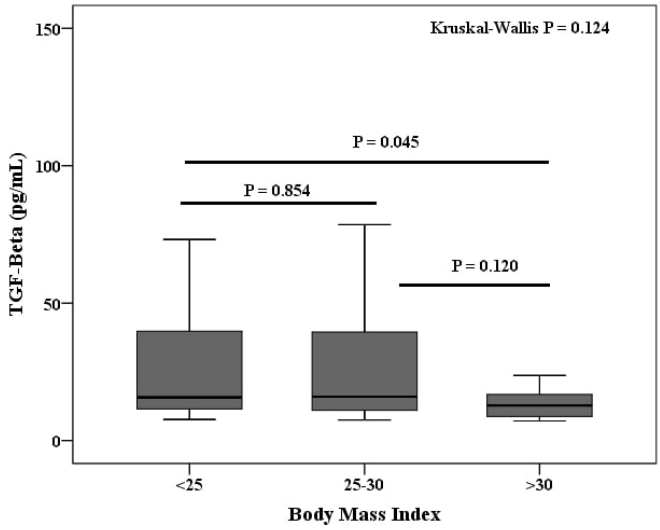

Figure 1. Serum TGF-β; levels in normal, overweight and obese patients
TGF: Transforming growth factor

an inhibitory effect on adipocyte precursor cells (12). In the literature review, we could not find any study that investigated the effects of obesity on TGF-β levels and clinical parameters in SSc patients. In this preliminary study, we investigated the serum TGF-β levels of normal weight, overweight, and obese patients in SSc patients and the relationship between obesity and clinical findings. The main source of pro-inflammatory cytokines in obese individuals is thought to be the visceral adipose tissue. It is known that the levels of some cytokines (adiponectin, resistin, leptin, interleukin-6, TNF-alpha, vascular endothelial growth factor, and TGF-β) associated with visceral adipose tissue are altered in obese individuals (13). Some of these cytokines are associated with inflammation and their roles in the pathogenesis of SSc have been the subject of research (14). Tomčík et al. (15) found that adiponectin was negatively correlated with the skin involvement in SSc. In the study of Winsz-Szczotka et al. (16), it was observed that adiponectin was lower in patients with diffuse skin involvement and negatively correlated with acute phase responses. Similarly, in the study of Budulgan et al. (17), it was shown that leptin levels were negatively associated with disease activity. On the other hand, contrary to this study, Pehlivan et al. (18) showed that serum levels of leptin were higher than in the control group, but this study did not show any correlation with disease activity. As it can be understood from these studies, it can be predicted that certain cytokine profiles may change in obese patients, and thus the severity of SSc disease may also change. In the study of Petruschke et al. (12), in which they examined the effect of TGF-β on human adipocyte precursor cells *in vitro*, it was shown that TGF-β had an inhibitory effect on human adipose tissue development and reduced the activity of a lipogenic enzyme in newly formed adipose cells. In our study, the low TGF-β level in obese SSc patients may have resulted in an insufficient inhibitory effect on adipose tissue and an increase in subcutaneous adipose tissue. On the other hand, gastrointestinal involvement is seen in more than 70% of SSc patients, which limits oral food intake and results in a low BMI (19). As we have shown in our study, considering that patients with low BMI have higher TGF-β, it can be said that these patients may be more active. There is a need for studies in which the BMI of the patients at the time of diagnosis and during follow-up is compared with the control group in order to state more clearly the paradox that whether SSc has an effect on BMI or whether BMI has an effect on SSc disease severity.

In Brezovec et al. (9), it was shown that in the pathogenesis of SSc, adipose fat cells turn into myofibroblasts and contribute to fibrosis. It is expected that patients with high TGF-β levels will inhibit adipose fat cells, preventing myofibroblast formation and therefore having a lower mRSS. These conflicting results may be explained by the fact that myofibroblasts originate from many cells. In addition, it is thought that different cytokines and pathways play a role in SSc patients and different clinical presentations have different pathogenic processes (2). Our results suggest that pathways other than TGF-β may be responsible for SSc severity in obese SSc patients. The fact that normal weight patients, which we confirmed in our study, have a higher rate of diffuse disease and higher TGF-β levels than overweight and obese patients confirms the relationship between high TGF-β and high disease activity in the literature (20).

TGF-β has both anti-and pro-inflammatory effects (5). There is low-grade chronic inflammation in overweight and obesity (21). In our study, we found that obese patients had lower TGF-β levels. This result suggests that low TGF-β level in obesity triggers inflammation by causing disruption of the inflammatory/anti-inflammatory balance. In the study of Oeser et al. (22) on 33 normal BMI, 28 overweight and 39 obese systemic lupus erythematosus patients, it was shown that obese patients had worse functional capacity, reported more fatigue complaints and had a higher acute phase response. In the review of Moroni et al. (23), it was observed that obesity has negative effects on both disease activity and treatment response in patients with rheumatoid arthritis and psoriatic arthritis (PsA), and relapses are higher in obese individuals. Obesity was associated with a lower rate of disease remission, according to the results of 12-month follow-up in rheumatoid arthritis patients by Ellerby et al. (24). In a study by di Minno et al. (25), 135 obese PsA patients

compared with 135 normal-weight control groups showed that obese patients reached low disease activity at a lower rate at 12-month follow-up, and obesity was found to be an indicator of relapse. In our study, we could not detect a clinically unfavorable difference in obese individuals.

Study Limitations

There are some limitations to our study. One of the limitations of the study is that the patients included in the study were under the treatment regimen at the time of enrollment. Because, TGF-β level may have been affected by treatment regimens. Another limitation of our study is that SSc patients have not been compared with healthy individuals with the same BMI. Another limitation of our study is the relatively small number of cases.

CONCLUSION

These results suggest that obesity does not affect SSc severity. The cause of decreased serum TGF-β level in obese patients may be increased by fat tissue instead of SSc. Despite decreased TGF-β level, the severity of SSc is not different between obese and non-obese patients. These differences apart from TGF-β may be responsible for the SSc severity in obese SSc patients. To better understand the effect of obesity on TGF-β level, which play an important role in the pathogenesis of SSc, there is a need for new clinical studies with a larger number of patients, including untreated patients, and to compare them with control groups.

Ethics

Ethics Committee Approval: Before starting the study, the approval of the Fırat University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee was obtained with the decision number 97521439-8b dated 02.05.2013.

Informed Consent: Written informed consent was obtained from all subjects included in the study regarding the purpose of the study and the issues related to blood sampling.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ö., A.K., Concept: İ.G., B.G., Design: B.G., Data Collection or Processing: B.G., Analysis or Interpretation: B.G., S.A., Literature Search: F.A., B.Ö., Writing: İ.G., A.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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SECOND-TO-FOURTH DIGIT RATIO (2D:4D) IN RHEUMATOID ARTHRITIS: A CASE-CONTROL STUDY

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Abstract

Aim: The second-to fourth-digit ratio (2D:4D), the ratio of the second finger length to the fourth finger length, is associated with exposure to prenatal sex steroids. Rheumatoid arthritis (RA) is more common in women, suggesting the effect of hormonal factors. The aim of the present study was to determine whether 2D:4D, which is associated with sex hormone levels, is affected in patients with RA.

Material and Methods: Digital images of the right and left hands of 205 RA patients (mean age 47.8±11.3 years; 84% female) and 205 age and gender matched healthy controls (mean age 47.3±11.6 years; 84% female) were obtained. 2D:4D was calculated by dividing the 2nd digit length by the 4th digit length. The 2D:4D difference between the right and left hand (ΔR-L 2D:4D) was obtained by subtracting the left hand 2D:4D ratio from the right hand 2D:4D ratio.

Results: No difference was found between patients with RA and the control group in terms of the 2D:4D ratio in the right and left hand. In female patients with RA, ΔR-L 2D:4D was higher compared with the control group. For both hands, the 2D:4D increase rate in women compared to men was higher in patients with RA compared to the control groups.

Conclusion: The detected 2D:4D ratio differences suggest that prenatal estrogen/androgen balance may be altered in female patients with RA. To the best of our knowledge, this is the first study to evaluate 2D:4D change in patients with RA.

Keywords: 2D:4D, digit ratio, rheumatoid arthritis, sex hormones

INTRODUCTION

Rheumatoid arthritis (RA) is the most common systemic, autoimmune, and inflammatory rheumatic disease and affects 0.5-1% of the adult population. RA is approximately 4 times more common in women (1,2), and the disease activation and progression tend to be more serious in women than in men (3). Although the pathogenesis of RA is not fully understood, the current consensus is that it occurs as a result of activation of the immune system due to environmental factors in individuals with genetic predisposition. The high prevalence of RA in women suggests that hormonal factors play a role in the development of the disease, and there are many arguments

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about this issue. Both factors related to low and high estrogen exposure have been associated with increased RA risk. In general, estrogens have pro-inflammatory effects and androgens have anti-inflammatory effects (4). However, estrogens may have different effects on different immune cells due to various factors such as serum concentration and reproductive stage (5,6). In animal experiments, estradiol suppresses T-cell autoimmunity, stimulating the production of autoantibodies from B cells (7). The 2D:4D ratio obtained by dividing the 2nd digit length by the 4th digit length is sexually dimorphic and lower in men than in women. Manning et al. (8) suggested that the 2D:4D ratio was associated with exposure to prenatal sex steroids. A low 2D:4D ratio is associated with low prenatal estrogen and high androgen levels, while a high 2D:4D ratio is associated with low prenatal androgen and high estrogen levels (9). The relationship between the 2D:4D ratio and prenatal sex steroids was found to be stronger in the right hand. The difference between the right and left hand 2D:4D ratio (ΔR-L 2D:4D) is also associated with high prenatal estrogen and low androgen levels (10). This relationship between exposure and prenatal sex steroids and the 2D:4D ratio have also been reported in animal experiments. These studies showed that gender differences in the 2D:4D ratio were due to the balance between prenatal testosterone and estrogen during fetal digit development (11,12). Studies investigating early-life risk factors in autoimmune diseases that develop in adult life, such as RA are few. These studies have investigated many factors such as birth weight, breastfeeding status, and infections in early life (13). Similarly, there are very few studies on the relationship between hormonal environment and RA in the prenatal period, and the sample size is very small in these studies (14-16). Since it is difficult to evaluate hormones in the prenatal period for ethical and technical reasons, the 2D:4D ratio can indirectly provide information about the prenatal hormonal environment. Therefore, the aim of this study was to compare the 2D:4D ratio between patients with RA and healthy controls.

MATERIAL AND METHODS

Participants

This case-control included 205 consecutive patients who applied to the rheumatology clinic at Fırat University Hospital between 2019 and 2020 and were diagnosed with RA according to the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria. The control group consisted of 205 patients who applied to the rheumatology clinic with the complaint of joint pain in the same period and were compatible with the RA group in terms of age and gender. The patients in the control group did not have inflammatory rheumatic disease or systemic disease in the evaluations and follow-ups, and the autoantibody profile was negative for RA. Participants with a disorder in the fingers that would affect digit measurement, such as arthritis, deformity, and scars, and participants with a previous history of surgery on the upper extremity were excluded from the study. Basic demographic data of the participants were recorded.

Ethical approval was obtained from the Ethics Committee of Fırat University (decision no: 06, date: 05.01.2018). Informed consent was obtained from all patients before the study.

Measurements

The palmar side of the hands of all participants was scanned by a researcher blinded to the study groups (S.H.) with the same digital scanner in accordance with previous literature recommendations and the image of both hands was obtained. Participants were informed about the procedure before the scan and were asked to place their hands firmly on the scanner without applying too much pressure and with all fingers straight, and not to move their hands during the scan (17,18). All images were examined to determine if the folds on the base of the finger were clearly visible. If not, the hands were rescanned. Measurements of the second and fourth digit lengths were made from digital images by two independent researchers (M.G. and A.K.) who were blinded to the study groups. The distance from the midline of the 2nd and 4th digit basal fold to the fingertips was measured. Each finger was measured three times and the measurements were averaged. Then, the 2nd and 4th digit lengths were determined by averaging the results of the two researchers. 2D:4D was calculated by dividing the 2nd digit length by the 4th digit length. ΔR-L 2D:4D was obtained by subtracting the left hand 2D:4D ratio from the right hand 2D:4D ratio. The height and body weight of all participants were measured and the Body Mass Index (BMI) [body weight (kg)/height^2(m^2)] was calculated.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Science (SPSS) 26 program. Intraclass correlation coefficients (ICCs) were calculated for the second and fourth digit lengths in men and women to assess the reliability of digit length measurements. Descriptive statistics were presented as number, percentage, mean ± standard deviation. Kolmogorov-Smirnov test was used to test whether the data were normally distributed or not. Pearson correlation test was used to evaluate the correlation between height, weight, BMI, and 2D:4D ratio. Student's t-test was used to compare the 2P:4P ratio in men and women between the RA and control groups. The receive

operating characteristic (ROC) mode was used to detect the prediction performance of 2D:4D ratio and ΔR-L 2D:4D for RA. P<0.05 was considered statistically significant in all analyses.

RESULTS

The demographic characteristics, height, body weight, and BMI values of the RA and control groups are summarized in Table 1. No statistical difference was found between the RA and control groups in terms of age and gender characteristics (p>0.05). While body weight and BMI were higher in the control group, height was significantly higher in the RA group (p=0.002, p<0.001 and p<0.001, respectively). In both the RA and control groups, the 2nd and 4th digit lengths measured for the right and left hand were normally distributed. ICC were computed to determine inter-rater reliability. ICC for right - hand 2nd digit lengths was calculated as 0.920 and 0.932, respectively, and ICC for left - hand 4th digit lengths was calculated as 0.927 and 0.926, respectively. These results indicated that the measurements were highly similar and reliable. No statistically significant correlation was found between the 2D:4D ratio and height, weight, and BMI for both hands (p>0.05). Measurements in male and female patients in the RA and control groups are summarized in Table 2. When all patients were evaluated, 2D:4D ratios for the right and left hand were higher in women (right hand: 0.956±0.304; left hand: 0.958±0.323) compared to men (right hand: 0.946±0.324; left hand: 0.946±0.334) (p=0.015 and p=0.07, respectively). No significant difference was found between the 2D:4D ratios for the right and left hand between the two groups (p>0.05). ΔR-L 2D:4D values were significantly higher in the RA group compared to the control group (p=0.004). In men and women, no significant difference was found between the 2D:4D ratios for the right and left hand between the two groups (p>0.05). ΔR-L 2D:4D values in women were significantly higher in the RA group compared to the control group (p=0.011). In addition, the 2D:4D ratio of women in the RA group was 1.35% higher in the right hand and 1.67% higher in the left hand compared to the men, while it was 0.73% higher in the right hand and 0.83% higher in the left hand in the control group. ROC analysis showed that of ΔR-L 2D:4D was predictive for the diagnosis of RA [area under the curve (AUC): 0.574, 95% confidence interval (CI): 0.517-0.630, p=0.011]. For -0.002 cut-off value of ΔR-L 2D:4D, sensitivity and specificity was 53% (Figure 1). The AUC for the right hand 2D:4D ratio in patients with female RA was 0.543 (95% CI: 0.481-0.604, p=0.174) but not meaningful. The optimal cutoff point of the right hand 2D:4D ratio in female patients for RA was 0.953 with sensitivity of 54% and specificity of 53% (Figure 2).

Table 1. Demographic characteristics of the study groups

Parameter	RA	Control	p value
Number	205	205	
Age (mean ± SD)	47.8±11.3	47.3±11.6	0.648
Gender			
Males (%)	34 (16)	34 (16)	
Females (%)	171 (84)	171 (84)	
Weight (kg)	71.8±12.6	75.8±14.0	0.002
Height (cm)	164.2±7.8	160.2±7.8	<0.001
BMI	26.7±4.9	29.6±5.7	<0.001

RA: Rheumatoid arthritis, SD: Standard deviation, kg: kilogram, cm: centimeter, BMI: Body Mass Index

DISCUSSION

According to the results obtained in this study, no significant difference was found between the RA group and the control group in terms of the left and right hand 2D:4D ratio of male and female patients. In women, ΔR-L 2D:4D values were higher in the

Table 2. Comparison of digit ratios of patients with RA and the control group

Parameter (mean ± SD)	RA	Control	p value
Both gender right-hand 2D:4D	0.956±0.297	0.953±0.341	0.271
Female right-hand 2D:4D	0.958±0.288	0.954±0.317	0.163
Male right-hand 2D:4D	0.945±0.321	0.947±0.331	0.758
Both gender left-hand 2D:4D	0.954±0.342	0.958±0.313	0.210
Female left-hand 2D:4D	0.957±0.331	0.959±0.317	0.423
Male left-hand 2D:4D	0.941±0.371	0.951±0.289	0.202
Both gender ΔR-L 2P:4P	0.002±0.026	-0.005±0.023	**0.004**
Female ΔR-L 2P:4P	0.002±0.257	-0.004±0.024	**0.011**
Male ΔR-L 2P:4P	0.004±0.026	-0.004±0.021	0.178

RA: Rheumatoid arthritis, SD: Standard deviation, 2D:4D: Ratio of the second-to-fourth digit length, ΔR-L 2P:4P: Right hand 2D:4D-left hand 2D:4D

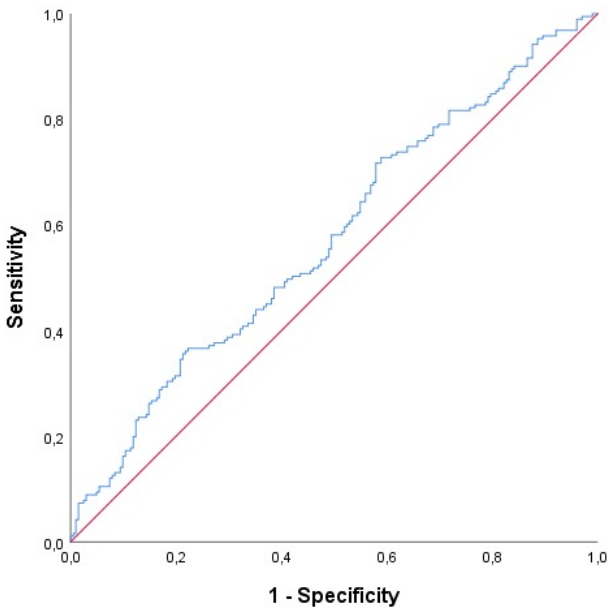

Figure 1. Receiver operating characteristic curve for predictive value of ΔR-L 2D:4D in rheumatoid arthritis patients

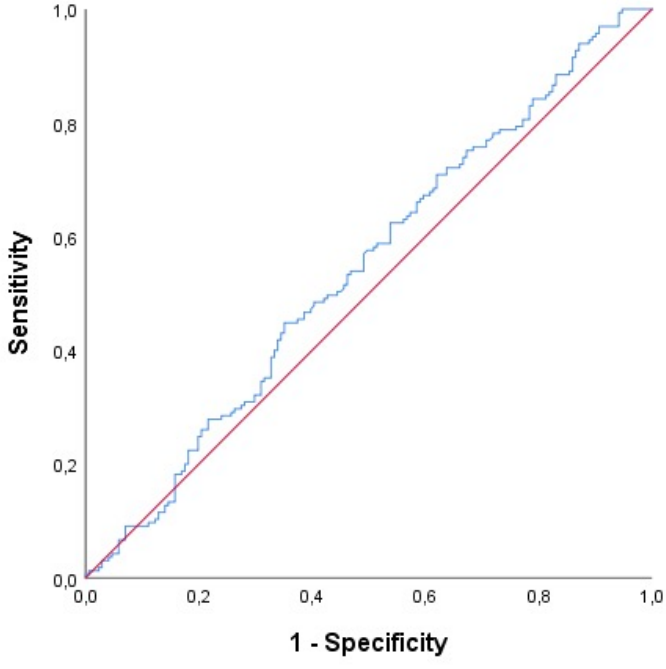

Figure 2. Receiver operating characteristic curve for predictive value of the right hand 2D:4D ratio in female rheumatoid arthritis patients

RA group than in the control group. In the RA group, the rate of increase in the 2D:4D ratio between men and women was higher compared with the control group. To the best of our knowledge, this is the first study in the literature comparing 2D:4D ratios of patients with RA with a healthy control group. In general, studies show that factors related to the reduction of estrogens are risk factors for RA, whereas factors related to high exposure to estrogens are protective against RA (19). The postmenopausal period and anti-estrogen drug use reduce estrogen levels. The increased risk of seronegative RA development during the postmenopausal period has been shown in various studies (20,21). The use of selective estrogen receptor modulators and aromatase inhibitors, which are anti-estrogen drugs, has been associated with the development of RA depending on the dose and duration (22).

Oral contraceptive (OCC) use and hormone replacement therapy (HRT) are among the situations that increase estrogen exposure. The relationship between OCC use and RA is controversial (19). Meta-analyses investigating the relationship between RA development and OCC found no significant relationship (23-25). Previous studies reported that OCC was predominantly protective against RA, which was associated with higher estrogen doses at the time of these studies (25). In general, the available evidence supports the protective effect of OCCs against RA, especially when used for a long time or at high doses. In a case–control study on HRT, a protective relationship was reported between the use of combined HRT and anti-citrullinated peptide antibody positive RA. However, this relationship could not be demonstrated in HRT containing only estrogen (26). In situations such as pregnancy and breastfeeding, multiple hormone changes are seen. Pregnancy is a condition characterized by high estrogen exposure, but these effects are modified with other hormones such as high levels of progesterone. Cohort studies reported that pregnancy is protective against RA development (27,28). Breastfeeding was shown to be associated with a decrease in RA risk (29,30). A systematic review reported that breastfeeding for more than 12 months is protective against RA (31). In contrast, the postpartum period in which estrogen levels decreased was associated with an increased RA risk (28,32).

Androgens suppress peripheral mononuclear cell activity and inhibit the differentiation of Th1 and Th17 (23). Androgen levels were found to be lower in men with RA compared with healthy controls (33,34). Men and women diagnosed with RA had a lower androgen/estrogen ratio (35). It was reported that men with hypogonadism had higher RA risk compared with those without hypogonadism (36). Although there are limited studies on androgen levels in patients with RA during the preclinical period, it was shown that androstenedione levels were lower in women in the period before RA diagnosis compared to the control group (37). Systemic estrogen/androgen ratio is increased in patients with RA. In patients with RA, the estrogen/androgen

ratio in synovium is also increased and is higher than in the systemic circulation (38). There are no clinical trials investigating estrogen/androgen ratio in the prenatal period in patients with RA. The 2D:4D ratio, which is an indirect indicator of estrogen/androgen ratio during this period, may provide information about the hormonal environment in the prenatal period in patients with RA. According to the results of this study, no significant difference was found in the 2D:4D ratio in both hands between patients with RA and the control group. However, the change in the 2D:4D ratio between men and women was greater in the RA group. The relationship between sex steroids and digit length was stronger in the right hand. Therefore, high ΔR-L 2D:4D is associated with an increased estrogen/androgen ratio (8). In this study, ΔR-L 2D:4D values in women were higher in the RA group than in the control group. These results suggest that the estrogen load in the prenatal period may be higher in patients with RA. It can also be an indirect evidence of increased estrogen/androgen ratio in patients with female RA during the prenatal period.

Study Limitations

This study has certain limitations. First, it should be remembered that the 2D:4D ratio is not a direct but rather an indirect indicator of the prenatal hormonal environment. Second, measuring digit lengths indirectly using digital images reduces digit length ratios and reduces the strength of the study (39). The high number of patients included in the study and the measurements made by two independent researchers who were blinded to the study groups are the strengths of the present study.

CONCLUSION

Many factors play a role in RA pathogenesis. The effect of hormonal factors on RA pathogenesis is complex, but, in eneral, systethe systemicogen/androgen ratio is increased in patients with RA. In RA patients, the ΔR-L 2D:4D value in women and the rate of increase in the 2D:4D ratio in women compared to men was higher compared to the control group. These results suggest that the sex steroid balance may be more predominantly altered in female patients diagnosed with RA, especially during the prenatal period.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Fırat University (decision no: 06, date: 05.01.2018).

Informed Consent: Informed consent was obtained from all patients before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., A.D.K., R.F.A., A.K., Concept: M.G., R.P.S., R.F.A., A.K., Design: M.G., A.D.K., R.F.A., N.G., A.K., Data Collection or Processing: M.G., M.S.A., R.P.S., İ.G., R.F.A., A.K., Analysis or Interpretation: M.G., T.K.K., N.G., A.K., Literature Search: M.G., İ.G., T.K.K., R.F.A., A.K., Writing: M.G., A.K.

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INVESTIGATION OF KNOWLEDGE ABOUT FOOT HEALTH IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Aim: Foot involvement is frequently observed in patients with rheumatoid arthritis (RA). However, the knowledge about foot health in patients with RA is limited and the awareness of physicians is not sufficient. The purpose of this study was to investigate knowledge about foot health and related factors in patients with RA.

Material and Methods: This study included 115 patients diagnosed with RA. Demographics of patients were recorded. The Overall Foot Health Questionnaire (OFHQ), Foot Function Index (FFI), and Health Assessment Questionnaire (HAQ) were used to evaluate knowledge level about foot health, foot function, and general health status, respectively.

Results: The study was completed with 111 patients with RA. It was found that the foot health knowledge level of patients with RA was 9.03±3.9, out of 18. A significant difference was found in gender, occupation, smoking, and education level according to OFHQ, and correlation was found between OFHQ and disability subscale of FFI ($p<0.05$). There was no significant correlation between OFHQ and pain and activity restriction subscales of FFI and HAQ ($p>0.05$).

Conclusion: It was found moderate level of knowledge of foot health in patients with RA. Therefore, it is important to provide more information about foot health protection and to include patients' education as a part of treatment.

Keywords: Foot health, knowledge, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, inflammatory, chronic rheumatic disease that progresses with articular and non-articular findings, especially small joint involvement. The etiology of the disease is not known and it is seen two times more in women than in men (1,2). Synovial inflammation and joint destruction result in pain, loss of function, and muscle atrophy. These symptoms cause disability and decreased the quality of life (3). The foot involvement is commonly seen in RA. More than 80% of patients with RA complains of constant foot pain (4,5). Metatarsophalangeal joint and midfoot involvement is frequently observed. The transverse arch flattened may occur as a result of damage to the subtalar, tibiotalar, and talonavicular joints. Hammer or trigger finger may develop due to subluxation of metatarsal heads. Foot pain and paresthesia due to comprthe compressionostethe posterioral nerve, hallux

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valgus and, rheumatoid nodule may be observed in RA patients. Rheumatoid nodule in Aschilles can cause spontaneous rupture in the tendon. Calluses in subcutaneous tissue caused deformities and skin ulcerations may cause foot pain (6). Although foot pain and disability are common in patients with RA, the foot is often overlooked in the routine examinations. There is no evaluation of foot and ankle in Disease Activity Score-28, which is used commonly for evaluating disease activity. Therefore, needs about foot remain in the background in these patients (7,8). Professional foot care is important for patients with RA in preventing new foot problems or reducing existing ones. However, some patients receiving podiatric support complain about just focusing on skin and nail care and not evaluating joint pain, self-care, or more detailed assessment of foot (9,10). It is important to evaluate foot in detail for determining potential problems and monitoring foot health (11). Therefore, patients should have a high level of knowledge about foot health to protect their foot health. Studies investigating knowledge of the disease in RA concluded with different results (12-14). However, to the authors knowledge, there is no study investigating knowlthe knowledgeoot health in patients with RA. The aim of this study was to evaluate knowledge of foot health and investigate the relationship between knowledge of foot health and demographics, foot function, and general health in patients with RA.

MATERIAL AND METHODS

This study was approved by the Fırat University Clinical Research Ethics Committee (decision no: 2022/06-33, date: 21.04.2022). A written consent form was obtained from the patients. This study was applied properly according to the Helsinki Declaration and ethical principles.

Patients

This study included 115 patients who had been diagnosed with RA on the basis of the American College of Rheumatology/European League Against Rheumatism 2010 criteria, aged between 18 and 65 years and had no changes in medical treatment in the last three months. Patients who had malignancy and pregnancy were excluded from the study. Demographics including gender, age, length, weight, smoking, and education level were asked and recorded.

Outcome Measurements

Overall Foot Health Questionnaire

The Overall Foot Health Questionnaire (OFHQ) was developed by Reina-Bueno et al. (15) in 2019. The questionnaire includes 12 questions evaluating knowlthe knowledgeoot health in patients with RA. Patients want to reply as “yes”, “no”, “do not know” or “do not answer” in questions 1 to 7, 9 and 10. The role of podiatrist is asked and the patients are asked to mark among various options in question 11. Question 12 is only informative. Total score is calculated for questions 1 to 7, and 10, have 1 point each, when patients answer “yes”, and 0 points when the answer is any other, for question 8 has 1 point when patients answer “straight, without trimming the tips”, and 0 points when the answer is any other, for question 9 has 1 point when patients answer “no”, and 0 points when the answer is any other and for question 11 has 1 point for each selected option, except “do not know” and “do not answer”, which has 0 points. High scores indicate a high knowledge level of foot health in RA.

Health Assessment Questionnaire

The Health Assessment Questionnaire (HAQ), which evaluates disease-specific functional status, was modified by Pincus et al. (16). Turkish validity and reliability was conducted by Küçükdeveci et al. (17). The questionnaire is frequently used to evaluate functional status and level of daily living activities in patients with rheumatic diseases. It consists of 20 questions evaluating 8 activities including dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Scoring for each activity was determined according to the highest score obtained from the questions in that group. The total score is calculated by adding the obtained scores and dividing by eight. The total score ranges between 0 and 3, and high scores indicate more functional dependence (17).

Foot Function Index

The Foot Function Index (FFI) is a widely used questionnaire developed to measure the impact of foot pathologies (18). The index consists of 23 questions including 3 subscales of pain, disability, and activity restriction. The pain subscale consists of 9 questions evaluating foot pain level. The disability subscale, which consists of nine questions, assesses the difficulty in functional activities due to foot problems. Activity restriction includes 5 questions and evaluates the activity restriction due to foot problems. Each item scored between 0 and 10, and a high score indicates more disability, pain, or activity restriction. A Turkish validity and the reliability study was published in 2014 in patients with plantar fasciitis (19).

Statistical Analysis

Statistical analysis was performed using SPSS 21.0. Categorical measurements were expressed as number and percentage, and numeric measurements were presented as the mean and

standard deviation. The Independent samples t-test was used for two-group variables and one-way ANOVA was used for variables with more than two groups. Pearson correlation test was used for correlation analysis. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 115 patients were enrolled in the study. Four of them were excluded from the study because 3 patients had pregnancy and one were not fulfill the questionnaires. Thus, the study was completed with 111 patients with RA. Demographics and measurement results are summarized in Table 1. Significant differences were found in gender, occupation, smoking, and education level ($p<0.05$). The scores of OFHQ were significantly higher in males than females, having occupation than non-occupation, smoking than non-smoking, and high school and graduate than primary school ($p<0.05$) (Table 2). A significant correlation was observed between OFHQ and FFI disability subscale, while no significant differences were observed between OFHQ and HAQ and pain and activity restriction subscales of FFI. Other correlations are summarized in Table 3.

DISCUSSION

This study was designed to evaluate the knowledge of foot health in patients with RA. As a result, patients participating in this study had a moderate level of knowledge of foot health. Gender, occupation, smoking, and education level were found to affect knowledge of foot health. Additionally, a correlation was found between knowledge level and foot disability. In the light of these results, knowledge of foot the foot health of patients with RA was found to be insufficient and demographics were concluded to be effective on knowledge level.

Although there are studies investigating knowledge level about the disease (20), general health (21), pain (21), self-control of the disease (21), perception of general health (22) and satisfaction (23) in patients with RA, to the authors knowledge, there is no study investigating knowledge about foot health and related factors. Foot involvement in RA is frequently seen and causes disability, physical inactivity and decreased quality of life in RA patients. In addition, it affects mobility, balance and gait (6). Therefore, protection of foot health is essential in patients with RA. A moderate level of knowledge about foot health was concluded in the study, which may be insufficient to protect foot health. This result indicates the necessity to provide more information about foot health. There was no chance to compare the results with other studies in the literature since no other study evaluating the knowledge level of foot health in patients with RA. Studies investigating knowledge about illness concluded a moderate or subpar level of knowledge in RA patients (12-14, 24). Long- or short-term patient education was suggested because

Table 1. Characteristic features and measurement results of patients with RA

Characteristic or measurements	Mean (± SD) or n (%) (n=111)
Age (years)	51.70±11.65
Height (m)	1.61±0.08
Weight (kg)	70.08±13.88
BMI (kg/m^2)	27.00±5.52
Gender	
Female	73 (65.8%)
Male	38 (34.2%)
Disease duration	12.10±9.95
Smoking	
Yes	25 (22.5%)
No	86 (77.5%)
Marital status	
Married	83 (74.8%)
Single	28 (25.2%)
Occupation	
Yes	19 (17.1%)
No	92 (82.9%)
Chronic diseases	
Yes	-
No	-
Education level	
Primary school	92 (82.9%)
High school	8 (7.2%)
University	11 (9.9%)
OFHQ	9.03±3.9
FFI	
Pain subscale (L)	40.24±20.22
Pain subscale (R)	40.41±20.72
Disability subscale (L)	53.19±27.97
Disability subscale (R)	52.68±28.15
Activity restriction subscale (L)	32.27±23.84
Activity restriction subscale (R)	32.53±23.84
HAQ	1.54±5.39

BMI: Body Mass Index, OFHQ: Overall Foot Health Questionnaire, FFI: Foot Function Index, HAQ: Health Assessment Questionnaire, SD: Standard deviation, RA: Rheumatoid arthritis

of these studies (23). Studies investigating the knowledge and practice of foot care are focused on diabetic foot (25-28). It was found that one third of diabetic patients had poor knowledge about foot care (28) and needed a targeted educational program to promote knowledge of foot care and self-care management of patients with diabetes (25,26). A significant difference among knowledge about foot health and gender, occupation, smoking, and education level was found in this study. It was concluded that males, working patients, smokers, high school or university graduates had a high knowledge level about foot health according to females, non-working patients, non-smokers, and primary school graduates, respectively. Education level and having a profession that brings many innovations in socio-cultural terms (29) may affect knowledge level. Although RA mostly affects women, the study concluded that men had a higher level of knowledge. Males who participated in our study had a higher education level than females, which may be a reason for the difference. Similarly, most smokers were male, which may explain the high levels of knowledge about foot health according to non-smokers. Wardt et al. (30) found a positive correlation between education level and patient awareness level. In addition, they concluded that individuals with a higher education level were less prone to have information about rheumatic diseases than those with a lower level of education. It was underlined that training or talks on rheumatic diseases may provide an earlier diagnosis or treatment (31). A positive correlation between scores of knowledge about RA and education level in Bangladeshi patients (32). Vignos et al. (33) and Hill et al. (13) also concluded a positive correlation between the level of education and knowledge scores. Our results were parallel to the results of these studies. HAQ and FFI were used to evaluate general health status and foot function, respectively. A significant correlation was found between knowledge of foot health and disability subscale of FFI, although no significant correlation was found between knowledge level and HAQ, pain subscale, and activity restriction subscale of FFI. These results

Table 2. The comparison of foot health knowledge level according to characteristic features

Demographics		n	Mean ± SD	p
Gender	Female	73	8.41±3.87	**0.019***
	Male	38	10.23±3.71	
Occupation	Yes	19	11.52±3.06	**0.002***
	No	38	2.16±9.09	
Smoking	Yes	25	11.00±3.64	**0.004***
	No	86	8.46±3.81	
Marital status	Single	28	9.42±4.41	0.541
	Married	83	8.90±3.74	
Education level	Primary school	92	8.34±3.83[A]	**0.000****
	High school	8	12.50±2.61[B]	
	Graduate	11	12.27±1.84[B]	

*p<0.05, **p<0.001, Significant difference was observed among different letters (p<0.05).
SD: Standard deviation

Table 3. Correlations among OFHQ, HAQ and pain, disability, and activity restriction subscales of FFI

	OFHQ	HAQ	FFI (Pain) (L)	FFI (Pain) (R)	FFI (Disability) (L)	FFI (Disability) (R)	FFI (Activity restriction) (L)	FFI (Activity restriction) (R)	FFI (Total) (L)	FFI (Total) (R)
OFHQ	1	0.042	-0.010	-0.011	**-0.211***	**-0.225***	-0.158	-0.149	-0.151	-0.152
HAQ	0.042	1	0.124	**0.221***	0.152	-0.002	0.049	0.164	0.118	**0.540****
FFI (Pain) (L)	-0.010	0.124	1	**0.986****	**0.827****	**0.814****	**0.745****	**0.747****	**0.908****	**0.905****
FFI (Pain) (R)	-0.011	**0.221***	**0.986****	1	**0.820****	**0.793****	**0.730****	**0.744****	**0.97****	**0.905****
FFI (Disability) (L)	**-0.211***	0.152	**0.827****	**0.820****	1	**0.987****	**0.839****	**0.843****	**0.962****	**0.962****
FFI (Disability) (R)	**-0.225***	-0.002	**0.814****	**0.793****	**0.987****	1	**0.843****	**0.829****	**0.954****	**0.961****
FFI (Activity Restriction) (L)	-0.158	0.049	**0.745****	**0.730****	**0.839****	**0.843****	1	**0.993****	**0.923****	**0.927****
FFI (Activity restriction) (R)	-0.149	0.164	**0.747****	**0.744****	**0.843****	**0.829****	**0.993****	1	**0.924****	**0.927****
FFI (Total) (L)	-0.151	0.118	**0.908****	**0.897****	**0.962****	**0.954****	**0.923****	**0.924****	1	**0.999****
FFI (Total) (R)	-0.152	0.540	**0.905****	**0.905****	**0.962****	**0.961****	**0.927****	**0.927****	**0.999****	1

*p<0.05, **p<0.001.
OFHQ: Overall Foot Health Questionnaire, FFI: Foot Function Index, HAQ: Health Assessment Questionnaire

indicate that difficulties experienced by patients with RA during activities of daily living affect their level of knowledge. However, the fact that the level of knowledge was not correlated with general health status on other subscales of FFI may be due to patients' ignorance of the necessity of protecting foot health in coping with foot problems. Foot skin care choosing suitable shoes, and getting support from podiatrists in necessity may be beneficial for these patients. Talks or educaeducationuding foot health should be provided to patients with RA.

Study Limitations

Foot deformities of patients were not recorded and the correlation between knowledge level and presence of foot deformities was not investigated in this study, which may be considered a limitation.

CONCLUSION

Patients with RA have moderate level of knowledge about foot health according to this study. In addition, gender, occupation, smoking, education level and disability of foot were found to effect knowledge level about foot health in RA patients. It may be beneficial to inform RA patients by organizing talks or enlightening them during individual appointment. Future studies should contain the effects of educations about foot health protection.

Ethics

Ethics Committee Approval: This study was approved by the Fırat University Clinical Research Ethics Committee (decision no: 2022/06-33, date: 21.04.2022).

Informed Consent: A written consent form was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.P.S., Concept: S.B.Y., Design: S.B.Y., Data Collection or Processing: S.B.Y., Analysis or Interpretation: S.B.Y., Y.G., Literature Search: S.B.Y., R.P.S., Writing: S.B.Y.

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CHARACTERISTICS OF PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER IN ERZINCAN PROVINCE: A CROSS-SECTIONAL STUDY FROM A SINGLE CENTER

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Abstract

Aim: Familial Mediterranean fever (FMF) is the most common monogenic periodic fever syndrome characterized by recurrent attacks of fever, peritonitis, and pleuritis. The disease usually occurs in the first two decades of life. It is frequently seen in the Central-North Anatolian Region of the country. In this study, it was aimed to investigate the first complaints, age at diagnosis, delay in diagnosis, most common clinical findings, and *MEFV* gene of patients with FMF living in Erzincan province.

Material and Methods: In this cross-sectional study, patients diagnosed with FMF who applied to rheumatology and physical medicine and rehabilitation outpatient clinics between January 2023 and May 2023 were included. Demographic data and genetic features were collected from patient interviews and medical records.

Results: The study comprised 142 (64 female, 78 male) patients with the diagnosis of FMF. The mean age of the patients was 31.60±9.91 years. In the patient group, the mean age of first attack was 16.39±7.55, delay in diagnosis was 3.57±2.35. Genetic analysis revealed that 24% of the patients were homozygous for M694V, followed by heterozygous M694V mutation (12.6%). The most common clinical symptoms in patients were peritonitis (86.6%). All patients were using colcicine.

Conclusion: It was observed that FMF patients treated with Erzincan were similar to the results of studies in Turkey in terms of mutation type and clinical complaints. Delay in diagnosis was found to be shorter compared with other studies. This study is important because it is the first comprehensive study in Erzincan province.

Keywords: Familial Mediterranean fever, genetic mutation, clinical features, Erzincan

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common monogenic periodic fever syndrome characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis, or erysipelas-like skin lesions. The disease typically progresses with attacks and is mostly self-limiting attacks lasting between one and three days. Abdominal pain is the most common symptom of fever in patients with FMF. The disease usually occurs in the first two decades of life, and rarely it can start after the age of 40. The disease usually occurs in the first two decades of life, and rarely it can start after the age of 40 (1).

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Although the disease is Mediterranean-originated, it is frequently seen in the Central-North Anatolian Region of the country. The prevalence of consanguineous marriages in Turkey also increases the incidence of FMF, which is a genetically transmitted disease. FMF prevalence in Turkey is nearly 1:400 to 1:1000 (2). FMF is inherited autosomal recessively and the responsible gene, MEFV (Mediterranean fever), is localized in the short arm of chromosome 16 and encodes a protein (pyrin) found especially in granulocytes (3). The most common mutation in patients in the Turkish population is M694V and followed by M680I, V726A, and E148Q (4). There is no diagnostic test for the diagnosis of FMF and clinical features make the diagnosis. Diagnosis is made by the typical features of attacks, patients' response to colchicine, family history, and exclusion of other causes of periodic fever (5,6). The Tel-Hashomer and Livneh criteria were originally developed for diagnosis in adult FMF patients. If patients have atypical clinical symptoms, genetic analysis may be required if clinical criteria are not sufficient and if it is necessary to confirm the diagnosis (7). One of the devastating complications of FMF in the long term is the development of amyloidosis. Because of the amyloid deposition, mainly the kidneys are involved, and other organs may also be affected (8). Colchicine has also been found to be effective in preventing FMF attacks, reducing the frequency of attacks, and preventing the development of amyloidosis (9). Early recognition of the disease is essential to reduce the progression to kidney failure, which is the most feared complication of the disease. In this study, it was aimed to investigate the first complaints, age at diagnosis, delay in diagnosis, most common clinical findings, and *MEFV* gene of patients with FMF living in Erzincan province. This study will contribute to the earlier detection of the disease and thus to the prevention of complications.

MATERIAL AND METHODS

In this cross-sectional study, patients aged between 18 and 65 years who were diagnosed with FMF according to Tel-Hashomer criteria and who were referred to the Erzincan Binali Yıldırım University Mengücek Gazi Training and Research Hospital Rheumatology and Physical Medicine and Rehabilitation clinic between January 2023 and May 2023 were included. Permission was obtained from the Erzincan Binali Yıldırım University Clinical Research Ethics Committee with the decision dated 22/12/2022 and numbered 2022-08/1. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients consented to the use of their information in this study. Main demographic and clinical data including (age, gender, first complaints and onset time, age of diagnosis, number of attacks in the last 1 year, treatments they received and whether they benefited from the treatment, and accompanying autoimmune diseases, family histories) and clinical features were recorded. The age at the first attack of the disease was recorded, and the age at the time of diagnosis was accepted as the age of diagnosis. Laboratory values, *MEFV* gene analysis, and HLA-B27 test results were recorded from the hospital database. Patients with a suspicious diagnosis were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA) 22.0 package program. Quantitative variables were expressed as mean ± standard deviation or median (minimum and maximum) as appropriate. and qualitative variables were presented as numbers and percentages. Chi-square test's were used to analyze categorical data. Student's t-test and Mann-Whitney U test were used to analyze continuous data. At the $p \leq 0.05$, all results were considered statistically significant.

RESULTS

A total of 142 (68 female, 74 male) FMF patients were enrolled in this study. The male/female ratio was 1.21. The mean age of patients (aged between 4 and 63) were 31.60±9.91 (in female was 30.67±9.06) years). Age at the onset of symptoms, age at diagnosis, and delay in diagnosis were not statistically different between the genders ($p>0.05$). Haemoglobin, mean platelet volume, erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A levels were higher in male patients ($p<0.05$). When family history was questioned in terms of FMF, 69.7% (99 patients) of all patients had a positive family history. Comparison of demographic and laboratory characteristics between gender in FMF are summarized in Table 1. One hundred patients (70.4%) stated that their first attack was before the age of 18. Two patients stated that their first attack was after the age of 40. Due to the delay in the diagnosis, 8 (4 female patients and 4 male) (5.6%) patients were diagnosed over the age of 40. Adult patients (23 patients) were diagnosed most frequently by internal medicine physicians in secondary care clinics. One hundred and thirteen patients (79.5%) responded well to colchicine therapy (tablets contain 0.5 mg, 2-3 times a day). Twenty-nine (20.4%) colchicine-intolerant patients were switched to alternative colchicine (2 times a day, tablets contain 1 mg). One hundred and ten patients (77.5%) showed good compliance with the treatment, while 22.5% of them had irregular usage of colcicine. All irregular users relapsed after a mean period of 1.89±1.24 months. Seventeen (12%) patients were using Anakinra in addition to colcicine, and 7 (4.9%) patients were using canakinumab. When

Table 1. Comparison of the demographic and laboratory characteristics between gender in familial Mediterranean fever (FMF)

Variables	Female (n=64, %45)	Male (n=78, %55)	p
Age (years) (min-max)	30.67±9.06 (18-51)	32.37±10.56 (18-63)	0.316
Age at the onset of symptoms (mean ± SD) yr	15.89±8.23	16.80±6.98	0.471
Age at diagnosis (mean ± SD) yr	19.56±9.61	20.28±8.60	0.632
Delayed diagnosis (mean ± SD) yr	3.70±2.22	3.46±2.45	0.541
The duration of follow-up (mean ± SD) yr	9.12±4.22	11.64±7.46	0.182
Positive family history (n, %)	45 (70%)	59 (75%)	0.473
Attack frequency (number/year);(min-max)	1.09±0.91 (1-6)	1.46±1.43 (1-8)	0.081
Hemoglobin (g/dL)	12.78±1.18	13.55±1.57	**0.012**
WBC (10^3/µL)	7.17±2.12	7.44±2.92	**0.474**
MPV (fL)	9.52±0.71	10.02±1.21	**0.040**
Serum amyloid A (mg/dL)	26.75±30.52	41.92±59.27	**0.049**
ESR (mm/hour)	24.18±9.18	31.74±16.04	**0.021**
CRP (mg/dL)	8.67±4.04	13.11±8.67	**0.023**
HLA B-27 (n, %)	20 (31.2)	24 (30.7)	0.147

SD: Standard deviation, yr: Year, min-max: Minimum-maximum, WBC: White blood cell, MPV: Mean platelet volume, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, HLA: Human leukocyte antigens

comorbid diseases were questioned in FMF patients, 37 (13 female, 24 male) (26%) patients had spondyloarthritis (SpA), 6 (4.2%) patients had Behcet's disease, 5 (3.5%) patients had Inflammatory Bowel disease (IBD), and 4 (2.8%) patients had systemic lupus erythematosus (SLE). The patients in the study (87 patients) were diagnosed in childhood (<18 years), fever (42 patients, %42.8) was often the first and only symptom in their attacks. The complaints of the patients during the attacks were recorded. The most common clinical finding during an FMF attack was that abdominal pain (peritonitis) was detected in 86.6% of patients. This was followed by arthralgia (61.2%) and fever (60.5%). There was no gender difference between fever and abdominal pain. Arthralgia was more common in male patients (p=0.13). Arthralgia was more common in male patients, and the difference was significant (p=0.13). The difference was significant in arthritis (p=0.35) and ankle involvement was the most common joint involvement. Twenty-one (14.7%) patients had abdominal operations (9 were acute appendicitis) and the difference between genders was significant (p=0.09). The patients in the study (87 patients) were diagnosed in childhood (<18 years), fever often the first and only symptom in their attacks. A comparison of the clinical features of the patients with FMF is shown in Table 2. The *FMF* gene test results of 138 patients were accessed from computer records. The most frequently observed mutation was M694V homozygous mutation (34 pateints, 24%) patients, followed by heterozygous M694V mutation (18 patients, 12.6%). Heterozygous P369S (4 patients, 2.8%) and heterozygous

Table 2. Comparison of the clinical features of patients with FMF

Clinical symptoms	Female n=64 (%)	Male n=78 (%)	Total n=142 (%)
Clinical findings in attack abdominal pain	57 (89)	66 (84.6)	123 (86.6)
Fever	36 (56.2)	50 (64.1)	86 (60.5)
Arthralgia	32 (50.0)	55 (70.5)	87 (61.2)
Arthritis	10 (15.6)	24 (30.7)	34 (23.9)
Pleuritis	11 (17.1)	12 (15.3)	24 (16.9)
Myalgia	19 (29.6)	23 (29.4)	42 (29.5)
ELE	5 (7.8)	7 (8.9)	12 (8.4)
Back pain	20 (31.2)	28 (35.9)	48 (33.8)
The abdominal operation (n%)	4 (2.8)	17(12)	21 (14.7)
Good response to colchicine	54 (84.3)	56 (71.7)	110 (77.5)
Secondary amyloidosis	2 (1.4)	2 (1.4)	4 (2.8)
Renal failure	3 (4.6)	5 (6.4)	8 (5.6)
Sakroileitis	8 (12.5)	14 (18)	22 (15.5)

n: Number, ELE: Erysipelas-like erythema, FMF: Familial Mediterranean fever

V726A (4 patients, 2.8%) mutations were rarer. Genotypic distribution of MEFV mutations in patients with FMF is shown in Table 3. Twenty-three patients had proteinuria (>200 mg/day in 24-hour urine). Renal amyloidosis was found in the biopsy results of 4 patients with nephrotic proteinuria. Two of the patients who developed amyloidosis had homozygous M694V mutations, 1 had heterozygous M694V mutation, and one had M694V/E148Q mutation. Three patients with a diagnosis of amyloid were male and had a family history of FMF. The clinical features of the most common mutation (homozygous M694V) in patients are summarized in Table 4.

Table 3. Genotypic distribution of MEFV mutations in patients with Familial Mediterranean fever

Mutations detected	The number of patients (%)
Homozygous M694V	34 (24%)
Heterozygous M694V	18 (12.6%)
Homozygous M680I	14 (10%)
Heterozygous M680I	10 (7%)
M694V/M680I	10 (7%)
M694V/V726A	7 (4.9%)
M694V/R202Q	7 (4.9%)
M694V/E148Q	6 (4.2%)
M680I/E148Q	7 (4.9%)
M680I/R202Q	6 (4.2%)
Heterozygous E148Q	6 (4.2%)
Heterozygous R202Q	5 (3.5%)
Heterozygous P369S	4 (2.8%)
Heterozygous V726A	4 (2.8%)

Table 4. Clinical features of patients with homozygous M694V

Variables	Number of the patients=34 (%)
Male sex (%)	24 (70.5)
Age at the onset of symptoms (mean ± SD) yr	16.01±6.09
Age at diagnosis (mean ± SD) yr	18.46±6.98
Delayed diagnosis (mean ± SD) yr	2.46±1.72
Positive family history (n, %)	25 (73.5)
Secondary amyloidosis (n, %)	2 (5.8)
SD: Standard deviation, yr: Year, n: Number	

DISCUSSION

In this study, demographic, clinical characteristics and recorded data in the files of patients with FMF followed up in a single center were analyzed. Although FMF was observed in certain ethnic groups originating in the Mediterranean and Middle East regions, it is seen more intensely in provinces such as Sivas, Tokat, and Erzincan in the country. The results of the study conducted by the Turkish FMF group showed that the incidence of the disease was almost equal in both sexes (M/F: 1.2/1) (9,10). In this study, in which 142 patients (64 females, 78 males) were evaluated, the male/female ratio was found to be 1.21/1, which is similar to the literature.

FMF usually occurs at a young age, the first attack occurs before ten years of age in approximately 60% of the patients, and onset in the majority of patients (90%) begins before the age of 20 years. Rarely, the first complaints may start over the age of 40 years (10). In a recently published large cohort of Armenians, the proportion of patients with onset ≥40 years was 3.4% (11). The mean age of first attack in the patients in the study was 16.39±7.55 (female 15.89±8.23, male 16.80±6.98), and 2 (1.4 %) patients had their first attack over the age of 40 years. The variable nature of the disease, the different clinical presentation in each patient, and the exacerbation of symptoms cause a diagnostic challenge in FMF. It causes considerable diagnostic delay even in endemic areas. In a nationwide study conducted in Turkey, the age at diagnosis was 16.4±11.5 years, and the diagnosis delay time was 6.9±7.6 years (12). Tamir et al. (13) reported the median delay in diagnosis for FMF populations as 8 years. The diagnostic delay of the patients in the study was shorter, unlike these studies. The diagnostic delay of the patients in the study was shorter, unlike the other studies. The mean delay in diagnosis in all patients was 3.57±2.35 (female: 3.70±2.22, male: 3.46±2.45) years ($p<0.05$). The reason for the delay in diagnosis in female patients compared with male patients was considered to be the inability to recognize abdominal pain attacks because they coincided with monthly menstrual periods. Although FMF has a heterogeneous clinical spectrum, fever and peritonitis are the most common symptoms reported in over 90% of patients of all ages and ethnicities (13,14). The clinical picture and laboratory findings are compatible with acute peritonitis. The fever usually 38-40 °C during the attack and lasts for 12-72 hours. Fever often the only symptom in childhood but may not accompany every FMF attack (14). In the study, the most common finding during FMF attack was abdominal pain in 123 (86.6%) patients, followed by arthralgia (861.2%) and fever (60.5%). The incidence of arthritis in Mediterranean fever is 40-70% and it is usually lower extremity involvement (9,15). Ankles (12.6%) and knees (7.0%) were more

frequent involvement in the patients, and similar to studies, arthralgia (61.2%) was a more common symptom than arthritis (23.9%) in the patients group. Studies show that the incidence of sacroiliitis is high in FMF patients and its close relationship with SpA. It was emphasized in studies that axial signs of symptoms were more severe in HLA-B27-positive cases (16). The patients in the study, 48 (33.8%) patients with FMF had inflammatory low back pain. When the magnetic resonance imaging (MRI) results of patients with inflammatory low back pain were examined, findings consistent with sacroiliitis were observed in 22 (15.5%) patients. In the whole patient group, 44 (30.9%) patients were HLA B-27 positive, and there was no significant difference between genders. The rate of HLA B-27 positivity was found to be 37.5% (18 patients) in patients with inflammatory low back pain. Many cases have been reported that underwent laparotomy considering acute abdomen with findings such as fever, abdominal pain, distension and tenderness in abdominal examination and air-fluid levels in standing abdominal X-ray (17). In a study conducted in Turkey, it was reported that the young population applied to the emergency department with acute abdomen and approximately 19% of these patients were operated on considering acute appendicitis (6,18). Before the diagnosis of FMF, a total of 21 (14.7%) patients were operated for acute abdomen, while 15 (10.5%) patients were operated for acute appendicitis. The gene that causes FMF (Mediterranean fever gene, *MEFV*) is located on the short arm of chromosome 16p13.3. The frequencies of 8 mutations (M694V, M680I, E148Q, V726A, A744S, R202Q, R761H, T267I) reported to be frequently encountered in the *MEFV* gene in the literature were investigated. Although the MEFV mutation in Turkish patients showed great variability, the most common mutation was M694V between 14.7% and 53.8% of MEFV alleles. This is followed by V726A, M680I and E148Q.8,9. Dundar et al. (19) found in a cohort showed that the most frequent mutations were M694V, E148Q and M680I, respectively. M694V homozygous mutation (24%) was the most frequently detected mutation in the study group, followed by M694V heterozygous mutation (12.6%) and homozygous M680I (10%) respectively. It was similar to the literature in terms of frequently found mutations. Heterozygous E148Q (4.2%) was found to be less in number than in the literature. In a study conducted in Turkey, the incidence of sacroiliitis on X-ray was found to be 10.5%. In the evaluation of clinical findings according to mutation type in the study, male sex (24 patients) was more dominant in patients with M694V homozygous mutations and sacroiliac joint involvements (18 patients) were found more frequently than all other mutation types. In contrast, sacroiliitis was evaluated with MRI in the study. Amyloidosis is the most serious complication of FMF and often affects the kidneys. It presents with proteinuria and leads to end-stage renal disease. According to the data of the FMF study, its incidence was found to be 12.9% (2,12). Differences in clinical cases and the development of amyloidosis are affected by the type of MEFV mutations and it has been associated with a severe course of the disease in some ethnic groups. In the study conducted in Turkey, FMF patients who are homozygous for M694V have a 6-fold risk of amyloidosis compared with FMF patients with other *MEFV* gene mutations. In addition, male gender and family history of amyloidosis were defined as another risk factors (9,12,20,21). In the study, two of 4 patients with renal amyloidosis had homozygous M694V mutation, one patient had heterozygous M694V mutation, and one patient had M694V/E148Q mutation, similar to the literature. Three patients with a diagnosis of amyloid were male and had a family history of FMF. One of these patients was diagnosed over the age of 40 and the first finding was proteinuria. The discovery of colchicine as an effective drug for FMF was a big step forward, and the response to this drug could also be used to confirm the diagnosis. Colchicine is the gold standard treatment that is effective in preventing attacks and protects against the development of amyloidosis (12,17). All patients were receiving at least 1 mg per day colchicine treatment. 77.5% of the patients showed good compliance with the treatment, 22.5% of them were on irregular colchicine use, and recurrence in irregular users recurred after a mean period of 1.89±1.24 months. It is defined as colchicine resistance with >6 attacks per year, and up to 5% of patients are considered to be resistant or inadequately responsive to colchicine (colchicine intolerance) (22). Blocking interleukin-1, which is involved in the pathogenesis of the disease, can be considered as alternative treatment options in resistant AAA cases and organ involvement (23). Twenty-four (16.9%) of the patients were using biological therapy (blocking the IL-1 cytokine) in addition to colcicine. FMF has many inflammatory disease comorbidities such as SpA, Behçet's disease, and ulcerative colitis. In one study, SpA prevalence was reported to be 0.4% in FMF (8,9). Among the vasculitides, it has been reported in some studies that the incidence of PAN and Henoch-Schönlein purpura is higher in FMF patients (24). In the study, 37 (13 female, 24 male) (26%) patients had SpA, 6 (4.2%) patients had Behçet's disease. Also, 5 (3.5%) patients had IBD and 4 (2.8%) patients had SLE. It was observed that FMF patients treated with Erzincan were similar to the results of studies in Turkey in terms of mutation type and clinical complaints. Delay in diagnosis was found to be shorter compared with other studies.

Study Limitations

Some strengths and limitations of the study should be addressed. The main limitation was the cross-sectional and single-center plan of the study. This prevented clear conclusions about the follow-up of the patients. Because it was a single-center, the number of patients was low.

CONCLUSION

FMF is a disease that is frequently observed in Erzincan province and its diagnosis can often be difficult. The fact that it is still a late-diagnosed disease and the delays in its referral to rheumatology causes patients to undergo unnecessary operations and increase the risk of amyloidosis. The aim of this study was to provide earlier recognition of this disease, which is common in Erzincan province, to increase awareness about the disease, and thus to enable patients to find a chance for earlier treatment.

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Ethics

Ethics Committee Approval: Permission was obtained from the Erzincan Binali Yıldırım University Clinical Research Ethics Committee with the decision dated 22/12/2022 and numbered 2022-08/1.

Informed Consent: All patients consented to the use of their information in this study.

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CASE REPORT AND LITERATURE REVIEW

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A CASE REPORT: CERTOLIZUMAB-INDUCED KOUNIS SYNDROME

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Abstract

Kounis syndrome (KS) is an important condition to consider in patients who present with acute coronary syndrome and have a history of allergies or anaphylaxis. It is caused by an inflammatory response to an allergen or anaphylactic trigger that can lead to the narrowing or spasm of the coronary arteries and can result in myocardial infarction or angina. The case you presented is interesting because it suggests that tumor necrosis factor-alpha (TNF-α) inhibitors such as certolizumab can also trigger an allergic or anaphylactic reaction that can lead to KS. It highlights the importance of monitoring patients for potential allergic reactions to these medications and considering KS in patients who present with acute coronary syndrome after receiving these drugs. Further research is needed to better understand the link between TNF-α inhibitors and KS and to develop strategies to prevent and manage to this potentially life-threatening condition. In the meantime, it is important for healthcare providers to be aware of the potential risk and to take appropriate precautions when prescribing TNF-α inhibitors to patients with a history of allergies or anaphylaxis.

Keywords: Allergy, certolizumab, Kounis syndrome, percutaneous coronary angiography

INTRODUCTION

Kounis syndrome (KS) is defined as acute coronary syndrome or angina associated with inflammatory cells triggered by allergic or anaphylactic conditions. It is a life-threatening condition that can be triggered by any substance, including drugs, food, or environmental agents such as insect bites. KS is often overlooked and patients cannon get a diagnosis because it is a rare cause of acute coronary syndrome, although it is not a rare topic of medical literacy. TNF-α inhibitors are also a group of drugs that can cause an allergic reaction; thus, patients receiving these drugs should be monitored closely for the development of symptoms that may indicate KS (1,2). We present a case not previously described in the literature who presented to the emergency department with anaphylactoid symptoms after taking certolizumab and was diagnosed with acute coronary syndrome.

CASE REPORT

While being followed up for rheumatoid arthritis (RA), a 39-year-old female patient experienced mild redness in the application area after the first dose of 400 mg certolizumab was administered subcutaneously to the abdomen for therapeutic purposes. The patient left the hospital after being kept under observation for a while. On returning home, about an hour and a half after the application, the patient developed itching, dyspnea, and syncope. She then applied to the emergency room. Among the risk factors of the patient were drug allergy and a history of RA. Previously an allergic reaction in the form of urticaria was observed against methotrexate and leflunomide, and skin rash, sore throat, shortness of breath, and hypotension developed with tocilizumab. Although the patient did not experience any reactions with prednisolone, hydroxychloroquine, diclofenac

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sodium, flurbiprofen, and 500 mg paracetamol, she had a history of urticaria with 1000 mg paracetamol. During the emergency follow-up, chest pain developed in the form of pressure radiating to the left arm, blood pressure was 70/40 mmHg at this time. Normal sinus rhythm and negative t waves in leads V1-V2 were observed in the 12-lead electrocardiogram (ECG). Arrival troponin I was 2.8 (0-15.6). Considering systemic allergic reaction and anaphylactic shock, the patient was administered 80 mg methylprednisolone 45.5 mg pheniramine with intravenous fluid support and intramuscular adrenaline. Troponin I levels were 46.3 at the third-hour control and 95.3 at the six-hour follow-up. KS was considered, and it was deemed appropriate to continue the follow-up under intensive care conditions. Since there was no room in our center, the patient was transferred to another center that could meet her intensive care needs. In the ECG taken at the center to which she was referred, ST elevations of 0.5 mm in D1 and 1 mm in aVL, as well as ST depressions in D2, D3, and aVF have been observed (Figure 1). After local anesthesia, a needle was used to puncture the patient's right femoral artery, and an introducer sheath was placed. The right and left coronary arteries were visualized at appropriate projection angles using appropriate diagnostic catheters. The left main coronary artery (LMCA) was found to be normal, but plaques that did not cause significant stenosis were observed in the proximal left anterior descending artery (LAD) after the procedure. Thereafter, it was suspected that the patient had developed drug-induced type I KS. During the subsequent clinical follow-up, negative T waves were observed in V1-V3, and non-specific ST changes were observed in V4-V6 in the ECG. This state was considered as pseudonormalization and it supports the ischemia that occurred when the patient presented with chest pain to our clinic, and thus the diagnosis of KS as well (Figure 2).

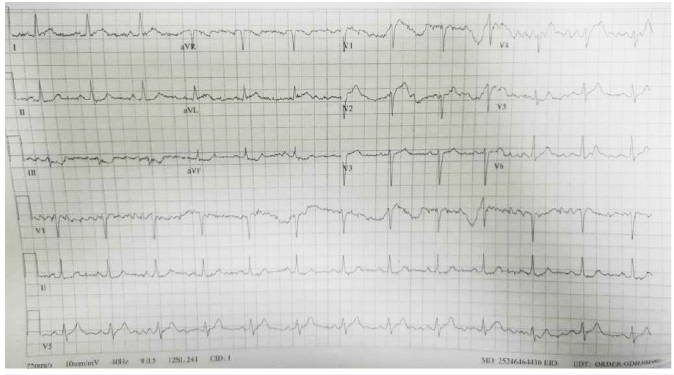

Figure 1. ECG showed ST elevations of 0.5 mm in D1 and 1 mm in aVL, as well as ST depressions in D2, D3, and aVF
ECG: Electrocardiogram

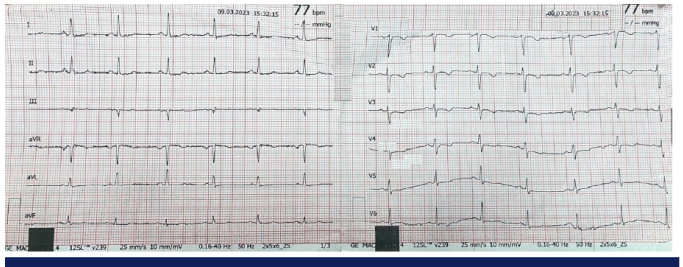

Figure 2. Negative T waves were observed in V1-V3, and non-specific ST changes were observed in V4-V6 in the ECG
ECG: Electrocardiogram

DISCUSSION

TNF-α inhibitors are used for treating rheumatological diseases such as RA, ankylosing spondylitis, and psoriatic arthritis, and the efficacy and safety of certolizumab for treating these diseases have been demonstrated. Certolizumab is a TNF-α inhibitor agent that does not contain the pegol Fc domain but instead contains polyethylene glycol, and it is approved for adult patients with moderately to severely active RA. To our knowledge, KS with certolizumab and other TNF-α inhibitors agents except infliximab has not been reported, whereas there have been rare reports of anaphylactic reactions to certolizumab (3). In an article prepared in the form of a letter to the editor in 2014, KS was suspected in 3 patients who were given follow-up infliximab for inflammatory bowel disease, but this has not been proven (4). Here we present our case, which we think is the first report of type I KS caused by certolizumab. Our patient was followed up with moderate RA and certolizumab treatment was started because an allergic reaction developed with conventional synthetic disease-modifying antirheumatic drugs that had been previously started. She applied to the emergency department with complaints that started an hour and a half after the first dose of the drug. Type I KS caused by certolizumab was considered due to the pressure-like angina lasting longer than 30 min and the observation of plaques that did not cause significant stenosis in the proximal LAD by percutaneous coronary angiography (PCAG) performed upon the significant gradual increases in troponin I during follow-up in the emergency department. Mast cell granules contain various mediators, particularly heparin and histamine, and also tryptase, chymase, carboxypeptidase, cathepsin C and G (5). KS is an acute coronary syndrome characterized by coronary artery spasm caused by these inflammatory mediators released into the environment as a result of endothelial dysfunction or mast cell degranulation with microvascular manifestation. This allergic angina syndrome caused by allergic reactions was first described in 1991 (6). Most cases (80%) occur within 1 h of exposure to the trigger. KS should be suspected in patients presenting with chest pain, shortness of breath, wheezing, and erythema. Three variants of KS have been described, the most common type I KS

(73%) developing coronary artery spasm without an underlying atherosclerosis. It occurs due to plaque erosion or rupture of type II (22%), seen in patients with pre-existing but asymptomatic coronary artery disease. Type III (5%) represents thrombosis due to an allergic reaction to the coronary stent (7). Risk factors include a previous history of allergies, diabetes, hypertension, dyslipidemia, and smoking. In clinically suspected patients, blood biochemical tests such as serum histamine, immunoglobulin E (IgE), eosinophils, tryptase, myocardial enzymes, and ECG and coronary angiography results support the diagnosis of KS. Tryptase, histamine, and IgE levels were not measured in our patient. However, a negative serum histamine level does not exclude the diagnosis of KS because serum histamine has a very short half-life of 8 min (8). In addition, the application of IgE levels in the diagnosis of KS is uncertain, and a normal IgE level does not exclude the diagnosis of KS (8). However, IgE levels may also be elevated in patients with acute coronary syndrome. Clinicians should carefully review the patients medical history, including medication use and allergic reactions critical to the diagnosis of KS. In this study, the diagnosis was suspected mostly based on the history and clinical findings. Treatment management for KS involves the management of allergic reactions and myocardial revascularization. Allergic reaction control with antihistamines and corticosteroids in patients with type I KS may also relieve cardiac symptoms (9). Existing vasospasm can be easily reversed by vasodilators. Fluid resuscitation is important in patients presenting with anaphylactic shock. The use of epinephrine may worsen myocardial ischemia and coronary vasospasm, prolong the QTc interval, and cause arrhythmias. In the type II variant, treatment should be initiated with an acute coronary event protocol in addition to antihistamines and corticosteroids (10). However, morphine, which is widely used in acute coronary syndrome, should be used with caution because of its mast cell degranulation effect and because beta-blockers have unmet alpha-adrenergic effects (7). Treatment management in type II and type III KS includes timely PCAG. In this study, PCAG was performed because of persistent angina, a significant increase in troponin values in repetitive measurements, and ST depression in D1-AVL in ECG. Plaque that did not cause significant stenosis was detected in the proximal LAD; therefore, type I KS is considered. Vasospastic angina occurred one and a half hours after the administration of certolizumab, followed by an increase in troponin levels. No case of KS triggered by either the other TNF-α inhibitors is as etanercept, adalimumab, golimumab, or certolizumab has been reported to date. Regarding another TNF-α inhibitors, infiliximab, there were three suspicious case reports in the form of letters to the editor, but these have not been proven (4). Therefore, our case is important. Allergic reactions can be seen with TNF-α inhibitors, especially infiliximab, and patients may present with various presentations of these reactions. As a result, KS is not very rare but perhaps often overlooked. It is important to perform the necessary tests for diagnosis, especially in patients who present to the emergency department with shortness of breath and angina and who have a history of exposure to environmental agents such as insect bites and drug use before symptoms and KS should be kept in mind in these cases. In these patients, cardiac findings and allergic symptoms should be treated immediately. Therefore, considering the disease first and then confirming the diagnosis and appropriate treatment management can be lifesaving.

Ethics

Informed Consent: Informed consent was obtained from our patient included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.D.K., B.N.C., R.T.Ö., Y.P., Concept: N.D.K., Design: N.D.K., Data Collection or Processing: N.D.K., R.T.Ö., Analysis or Interpretation: N.D.K., B.N.C., Literature Search: N.D.K., Y.P., Writing: N.D.K., B.N.C.

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CASE REPORT AND LITERATURE REVIEW

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A FAMILIAL MEDITERRANEAN FEVER PATIENT WITH MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS: A CASE REPORT AND LITERATURE REVIEW

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Abstract

Amyloidosis is the most important kidney complication determining the prognosis of familial Mediterranean fever (FMF) and presents with proteinuria at a nephrotic level. Other than amyloidosis, several other different renal involvements have been reported in FMF. The case is here presented of a patient determined with mesangial proliferative glomerulonephritis (MsPGN) in the kidney biopsy taken because of proteinuria and a good response with colchicine and azathioprine (AZA) treatment is presented. In this study, evaluations were made of cases with glomerulopathy other than amyloidosis in the literature. The data of 31 cases were analyzed, and it was seen that MsPGN was reported in almost half of these. Hematuria was also reported in some of these patients, most whom had nephrotic range proteinuria. Although colchicine treatment was sufficient in most cases, some patients were administered corticosteroid and AZA treatment. In conclusion, in FMF patients determined with proteinuria and/or hematuria, it should be kept in mind that there may be not only amyloidosis but also renal involvement other than amyloidosis, and the differential diagnosis should be made with kidney biopsy. Although colchicine treatment seems to be effective in renal involvements other than amyloidosis, immunosuppressive treatments may be necessary in some cases.

Keywords: Familial Mediterranean fever, amiloidosis, glomerulonephritis, colchicine

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive transmitted disease characterized by recurrent inflammatory attacks in serous and synovial membranes and fever (1). Secondary amyloidosis is frequently seen and is the most important complication determining disease prognosis in FMF (2). In biopsies taken from FMF patients because of proteinuria, different renal involvements other than amyloidosis have been reported (3-6). The aim of this paper was to review the literature related to this topic by presenting the case of an FMF patient diagnosed with mesangial proliferative glomerulonephritis (MsPGN).

CASE REPORT

A 44-year-old female patient first presented at our outpatient clinic in April 2007 with complaints of pain in the soles of the feet, swelling on the dorsal foot, and heel pain. It was learned

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that 7 years previously the patient had experienced swelling, redness and restricted movement in the left knee which lasted for 1 week and recovered spontaneously. Swelling developed in the ankle 3 years previously, and with a diagnosis of rheumatoid arthritis from the doctor consulted, treatment was started with methotrexate and steroids. The complaints regressed in a short time with this treatment, which the patient took for 6 months and then terminated. When the patient had complained of heel pain and swelling on the dorsum of the feet for the past year, it was learned that for the last 17 years, the patient had experienced pain spread across the whole abdomen lasting 2-3 days accompanied by fever, which then recovered spontaneously. The patient also stated that at the same time she experienced chest pain and joint complaints. The attacks occurred every 10-15 days and sometimes once a month. With high acute phase reactants and no pathology determined in the physical examination, the patient was diagnosed with FMF and treatment was started with colchicine 3x1. From the family anamnesis, it was learned that the patient's son had been recently diagnosed with FMF and Behçet's disease, and there was consanguinity of the patient's parents (first cousins). The laboratory test results were as follows: Erythrocyte sedimentation rate: 35 mm/h, urea: 28 mg/dL, creatinine: 0.7 mg/dL, aspartate aminotransferase: 18 IU/L, alanino aminotransferase: 13 IU/L, total protein: 7.1 gr/dL, and albumin: 3.8 gr/dL. Mild microcytic anemia (hematocrit: 33%) was determined on the hemogram and proteinuria in the full urine analysis. As approximately 1.5 g proteinuria was determined in the 24-hour urine test, rectal biopsy was planned with respect to amyloidosis, but the biopsy result was normal. On abdominal ultrasonography, other than increased liver dimensions (19 cm), there was no pathology. Complement levels, IgA, IgM, and IgG levels were normal, and the autoantibodies examined (anti-nuclear antibody, extractable nuclear antigens, anti dsDNA, and anti-neutrophilic cytoplasmic antibody) were determined to be negative. As M694V homozygote mutation was determined in the Mediterranean fever) gene, kidney biopsy was performed. Because of the biopsy, increased cells and mesangial expansion in some glomerules, thickening in basal membranes, periglomerular fibrosis in one glomerulus, and lymphocyte infiltration in the interstitium. No accumulation was detected in the glomeruli in the immunofluorescence examination (Figure 1). Amyloidosis was not determined by Congo red staining. With a diagnosis of MsPGN, treatment was started of mg/day azathioprine (AZA) and 50 mg/day losartan. After 6 months, protein of 542 mg/day was determined in the 24-hour urine test, and at the end of one year, 258 mg/day. The patient had no complaints under treatment.

LITERATURE REVIEW

To identify FMF cases with renal involvement other than amyloidosis, the Web of Science and PubMed databases were scanned using the headings of "FMF and MsPGN", "membranoproliferative (MP) GN" and "non-amyloid renal involvement". A total of 19 relevant cases/case series were identified, of which 3 (7-9) were excluded from the evaluation as they were mentioned by the same author in a 1992 publication (3). Together with the current case, 31 GN or nephropathy (NP) cases were identified in the literature, of which 54.8% were adult cases (3-6,10-21). The most reported GN type was MsPGN (15 cases) of which half were adults. In 3 adult and 2 pediatric cases of MsPGN, IgA NP was reported and in 1 pediatric case, IgM NP. In addition, IgA NP was reported in another 1 adult and 1 pediatric case, giving 7 (22.6%) cases of IgA NP. Other than MsPGN, cases were reported of MPGN (n=4), focal segmental glomerulosclerosis (n=5), rapidly progressive (RP) GN (n=2) and 1 case each of membranous GN, focal proliferative GN, and fibrillar GN (Table 1). Despite insufficient data in the publications, approximately half of the cases were seen to have proteinuria at a nephrotic level (3,6,11,12,20,21) and 14% had hematuria (12,13,18,21). Henoch-Schönlein purpura (HSP) was reported in only 4 cases, of which 1 also had polyarteritis nodosa (PAN) (4,10,18). Although IgA, IgM, IgG, and C3 accumulation was reported in the kidney biopsies of most patients, cases with no immune accumulation determined were also reported (19,21). Of the 10 cases, including the current case, with known mutations, M694V homozygote mutation was determined in 6 (6,11,14,17,18), of which 4 were reported as MsPGN. In addition, E148Q heterozygous positivity

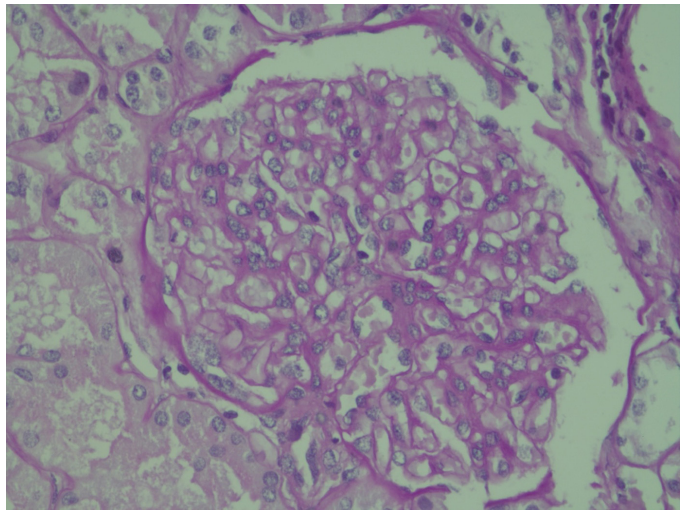

Figure 1. In the microscopic examination, there was mild swelling in the glomeruli, expansion in the mesangial matrix, and a slight increase in mesangial cells [Periodic acid Schiff (PAS)], X 200).

was determined in 2 cases with MsPGN. The publications were evaluated with respect to treatment; although treatment data for 4 cases could not be reached, it was observed that all of the cases used colchicine and 13 cases were in remission with only colchicine. A good response was reported to have been obtained with the other drugs corticosteroids (Cs) and AZA, as in the current case. The 2 cases of RPGN were given cyclophosphamide (CyP) in addition to Cs, and while one reached remission, the other was reported to have required chronic hemodialysis (3). In the case reported by Girisgen et al. (18), colchicine was administered for MsPGN (IgA), but it was emphasized that as the PAN clinical condition did not respond to Cs and CyP, intravenous immunoglobulin had to be administered.

DISCUSSION

Amyloidosis is the most important renal complication determining the prognosis of FMF and it presents with proteinuria. Long-term colchicine use can protect the patient

Table 1. Renal involvements other than amyloidosis in FMF patients

GN type (reference)		HSP/ PAN	n	Treatment	MEFV mutation	Outcome
Focal MsPGN (10)	Child (1)	HSP	2	Colchicine	ND	ND
Diffuse MsPGN[a] RPGN (3)	Child (3) Child	(-)	6 2	Colchicine Colchicine + CyP + Cs	ND	Improvement[b] 1 remission 1 hemodialysis
MPGN (5)	Child	ND	1	ND	ND	ND
MPGN FPGN (4)	Child	HSP (-)	1 1	ND	ND	ND
Fibrillary GN (12)	Adult	(-)	1	ND	M608I heterozygote	ND
MPGN (6)	Adult	(-)	1	Colchicine + Cs Azatioprin	M694V homozygote	Improvement[b]
MsPGN (11)	Child	(-)	1	Colchicine	M694V homozygote	Remission
MsPGN (IgA NP) (13)	Child	(-)	1	Colchicine	(-)	Remission
MsPGN (IgM NP) (14)	Child	(-)	1	Colchicine	M694V homozygote	Remission
IgA NPs (15)	Child	(-)	1	Colchicine	ND	Remission
Membranöz GN (16)	Adult	(-)	1	Colchicine	M680I/V726	Remission
IgA NP (17)	Adult	(-)	1	Colchicine	M694V homozygote	Remission
MsPGN (IgA NP) (18)	Child	HSP and PAN	1	Colchicine [c]Cs+CyP - IVIG	M694V homozygote	ND
MsPGN (19)	Adult	(-)	1	Colchicine	E148Q heterozygote	Remission
MPGN FSGS (20)	Adult	(-)	1 5	Colchicine + Cs Colchicine	ND	Non-nephrotic proteinuria
MsPGN (22)	Adult	(-)	1	Colchicine + Cs	E148Q heterozygote	Remission
MsPGN (current case)	Adult	(-)	1	Colchicine Azatioprin	M694V homozygote	Remission
Total	17 Adult 14 Child		31			

[a]Three adult patients had IgA NP, [b] Non-nephrotic proteinuria, [c]For PAN treatment
HSP: Henoch-Schonlein purpura, PAN: Polyarteritis nodosa, MsPGN: Mesangial proliferative glomerulonephritis, RPGN: Rapidly progressive glomerulonephritis, CyP: Cyclophosphamide, Cs: Corticosteroid, FPGN: Focal proliferative glomerulonephritis, MPGN: Membranoproliferative glomerulonephritis, FSGS: Focal segmental glomerulosclerosis

against the development of amyloidosis (2). Although there are no epidemiological studies of renal involvement other than amyloidosis, cases and case series have been reported. In a cohort of 106 FMF patients, Eliakim et al. (22) reported renal amyloidosis at a rate of approximately 12%, and renal problems other than amyloidosis in approximately 22% (temporary or permanent hematuria, recurrent acute pyelonephritis, typical acute post-streptcoccus GN, and other GN types). MsPGN has been reported in different systemic diseases such as systemic lupus erythematosus, HSP, rheumatoid arthritis, and vasculitis. The first publication related to glomerular diseases other than amyloidosis in FMF cases was by Flatau et al. (10) in 1982, in which focal MsPGN was determined in the biopsies of 2 cases with FMF and HSP. Subsequently, Said et al. (3) reported FMF cases with a diagnosis of IgA NP in whom a good response was obtained with colchicine (7,8). There have also been reports of MsPGN, MPGN, membranous GN, focal segmental glomerulosclerosis, and occasionally RPGN, IgM NP, focal proliferative GN, and fibrillar GN in FMF patients (13,23). The etiopathogenesis of GNs other than amyloidosis in FMF is not fully known. PAN has been reported in 1% of FMF cases and HSP in 5% (18). Kidney involvement in HSP is seen especially as IgA NP. In the review of literature performed in this study, HSP was determined in only 4 of 31 cases evaluated. Even if the other IgA NP cases were linked to HSP, the remaining cases couldnot be explained by this. The *MEFV* gene encodes pyrine, which is expressed in mature neutrophils and enables the suppression of inflammation. However, pyrite that has undergone mutation activates inflammasomes mediated by NF-kappa B and the activation of IL-1β and other inflammatory cytokines. Consequently, an abnormal immune response occurs. This increased inflammatory response is thought to facilitate immunological glomerular damage. Insufficient clearance of the immune complexes formed because of a hyper immune response can cause the development of glomerular disease (3,24-26). However, because immune complex accumulation was not seen in all cases, renal involvement other than amyloidosis cannon be explained by a single mechanism. Colchicine is effective in several non-amyloidosis renal involvements and has provided remission alone. The effect mechanism of colchicine in FMF is not exactly known, but it is thought to affect chemotaxis through its effect on microtubules. In addition, colchicine, which also has antioxidant properties, is thought to be effective in remission of proteinuria in FMF-related GN through these effects (11). However, in some cases, it is not sufficient alone, and remission can be achieved in these cases with immunosuppressive treatment and Cs use (6). In the case presented in this paper, because of GN developing under colchicine treatment, AZA was started and remission was obtained in the patient.

CONCLUSION

In FMF patients determined with proteinuria and/or hematuria, it should be kept in mind that there may be not only amyloidosis but also renal involvement other than amyloidosis, and the differential diagnosis should be made with kidney biopsy. Although colchicine treatment seems to be effective in renal involvements other than amyloidosis, immunosuppressive treatments may be necessary in some cases.

Ethics

Informed Consent: A written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., Ö.Ö.I., A.C., Concept: A.Y., D.K.Y., Design: A.Y., Data Collection or Processing: A.Y., Ö.Ö.I., A.C., Analysis or Interpretation: .A.Y., D.K.Y., Literature Search: A.Y., Ö.Ö.I., Writing: A.Y., Ö.Ö.I.

Conflict of Interest: The authors have no conflicts of interest to declare.

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IMAGE ARTICLE

Rheumatology Quarterly

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PALPABLE SWELLING IN THE NECK: MASS OR LYMPHADENOPATHY OR ANOMALY?

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Keywords: Neck mass, swelling, cervical rib

A 23-year-old woman with seropositive rheumatoid arthritis presented with the complaint of palpable swelling in the left neck region, which she had noticed for the last 1 year. Physical examination revealed a firm, painless mass in the left cervical region. A chest X-ray (A) shows the unilateral asymmetric cervical rib (Figure 1).

Cervical ribs are rare anatomical anomalies and the supernumerary ribs arising mostly from the seventh cervical vertebrae are believed to result from mutation of *HOX* genes (1). They are usually bilateral but often asymmetric and are more common in females. In 90% of cases, they tend to be asymptomatic but can cause thoracic outlet syndrome by compression of the brachial plexus or subclavian artery/vein.

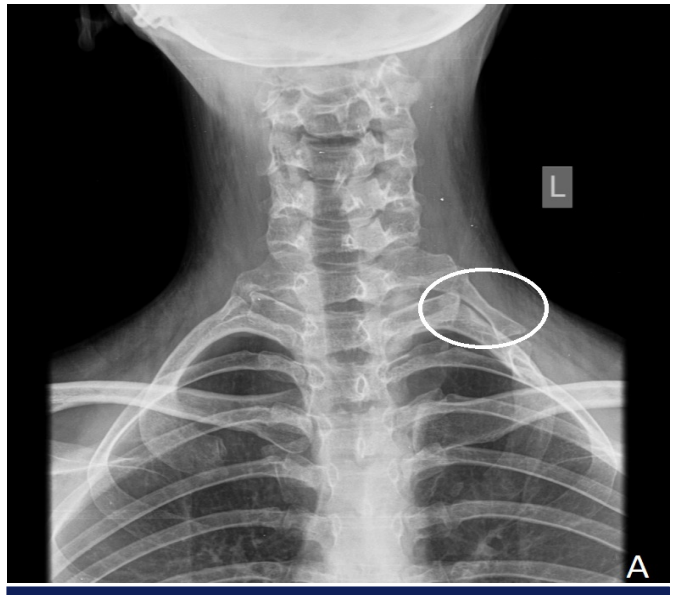

Figure 1. Cervical rib

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Ethics

Informed Consent: Informed consent was obtained from our patient included in this study.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

REFERENCE

Henry BM, Vikse J, Sanna B, et al. Cervical Rib Prevalence and its Association with Thoracic Outlet Syndrome: A Meta-Analysis of 141 Studies with Surgical Considerations. World Neurosurg 2018;110:e965-78.

IMAGE ARTICLE

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A CASE OF ATYPCAL BREAST CANCER

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Keywords: Lymphedema, breast cancer, rash

A 61-year-old female patient presented with complaints of widespread swelling, pain and numbness in the entire left arm (Figure 1A). There were skin blistering, brown erythematous papules, approximately 2x1 cm in size, on the upper left side of the sternum around the navigating 15, which was the complaint of 2 fragments (Figure 1B). No known comorbidity. Patient swelling was evaluated as lymphedema and chest computed tomography (CT) and mammography were performed to investigate the etiology. CT scan revealed a 9 mm nodule in the left upper lobe and a 1.5 cm conglomerate lymphadenomegaly in the left axilla (Figure 2A). Magnetic resonance imaging of the left arm showed intense edema around the brachial plexus and conglomerate lymphadenoma (Figure 2B). No mass was observed in the breast ultrasonography and mammography. Lengthening, operating functions, and complete blood count were normal in the examinations. Sarcoidosis and connective tissue diseases were excluded from the patient. The scan results from the papule was reported as carcinoma metastasis. After an excisional operation performed on left axillary lymphadenomegaly was reported as lobular breast carcinoma metastasis, the patient was referred to the oncology department and was maintained.

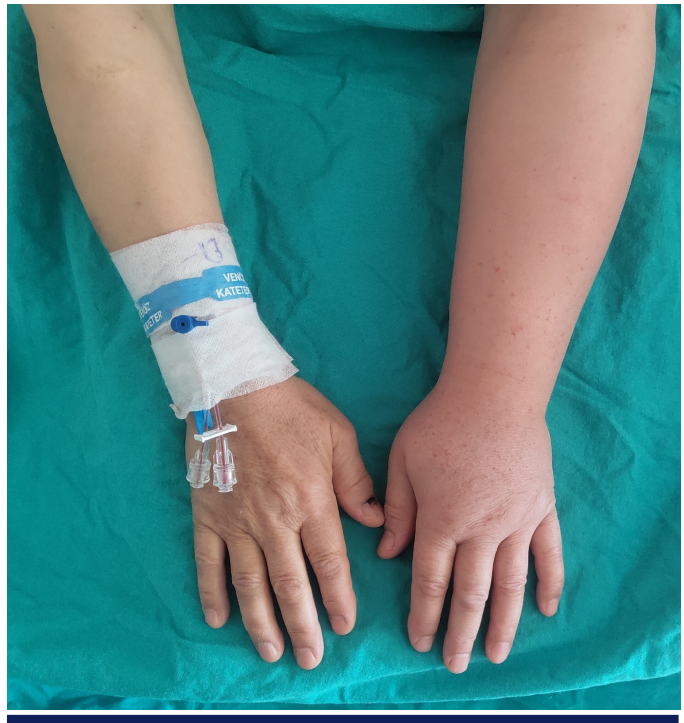

Figure 1A. Widespread swelling in the left arm

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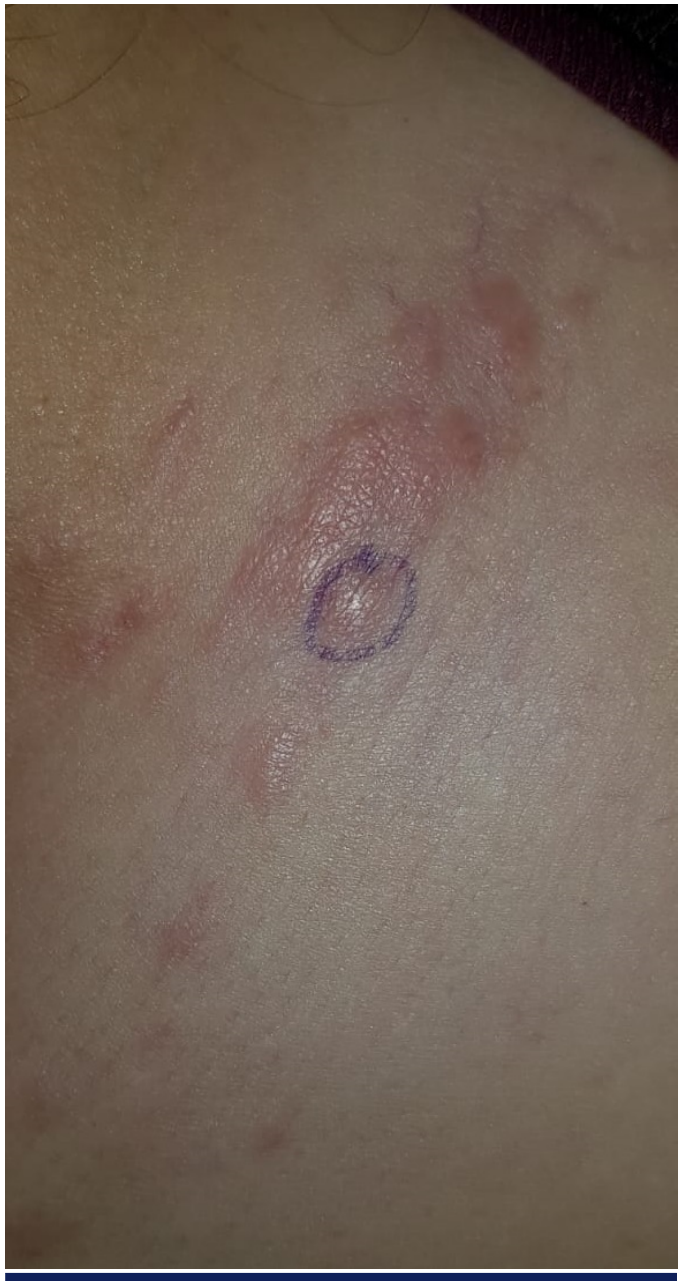

Figure 1B. Slightly reddened skin and puffy rash on the left side of the neck

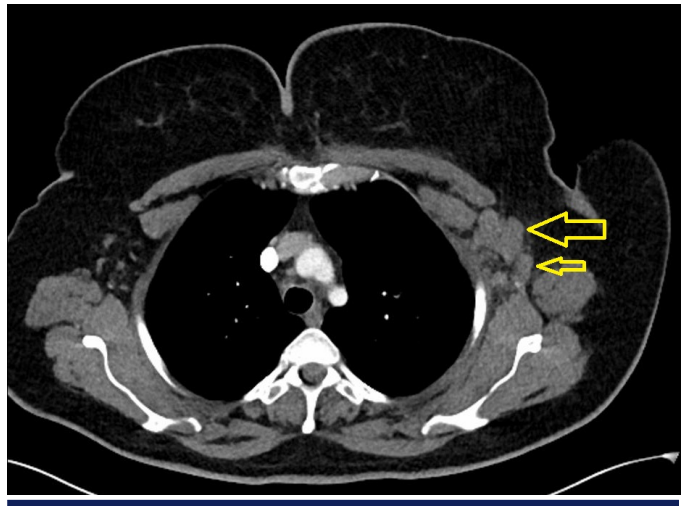

Figure 2A. Conglomerate lymphadenomegaly

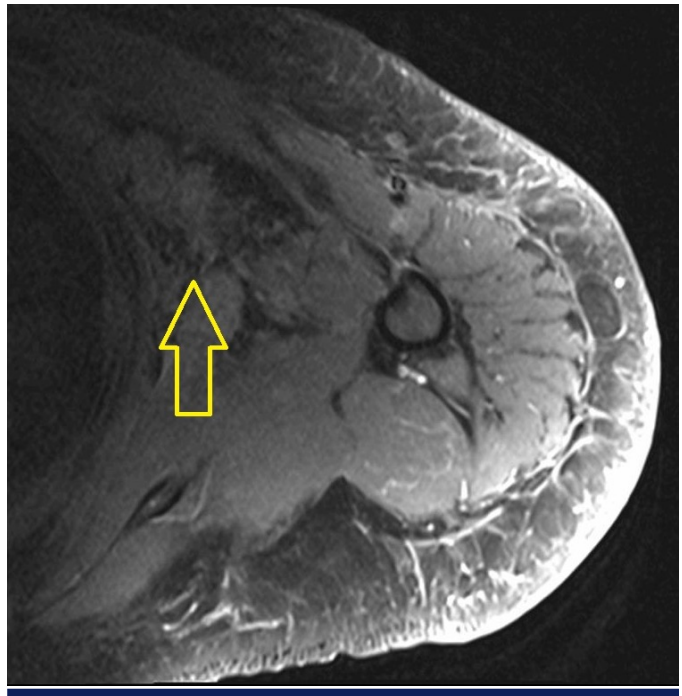

Figure 2B. Conglomerate lymphadenomegaly in the magnetic resonance

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.E., B.E.M., Concept: B.E., B.E.M., Design: B.E., B.E.M., Data Collection or Processing: B.E., B.E.M., Analysis or Interpretation: B.E., Literature Search: B.E., Writing: B.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Esserman LJ, Shieh Y, Rutgers EJ, et al. Impact of mammographic screening on the detection of good and poor prognosis breast cancers. Breast Cancer Res Treat 2011;130:725-34.

IMAGE ARTICLE

Rheumatology Quarterly

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CAVITARY LESIONS IN THE LUNG

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Keywords: Cavitarylesions, cavity, lymphoma

A 43-year-old female patient is being followed up with a diagnosis of rheumatoid arthritis. She presented with ulcerated lesions on the lower extremity, diffuse subcutaneous nodules, dyspnea, hemoptysis, and fever. Cavitary lesions were detected on the chest X-ray and thoracic computed tomography (Figure 1). The biopsy sample taken from the lesion in the lung was interpreted as "tumor necrosis". The biopsy sample from subcutaneous nodules was interpreted as "T-cell/histiocyte-rich large B-cell lymphoma".

There may be some similarities between various lung cavitary lesions, knowledge of the possible causes and a systematic approach will help to narrow down the huge list of differential diagnoses. CAVITY mnemonics can be used for diseases that may cause cavitary lesions in the lung (Table 1) (1). Pulmonary cysts are mimics of emphysema, cystic bronchiectasis, and bullous lung cavitary lesions, and before diagnosing a cavitary lesion, it should be ensured that it is not one of these mimics.

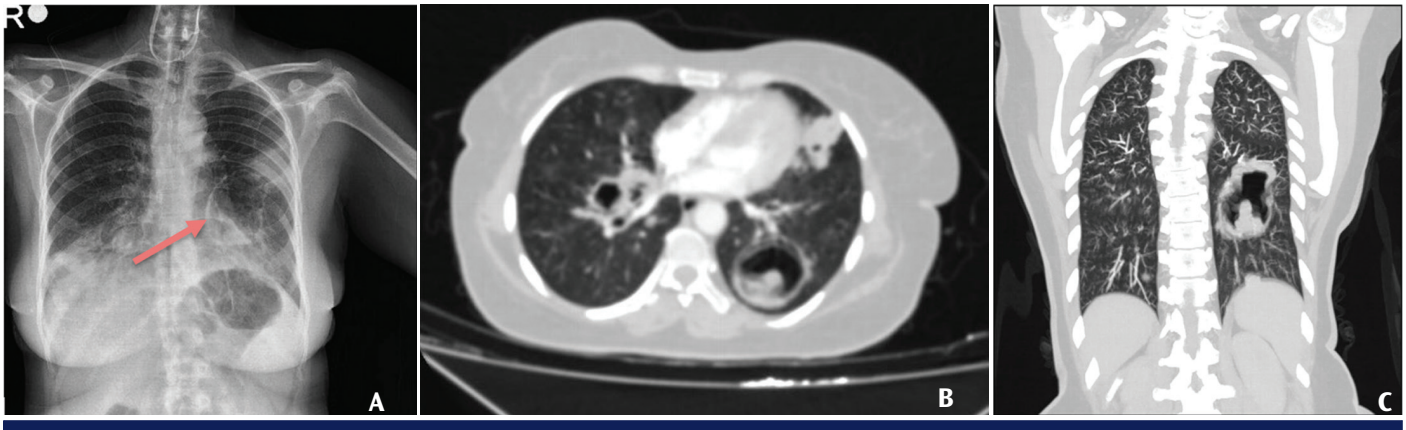

Figure 1. Cavitary lesions on posteroanterior chest X-ray (A) and computed tomography (B, C)

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Table 1. CAVITY mnemonic for lung cavitary lesions (1)		
C	Cancer	Cavitation can be seen in squamous cell carcinoma (the most common cavitating primary malignancy), adenocarcinoma, large cell carcinoma, lymphomatoid granulomatosis, lymphoma, Kaposi's sarcoma and metastatic cancers. In addition, cavitation may develop after chemotherapy/radiotherapy and radiofrequency ablation of masses in the lung.
A	Autoimmunity	Among rheumatological diseases, granulomatous polyangitis (Wegener's granulomatosis) and rheumatoid arthritis should be considered first. It should be borne in mind that although rare, it can be observed in necrotizing sarcoidosis, ankylosing spondylitis, eosinophilic granulomatous polyangitis, and systemic lupus erythematosus.
V	Vascular	The pulmonary cavity secondary to a pulmonary embolism can be seen. In addition, several cavitary and solid lesions may be observed due to septic embolisms.
I	Infection	Tuberculosis, aspergillosis, anaerobic bacteria, P. aureus, *K. pneumoniae*, *P. aeruginosa, Legionella pneumophilia, Haemophilus influenza type B, Nocardia, Actinomyces, Histoplasma capsulatum, Coccidioidomycosis immitis,* and *Cryptococcus neoformans* are infectious causes that can cause cavitary lesions in the lung.
T	Trauma	A cavitary lesion called a "traumatic pulmonary pseudocyst" can be seen after trauma.
Y	Youth-congenital	In some congenital anomalies (bronchogenic cyst, congenital pulmonary airway malformation and pulmonary sequestration), lesions similar to cavitary lesions may be observed.

Ethics

Informed Consent: Patient consent form was obtained.

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Authorship Contributions

Surgical and Medical Practices: İ.G., Concept: İ.G., M.S.A., A.K., Design: A.K., Data Collection or Processing: M.S.A., Analysis or Interpretation: A.K., Literature Search: M.S.A., Writing: İ.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCE

Canan A, Batra K, Saboo SS, Landay M, Kandathil A. Radiological approach to cavitary lung lesions. Postgrad Med J 2021;97:521-31.