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RHEUMATOLOGY QUARTERLY

RQ
Rheumatology Quarterly

galenos yayınevi

September
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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

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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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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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- ✓ **FAST AND LASTING relief at every step[1-3*]**
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- ✓ **Lasting REMISSION over 5 years[7]**
- ✓ **TREATMENT EXPERIENCE in more than 875,000 patients[8,†]**

*Efficacy was shown in disease symptoms that are important for patients with AS or nr-axSpA with VERXANT.
†All around the world and in 7 indications (adult and pediatric). VERXANT is indicated in treatment of adult patients with axial spondyloarthritis, psoriatic psoriasis and plaque psoriasis.
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: e339-46. **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-e346. **8.** Novartis data on file. Aralık 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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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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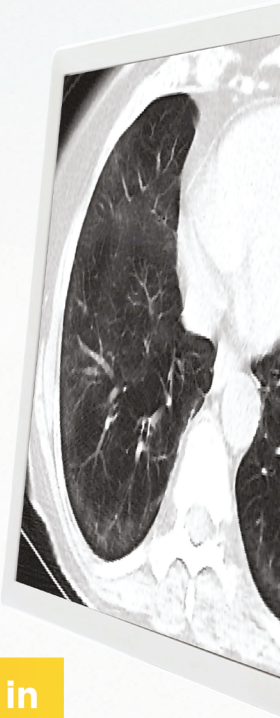

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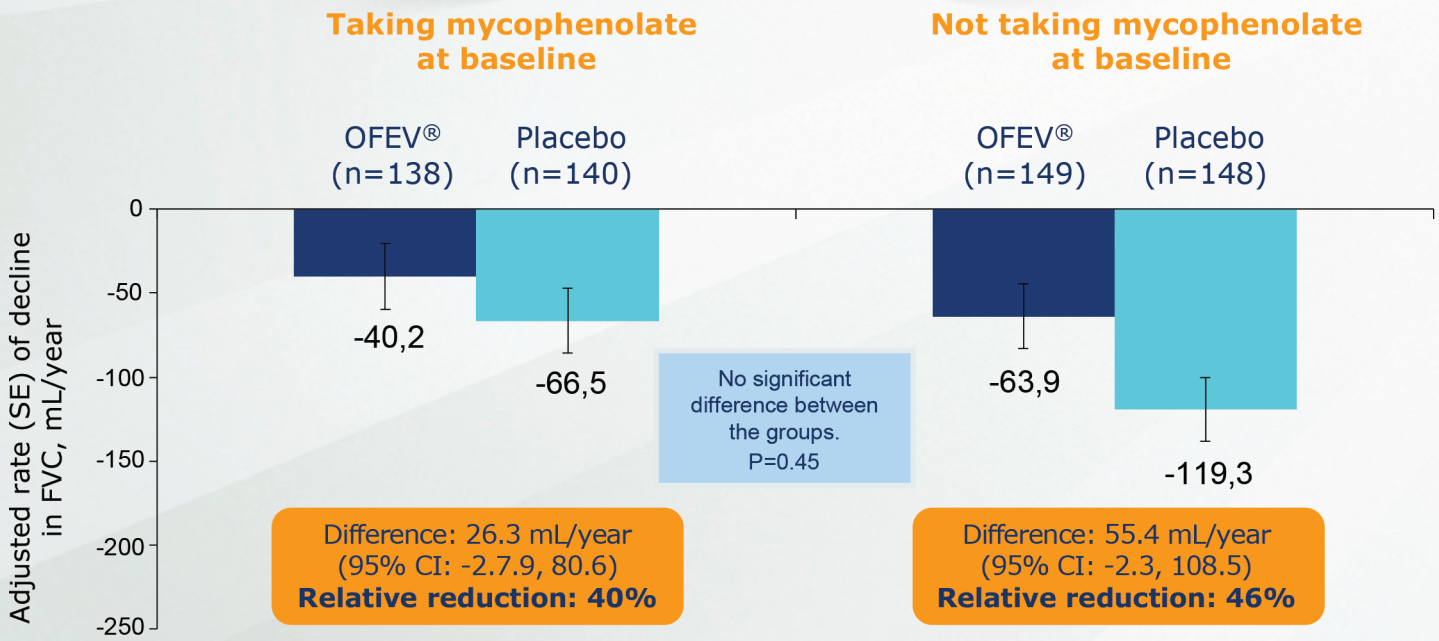

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References: 1. Strand V ve ark. Arthritis Res Ther. 2020 Oct 15;22(1):243. 2. Cohen SB ve ark. RMD Open 2020;6:e001395. 3. Xeljanz® XR Kısa Ürün Bilgisi.

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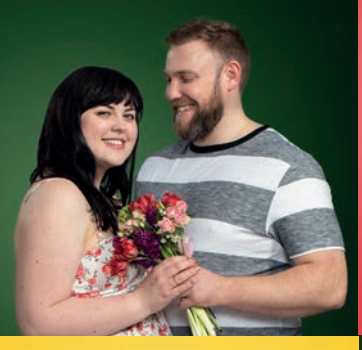
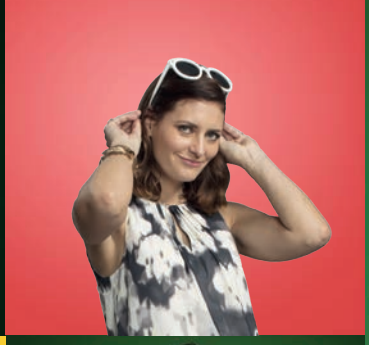

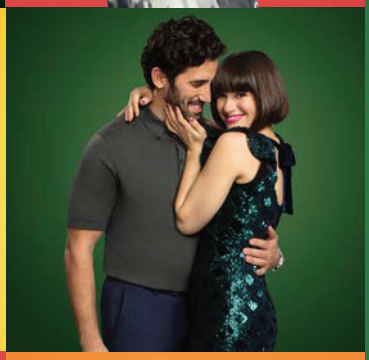
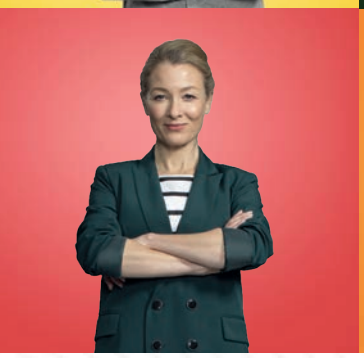
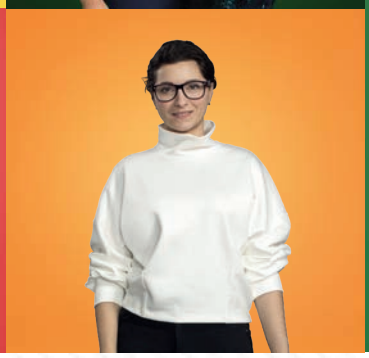

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REFERENCES: 1. CIMZIA® Summary of Product Characteristics. 2. Data on file. UCB, Inc.

[a] CIMZIA® was first approved by the FDA in April 2008 for adults with moderate to severe Crohn's disease.
[b] Human trials initiated in July 1998. First patient, first dose in rheumatoid arthritis December 1998. Clinical studies investigated patients with rheumatoid arthritis, Crohn's disease, psoriatic arthritis, and other diseases, as well as healthy patients.
[c] Patient exposure was estimated using the available sales data in rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, and psoriatic arthritis from 01 Sep 2007 to 28 Feb 2022 for the cumulative time interval. The exposure of CIMZIA was calculated using the following formula: Patient-years = ([total mg of product distributed]/[monthly maintenance dose])/12 months in year.

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Cimzia 200 mg/ml solution for s.c. injection in pre-filled syringe **Qualitative & Quantative composition:** Each pre-filled syringe of 1ml contains 200 mg certolizumab pegol. **List of excipients;** Sodium acetate; 1.36mg Sodium chloride; 7.31 mg and Water for injection. **Therapeutic indications: Rheumatoid arthritis;** Cimzia, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including methotrexate, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Cimzia, in combination with methotrexate (MTX), is indicated for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate. **Psoriatic arthritis;** Cimzia, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. **Axial spondyloarthritis;** Cimzia is indicated for the treatment of adult patients with axial spondyloarthritis, comprising: **Ankylosing spondylitis (AS):** Cimzia is indicated for treatment of severe active ankylosing spondylitis in adults who have had an inadequate response to conventional treatment. **Axial spondyloarthritis without radiographic evidence of AS:** Cimzia is indicated in adult patients with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by MRI (accompanied with elevated CRP or not), who have had an inadequate response to, or are intolerant to NSAIDs **Crohn's Disease:** Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. **Plaque psoriasis;** Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis or other severe infections such as sepsis or opportunistic infections. Moderate to severe heart failure (NYHA classes III/IV). **Special warnings and precautions for use:** Infections; Patients must be monitored closely for signs and symptoms of infections including tuberculosis before, during and after treatment with Cimzia. Treatment with Cimzia must not be initiated in patients with a clinically important active infection, including chronic or localised infections, until the infection is controlled. Tuberculosis; Before initiation of therapy with Cimzia, all patients must be evaluated for both active or inactive (latent) tuberculosis infection. Hepatitis B Virus (HBV) reactivation; Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Cimzia. Malignancies and lymphoproliferative disorders; There has been reports of leukemia-blood cancer development associated with use of TNF blockers. Chronic obstructive pulmonary disease (COPD); caution should be exercised when using any TNF antagonist in COPD patients and in patients with increased risk for malignancy due to heavy smoking. Haematological reactions: Reports of pancytopaenia, including aplastic anaemia, have been rare with TNF antagonists. Neurological events: Use of TNF antagonists has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis. Autoimmunity: Treatment with Cimzia may result in the formation of antinuclear antibodies (ANA) and uncommonly, in the development of a lupus-like syndrome. Vaccinations: Patients treated with Cimzia may receive vaccinations, except for live vaccines. If a surgical intervention is planned, Certolizumab's half life of 14 days should be considered. Cimzia may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. Serious infection risk which may be fatal is higher in patients ≥65 years of age compared to patients below 65 years of age. **Pregnancy and lactation:** Pregnancy category: B The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last Cimzia dose due to its elimination rate, but the need for treatment of the woman should also be taken into account.For women planning pregnancy, related with CIMZIA's elimination rate, continuing a contraception method for 5 months after the last CIMZIA injection can be considered however, Pregnancy period; Data from more than 500 prospectively collected pregnancies exposed to Cimzia with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of Cimzia. However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with Cimzia administration during pregnancy. Cimzia should only be used during pregnancy if clinically needed. Lactation period; Cimzia can be used during breastfeeding. **Effects on ability to drive and use machines:** Cimzia may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of Cimzia. **Undesirable effects:** Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1000 to < 1/100) Infections and infestations; bacterial infections (including abscess), viral infections (including herpes, papillomavirus, influenza), sepsis, tuberculosis, fungal infections Neoplasms benign, malignant and unspecified (including cysts and polyps); blood and lymphatic system malignancies (including lymphoma and leukaemia), solid organ tumours, nonmelanoma skin cancers, pre-cancerous lesions (including oral leukoplakia, melanocytic nevus),, benign tumours and cysts (including skin papilloma), gastrointestinal tumours, melanoma, Merkel cell carcinoma. Blood and the lymphatic system disorders; eosinophilic disorders, leukopaenia (including neutropaenia, lymphopaenia), anaemia, lymphadenopathy, thrombocytopaenia, thrombocytosispancyto-paenia, splenomegaly, erythrocytosis, white blood cell morphology abnormal. Immune system disorders ; vasculitides, lupus erythematosus, drug hypersensitivity, allergic disorders, autoantibody positive, angioneurotic oedema, sarcoidosis, serum sickness, panniculitis. Endocrine disorders; thyroid disorders. Metabolism and nutrition disorders; electrolyte imbalance, dyslipidaemia, appetite disorders, weight change, haemosiderosis. Psychiatric disorders; anxiety and mood disorders (including associated symptoms), suicide attempt, delirium, mental impairment. Nervous system disorders: headaches (including migraine), sensory abnormalities, peripheral neuropathies, dizziness, tremor, seizure, cranial nerve inflammation, impaired coordination or balance multiple sclerosis, Guillain-Barré syndrome. Eye disorders ; visual disorder, eye and eyelid inflammation, lacrimation disorder. Ear and labyrinth disorders; tinnitus, vertigo: Cardiac disorders; cardiomyopathies (including heart failure), ischaemic coronary artery disorders , arrhythmias, palpitations, pericarditis, atrioventricular block Vascular disorders; hypertension, haemorrhage or bleeding (any site), hypercoagulation, syncope, oedema, ecchymoses, cerebrovascular accident, arteriosclerosis, Raynaud's phenomenon, livedo reticularis, telangiectasia. Respiratory, thoracic and mediastinal disorders; asthma and related symptoms, pleural effusion and symptoms, respiratory tract congestion and inflammation, cough, interstitial lung disease, pneumonitis. Gastrointestinal disorders; nausea, ascites, gastrointestinal ulceration and perforation, gastrointestinal tract inflammation (any site), stomatitis, dyspepsia, abdominal distension, oropharyngeal dryness, odynophagia, hypermotility. Hepatobiliary disorders: hepatitis, hepatopathy, cholestasis, blood bilirubin increased, cholelithiasis. Skin and subcutaneous tissue disorders: rash, alopecia, new onset or worsening of psoriasis and related conditions, dermatitis and eczema, sweat gland disorder, skin ulcer, photosensitivity, acne, skin discolouration, dry skin, nail and nail bed disorders, skin exfoliation and desquamation, bullous conditions, hair texture disorder. Musculoskeletal, connective tissue and bone disorders; muscle disorders, blood creatine phosphokinase increased. Renal and urinary disorders; renal impairment, blood in urine, bladder and urethral symptoms, nephropathy. Reproductive system and breast disorders: menstrual cycle and uterine bleeding disorders, breast disorders, sexual dysfunction. General disorders and administration site conditions: pyrexia, pain, asthaenia, pruritus, injection site reactions, chills, influenza-like illness, altered temperature perception, night sweats, flushing, fistula. Investigations: blood alkaline phosphatase increased, coagulation time prolonged, blood uric acid increased. Injury, poisoning and. procedural complications: skin injuries, impaired healing. The additional following ADRs have been observed uncommonly with Cimzia in other indications: gastrointestinal stenosis and obstructions, general physical health deterioration, abortion spontaneous and azoospermia. **Interaction with other medicinal products and other forms of interaction:** Concomitant treatment with methotrexate, corticosteroids, nonsteroidal anti-inflammatory drugs and analgesics showed no effect on the pharmacokinetics of certolizumab pegol based on a population pharmacokinetics analysis. The combination of Cimzia and anakinra or abatacept is not recommended. **Posology and method of administration:** Posology, Loading dose: The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. For rheumatoid arthritis and psoriatic arthritis, MTX should be continued during treatment with Cimzia where appropriate. Maintenance dose; Rheumatoid arthritis; After the starting dose, the recommended maintenance dose of Cimzia for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. Psoriatic arthritis: After the starting dose, the recommended maintenance dose of Cimzia for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. Axial spondyloarthritis: After the starting dose, the recommended maintenance dose of Cimzia for adults patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks. After at least 1 year of treatment with Cimzia, in patients with sustained remission, a reduced maintenance dose of 200 mg every 4 weeks may be considered. Crohn's Disease: The recommended initial adult dose of Cimzia is 400 mg (given as two subcutaneous injections of 200 mg) initially, and at Weeks 2 and 4. In patients who obtain a clinical response, the recommended maintenance regimen is 400 mg every four weeks. After the starting dose, the maintenance dose of Cimzia for adult patients with plaque psoriasis is 200 mg every 2 weeks. A dose of 400 mg every 2 weeks can be considered. Method of administration: The total content (1 ml) of the pre-filled syringe should be administered as a subcutaneous injection only. Suitable sites for injection would include the thigh or abdomen. **Renal and hepatic impairment:** Cimzia has not been studied in these patient populations. No dose recommendations can be made **Paediatric population:** The safety and efficacy of Cimzia in children and adolescents below age 18 years have not yet been established. No data are available. Geriatric population: In elderly patients (fl65 years old) no dose adjustment is required. Population pharmacokinetic analyses showed no effect of age. **Overdose:** No dose-limiting toxicity was observed during clinical trials. Multiple doses of up to 800 mg subcutaneously and 20 mg/kg intravenously have been administered. In cases of overdose, it is recommended that patients are monitored closely for any adverse reactions or effect, and appropriate symptomatic treatment initiated immediately. **Special precautions for storage:** Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light. Keep it in it's original package, out of reach and sight of children. **Nature and contents of container:** 2 one ml pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber), containing 200 mg of certolizumab pegol and 2 alcohol wipes. **Registration date and number:** 13.12.2012 ve 135/01. **Retail price including VAT and approval date:** 11654,64 TL / 25.07.2023. This abbreviated summary of product characteristics has been prepared in accordance with the Summary of Product characteristic approved by TR MOH on 16.02.2023 TR-P-CZ-AS-2300017 July 2023 **Legal Category:** Sell by prescription. Call our company for detailed information **UCB Pharma A.Ş. Palladium Tower Barbaros Mah. Kardelen Sok. No:2 Kat:24/80 34746 Ataşehir, İstanbul Tel: 0 216 538 00 00**

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*Erelzi® was compared with reference etanercept in the EQUIRA study in adult patients with moderate-to-severe rheumatoid arthritis,[5] and in the EGALITY study in adult patients with chronic moderate-to-severe plaque psoriasis.[3,4]

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INVITED REVIEW

Rheumatology Quarterly

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Rheumatology Quarterly 2023;1(3):78-86

UPDATE IN TAKAYASU'S ARTERITIS

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Abstract

Takayasu arteritis (TAK) is a rare, chronic granulomatous large-vessel arteritis affecting mainly the aorta and its major branches. Inflammation of the vessel wall causes segmental stenosis, occlusion, dilatation, and/or aneurysm formation. Although all large arteries can be affected, the aorta, subclavian, and carotid arteries are the most commonly involved TAK is mainly observed in young females. Recent advances in the diagnosis, clinical course, disease assessment, and treatment of TAK are discussed in this review. In the presence of typical symptoms and physical findings such as loss of pulses and/or decreased arterial blood pressure and elevated acute phase responses, the diagnosis should be confirmed easily by angiographic imaging modalities. Magnetic resonance angiography is the gold standard modality for both diagnosis and longitudinal follow-up of patients with TAK. In recent years, positron emission tomography (PET) has become a widely used imaging method for the diagnosis of TAK with high sensitivity. The place of PET during follow-up in TAK is still controversial and requires further studies. Prognosis is recently possibly getting better with lower mortality, but a substantial damage is present even in early cases. It is critical to differentiate irreversible damage from disease activity and thus avoid potential over treatment with toxic agents such as corticosteroids in TAK. There is a clear need to develop a validated set of outcome measures for use in clinical trials of TAK. In daily practice, routine imaging follow-up is not recommended in clinically and laboratory silent TAK patients assessed as inactive by the physician. The level of evidence for TAK management is low, and expert opinion is still the main determinant when managing patients with TAK during daily practice. Glucorticoids are the mainstay of TAK treatment. While tapering glucocoticoids, non-biologic immunosuppressive agents should be added to the treatment. Leflunomide, methotrexate, azathiopurine, or mycophenolate mofetil could be chosen as the first-line immunosuppressive agent. If there is a treatment failure with first-line agents, switching to tumor necrosis factor inhibitors or tocilizumab should be considered.

Keywords: Takayasu's arteritis, diagnosis, disease assessment, treatment

INTRODUCTION

Takayasu arteritis (TAK) is a rare, chronic granulomatous large-vessel arteritis affecting mainly the aorta and its major branches. Inflammation in the vesssel wall causes segmental stenosis, occlusion, dilatation and/or aneurysm formation. Although all large arteries can be affected, aorta, subclavian and carotid arteries are the most commonly involved arteries (60-90%) (1,2). TAK is observed worldwide. However, it is more frequently reported in East Asian countries including Japan, India, and Korea and also recently from the Middle East, especially Turkey (3). Prevelance was found 40/million in Japan and 0.9/million in the USA. Prevelance was reported as 15-33/million in Turkey (4,5). TAK is seen more 1.6-12 times more frequently in women than men (6-8). Disease onset age had a peak around 20-130 years old (8).

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Clinical Manifestations

Arterial stenosis, occlusion, and aneurysms lead to various signs and symptoms such as extremity pain, claudication, light-headedness, constitutional features (such as fever, malaise, anorexia, andloss), bruits, absent or diminished pulses, and loss of blood pressure. TAK generally follows an insidious course at onset. However, atypical and/or catastrophic disease, such as acute visual loss or stroke, may also occur. The clinical course of TAK generally has three phases. The first phase is characterized by non-specific constitutional inflammatory symptoms such as fever, weight loss, and fatigue. In the second phase, inflammation of arterial walls is prominent, causing carotidynia, neck pain, and sometimes back pain in the thoracic and dorsal areas. The third phase, thought to be the late phase of the disease, is characterized by bruits, decreased or absence of pulses, and blood pressure difference between arms and extremity claudication. During the diagnostic phase, 10-20% of patients with TAK are asymptomatic (3). Carotidynia occurs in 2-32% of patients. Stenosis or aneurysm formation in the involved arteries causes the decreased circulation. This manifests as typical intermittent claudication in the extremities. Vertebral and carotid involvement may be asymptomatic or present with transient ischemic attacks, stroke, dizziness, syncope, headache, or visual changes. Mesenteric involvement is common, but gastrointestinal symptoms such as nausea, diarrhea, vomiting, and ischemic abdominal pain are not frequently observed. Hypertension may be seen due to atypical coarctation of the aorta, aortic valve regurgitation related to aortitis, or renal artery stenosis (9,10). Cardiac involvement, mainly as aortic regurgitation, is present in approximately one-third of patients. Takayasu retinopathy and scleritis are uncommon manifestations of the disease (1-3). Cutaneous manifestations range between 3-28% of patients, and the most common manifestation is erythema nodosum (11). Joint involvement may present as arthritis and arthralgia in almost half of the patients, but it does not have a destructive pattern (12,13).

There are an increasing number of studies reporting inflammatory bowel disease and other spondyloarthropathy features in TAK (14,15). Further investigations are needed to focus on possible shared immunopathogenic or genetic processes.

Differential Diagnosis

1990 American College of Rheumatology (ACR) criteria, which are the most widely used in clinical studies, require the presence of three of six criteria to differentiate TAK from other systemic vasculitis (Table 1) (16). However, this criteria set mainly covers the late stage of disease and includes conventional angiography as the only imaging modality. In a young patient with unexplained systemic inflammation, nine red flags should remind TAK to the clinician (Table 2) (12). Involvement of subclavian arteries, especially the left side, and common/internal carotid arteries are typical for TAK. TAK lesions mostly develop in a symmetric manner in paired vascular territories, and disease extension is contiguous in the aorta (17).

One of the most important diseases in the differential diagnosis of TAK as large-vessel vasculitis is giant-cell arteritis (GCA). Disease onset in young age (<40), striking female predominence and ethnic discrimination are important differeneces of TAK. It is not always possible, especially in elderly patients with risk factors for atherosclerotic vascular disease. While the vasculitic involvement is generally located in the proximal part of vessels, atherosclerotic lesions are generally located in bifurcation sites and ostia of the vessels. In the vessel wall, vasculitic involvement leads to diffuse and homogeneous thickening, whereas atherosclerosis leads more localized, irregular and hon-homogeneous thickening. Punctat, linear calsification and patchy involvement also suggest atherosclerosis, in contrast to mural and circumferential calcification suggesting diffuse involvement in vasculitis. In the differential diagnosis of TAK,

Table 1. 1990 criteria for the classification of Takayasu arteritis

Age of 40 years or younger at disease onset
Claudication of the extremities
Decreased pulsation of one or both brachial arteries
Difference of at least 10 mmHg in systolic blood pressure between arms
Bruit over one or both subclavian arteries or the abdominal aorta
Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the upper or lower extremities that is not due to arteriosclerosis, fibromuscular dysplasia, or other causes
At least 3 of 6 criteria are necessary for classification

Table 2. Red flags for investigating Takayasu arteritis

Carotidynia
Hypertension
Angina pectoris
Vertigo and syncope
Extremity claudication
Absent/weak peripheral pulses
Discrepant blood pressure in the upper limbs (>10 mmHg)

many rare entities leading to infectious or non-infectious aortitis should also be considered (18).

Disease Activity Assessment

Physical Examination in Clinical Activity Assessment

Physical examination for new or worsened vascular signs, such as bruits, pulse, or blood pressure difference between extremities, is the first step in TAK disease assessment. Although abnormal findings on vascular physical examination are highly associated with the presence of arterial lesions in imaging, at least 30% of arteriographic lesions can be missed with only physical examination (19).

Laboratory in Disease Activity Assessment

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are frequently advocated for disease assessment of TAK. In one study, active disease was present in the setting of normal laboratory parameters in 23% of the patients (20). Similarly, ESR was elevated in only 72% of patients considered to have active disease and was still high in 44% of patients considered to be in remission (21). Serum autoantibodies such as anti-aorta or anti-endothelial antibodies and serum biomarkers such as of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-8, IL-18, interferon gamma, matrix metalloproteinase (MMP)-2, MMP-9, YKL-40, A proliferation-inducing ligand and B cell survival factors activation factor are shown to be elevated in TAK, but are not disease-specific. The pentraxin (PTX) superfamily is a group of proteins that recognize various exogenous pathogens and behave as acute-phase response mediators. Despite the contoversial results, PTX-3 was suggested to be a discriminative marker for active disease in TAK (22).

Outcome Measures in Disease Activity Assessment

The simple definition of "active disease" that was used in a study from the National Institute of Health (NIH): 'Presence of constitutional symptoms, new-bruits, acute phase reactants (APR) or new angiographic features' is commonly applied in clinical studies (23). Birmingham Vasculitis Activity Score (24), and the "disease extent index for Takayasu's arteritis (DEI.TAK)" were not widely accepted and used in TAK (25). In 2010, the Indian Takayasu's Arteritis Score (ITAS) was introduced. ITAS-2010 has only 6 systems and scoring is weighted for vascular items (0-2). ITAS-2010 seems to have a sufficient comprehensiveness and the inter-rater agreement is better than (Physician's Global Assessment) (0.97 vs 0.82). The authors also incorporated acute phase response to the score (ITAS-2010-A) by adding an extra 1-3 points for elevated ESR or CRP (26). ITAS-2010 became more widely used assessment tool compared to previously mentioned tools (27-29). The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group completed a Delphi exercise to determine a consensus for candidate outcomes for disease activity assessment in large vessel vasculitis (LVV) in clinical trials, and a set of important items to measure were identified. OMERACT has been working on it (30). European League Against Rheumatism (EULAR) suggested new definitions for active disease, relapse, and remission. However, these new definitions are consensus-based and do not derive from a systematic literature review. EULAR suggests using the term 'relapse' and avoiding the term 'flare'. These definitions seem acceptable, but they need to be tested in prospective studies (31).

Prognosis and Disease Course

TAK generally has a relapsing-remitting course. There can be prolonged periods of seemingly clinically "inactive" disease during which arterial damage can still progress. Due to the lack of standardized assessment tools, physicians generally manage cases with TAK according to physician global assessment as the 'gold standart' in daily practice, combining clinical symptoms, APR, and imaging (13). Despite immunosuppressive treatments, relapses were observed in approximately one-third of TAK patients during follow-up (2,32). Accelerated atherosclerosis is an important risk factor for increased morbidity and mortality in TAK. In a comparative study of patients from USA and Turkey, cardiovascular (CV) risk factors were more common in patients with TAK, particularly hypertension (33). According to 2018 update of the EULAR recommendations for the management of LVV, aspirin should not be routinely used for treatment of LVV unless it is indicated for other reasons (31). Overall, current data suggest that patients with TAK should undergo careful assessment of CV risk factors, and an aggressive risk modification approach is warranted.

Damage Assessment in the TAK

It is critical to differentiate irreversible damage from disease activity and thus avoid potential over-treatment with toxic agents such as corticosteroids in TAK. Angiographic findings may not demonstrate whether changes in the vessel wall are associated with active vascular inflammation or irreversible damage (34). The Vasculitis Damage Index (VDI) is the standard tool for assessing damage in small vessel vasculitis (35). In a large series from Turkey, VDI scores in TAK were moderately high [mean: 4 (1-12)] and were mainly due to the disease itself with major vessel occlusion (36). Another damage score, TAK Damage Score (TADS), derived from DEI.TAK, consists of 7 categories, which are mainly focused on the CV system (37).

In a recent study comparing VDI and TADS, the median number of disease-related items was higher in TADS scoring (8 items vs 4 items) at the end of the follow-up (app. 77 months). At least 1 new corticosteroid-related damage item occurred in 35 patients (31%). The results confirmed that damage assessment with VDI seems to be predominantly evaluating treatment-related damage, whereas TADS provides more detailed information on disease-related damage in TAK (38). The large-vessel vasculitis index of damage score is used in GCA but is still in the revision process by Vasculitis Clinical Research Consortium (39).

Mortality

Although recent data is showing better prognosis in TAK, there is still a significant delay in the diagnosis of TAK. Both morbidity and mortality rates are still high because of new and severe manifestations after diagnosis (40). Overall survival was much better compared to earlier series (97% at 10 and 86% at 15 years), but mortality was still increased compared to the general population (41). In recent French series assessing 318 patients, mortality was 5% in a median follow-up of 6.1 years (42). Differences of mortality rates reported in different series may be explained by differences in disease phenotypes, medical therapy, and access to endovascular or surgical therapy.

Imaging

Angiographic imaging of vessels is necessary for both diagnosis and follow-up of TAK. Optimal imaging of vessels should visualize both the arterial lumen and the arterial wall in TAK (43). The earliest detectable sign in the vessel wall is usually thickening caused by inflammation. Wall thickness can be shown by ultrasonography, computarized tomography (CT) angiography (CTA) and magnetic resonance angiography (MRA). Conventional digital subtraction angiography (DSA) can detect stenosis, occlusions, and aneurysms, which are mostly late-stage findings of TAK. DSA has a very limited ability to detect wall thickness in TAK (1), and is not routinely recommended in recent EULAR guidelines for imaging in LVV (44).

CTA

CTA has become a widely accessible imaging tool for TAK. It is valuable for especially differentiating TAK from atherosclerosis. Circumferential aortic calcification is observed only in TAK, and this difference is quite helpful in differentiating vasculitis from atherosclerosis (45). CTA has a sensitivity higher than 90% for the diagnosis of TAK. Shorter acquisition time for CTA is an important advantage during daily practice compared with MRA. On the other hand, usage of iodinated contrast and exposure to radiation limits the usageof CTA in routine follow-up of TAK patients (46).

MRA

MRA has become the standard angiographic method for the diagnosis of TAK and is suggested as the first-choice imaging tool according to the EULAR guidelines (44). Lack of radiation exposure makes possible longitudinal imaging follow-up evaluations in patients with TAK. Thickening and enhancement in the vessel wall were suggested as the sign of active disease, and aslo reported a close correlation between wall thickness and/or edema of the vessel and APR (47,48) However, MRA showed activity in most patients seeming clinically in remission (49). Therefore, whether MRA can detect activity with only cross-sectional imaging. There are also efforts of MRA scoring systems aiming to assess cumulative vascular damage for the longitudinal follow-up TAK patients (49,50).

Positron Emission Tomography (PET)

Fluorodeoxyglucose (FDG)-PET imaging is based on the interpretation of FDG uptake by active inflammatory cells in vessel walls. It has become a widely used imaging tool for the diagnosis of LVV with high diagnostic sensitivity (>80%) (51). During semiquantitative analysis of PET images, 18F-FDG uptake of a vascular region of interest was compared with that of the liver [0= no uptake present, I= low-grade uptake (uptake present but lower than liver uptake), II= intermediate-grade uptake (similar to liver uptake), and III= high-grade uptake (uptake higher than liver uptake)] (52). Some studies also use the quantified 18F-FDG uptake such as standard uptake value (52,53).

A new scoring system, PET vascular activity score (PETVAS), was recently developed by Grayson et al. (54) The authors reported that PETVAS has a sensitivity and specificity of more than 80%. The total PETVAS score is calculated from nine arteries, which are the most frequently involved arteries in LVV. However, 58% of the TAK patients categorized as inactive according to the NIH criteria had active FDG-PET-CT findings in this study. Furthermore, 17% of non-vasculitic patients in the comparator group had active vasculitic lesions (54).

While it was suggested that glucocorticoid treatment decrease the FDG uptake (55), we did not find any affect of glucocorticoid or immunosuppressive treatment on PETVAS scores (56). Increased FDG uptake in the vessel wall in patients with LVV seeming in clinical remission may be associated with subclinical vasculitis (57) or non-vasculitic situations such as vascular remodeling, hypoxia (58), atherosclerosis (59). These all can be differentiated with only histopathologically.

PET is a very expensive imaging tool. Also, interpretation of FDG-PET-CT requires experience. One of the other limitations is the lack of standardization for the duration between FDG

administration and LVV acquisition. Radiation exposure during PET-CT imaging limits the use for follow-up of TAK patients (60). Promising results with PET-MRA showed that it is comparable with PET-CT. PET-MRA has better soft tissue resolution and anatomic definition and lower total radiation doses (61).

There are ongoing efforts focusing on the value of PET-MR on clinical activity assessment and treatment effects.

New ligand options in PET are also being assessed. Although promising results both in the diagnosis and activity assessment, PET is still not a standardized imaging method in TAK, especially for long-term follow-up of TAK patients.

Ultrasonography

US is a cheap and widely accessible imaging tool, and it can also be safely repeated during longitudinal follow-up. However, visualizing the aorta and subclavian arteries is difficult by US, with poorer detection of lesions. Carotid artery involvement can be visualized well with a high sensitivity (90%) and specificity (91%) in detecting stenotic lesions (62). Usage of mainly carotid, vertebral, subclavian, and axillary arteries and being an operator-dependent imaging modality are the main limitations of US during daily practice (63).

Treatment

Glucocorticoids are the mainstay of treatment for remission induction in TAK. The initial dose of prednisolone is 1 mg/kg/day (maximum 60 mg/day). The initial high dose should be maintained for a month and tapered gradually (1,20). According to the 2018 update of the EULAR recommendations for the management of LVV it was recommended that in patients who have reached 15-20 mg daily GC dose after 2-3 months, GCs should be decreased slowly targeting ≤10 mg/day at the end of one year (31). However, ≤10 mg/day doses of GCs in long-term remission are possibly too high compared with the recommendations in other disorders such as rheumatoid arthritis (usually ≤5 mg/day) and should be individually assessed in each patient according to the risk of GC-associated complications. Recent ACR guideline conditionally recommend tapering off glucocorticoids over long-term treatment with low-dose glucocorticoids for remission maintenance in TAK patients achieved remission while receiving GCs for ≥6-12 months (64). Both EULAR and ACR recommend the use of non-biologic disease-modifying agents in addition to glucocorticoids in all patients with TAK.

There are very low quality data coming from observational studies and case series showing the efficacy and safety of metotrexate (MTX), azathiopurine (AZA), mycophenolate mofetil (MMF), leflunomide (LEF), cyclophosphamide (CYC) in TAK treatment (1,22,65). Two open prospective series from China reported better outcomes with LEF than with CYC (66,67). Tacrolimus (68,69) and cyclosporine (70,71), which are calcineurin inhibitors widely used in transplant patients, were reported to be effective in very few cases with TAK. Tofacitinib compared with MTX and LEF in an open prospective series in TAK was found to be superior to LEF preventing relapse and decreasing the GC dose (72,73). There are only 2 double-blind RCTs on TAK treatment. Abatacept and tocilizumab (TCZ) failed in these studies when compared with plasebo (74,75). Long-term results of TCZ RCT study reported angiographic stabilization in patients (76). A recent open RCT reported similar clinical responses and angiographic stabilization in TAK patients treated with mycophenolate or methotrexate (29).

Several case series and observational studies reported the efficacy and safety of TNF inhibitors (TNFi) and TCZ in TAK (13,22). Two large retrospective comparison studies found similar clinical response rates and radiologic progression between TNFi or TCZ (77,78). A recent meta-analysis also confirmed similar clinical response, angiographic stabilization, and adverse events with TNFi or TCZ (79). In a head-to-head retrospective comparison, the drug survival rate of TNF was significantly higher than that of TCZ (67.2% vs 41.1%, p=0.028). Concomitant conventional immunosuppressive drug usage at baseline had a positive effect on the drug survival rate [HR = 3.79, 95% confidence interval (CI) = 1.49-9.60, p=0.005] (80). A retrospective, longitudinal follow-up cohort from Norway reported less angiographic progression at 2 years in patients with TAK receiving TNFi (10%) than in those receiving conventional immunosuppressive (40%). In this study, the angiographic progression rate was 90% in patients receiving glucocorticoid treatment only (81). According to EULAR recommendations, TCZ or TNFi can be equally considered in refractory patients (31). However, recent ACR guidelines recommend adding a TNFi over TCZ in refractory patients (64). A very recent open prospective study compared secukinumab and TNFi in patients with refractory TAK secucinumab and TNFi were found to be comparable regarding response rates at 3 and 6 months (82).

There are conflicting results with rituximab therapy in refractory TAK (83-85). Therefore, this limited experience of rituximab do not support a role for rituximab as the first or second line biologic therapy in TAK patients. There are case reports showing the efficacy of ustekinumab and anakinra in rafractory TAK patients (22,77,80,86,87). A phase 3 multicenter randomized control trial comparing upadacitinib vs placebo in TAK is currently active (https://clinicaltrials.gov/ct2/show/NCT04161898).

Vascular Interventions and Surgical Therapy

Except in emergency conditions, open or endovascular vascular interventions should be considered as the last option in case of medical treatment failure to prevent ischemic arterial symptoms or injury in TAK. As a general rule, such interventions should be avoided during the active phase of the disease and should be attempted only after suppression of vascular inflammation by appropriate IS treatment (88). According to data from case series, the main indications for surgery are as follows: refractory hypertension related to renal artery stenosis, aortic disease including coarctation and ascending aortic dilatation ± aortic valve regurgitation, ischemic heart disease, supra-aortic disease with cerebral ischemicemia, mesenteric ischemicemia, severe limb-threatening claudication, and aneurysm repair (89-93). In a recent meta-analysis comparing balloon angioplasty and stenting outcomes, there were no significant differences in the incidence of restenosis and other complications overall ($p=0.38$), but restenosis risk in stenting was significantly higher than that in balloon angioplasty (odds ratio = 4.40, 95% CI=2.14-9.02, $p<0.001$) in renal stenosis (94).

CONCLUSION

TAK is a rare systemic vasculitis mainly seen in young females. In the presence of typical symptoms and physical findings such as loss of pulses and/or decreased arterial blood pressure and elevated acute phase responses, the diagnosis should be confirmed easily by angiographic imaging modalities. Currently, conventional angiography is no longer considered as the "gold standard" imaging tool for the diagnosis of TAK. MRA is the gold standard modality for both the diagnosis and longitudinal follow-up of patients with TAK. Compared with DSA, three-dimensional MRA can effectively show vessel wall thickening, whereas contrast-enhanced MRA allows better soft tissue differentiation for assessing disease activity. In recent years, PET has become a widely used imaging tool for the diagnosis of TAK with high sensitivity. The place of PET during follow-up in TAK is still controversial and requires further studies. Prognosis is recently possibly getting better with lower mortality, but substantial damage is present even in early cases. It is critical to differentiate irreversible damage from disease activity and thus avoid potential overtreatment with toxic agents such as corticosteroids in TAK. There is a clear need to develop a validated set of outcome measures for use in clinical trials of TAK. In daily practice, routine imaging follow-up is not recommended in clinically and laboratory silent TAK patients assessed as inactive by the physician. The level of evidence for TAK management is low, and expert opinion is still the main determinant when managing patients with TAK during daily practice. Glucorticoids are the mainstay of TAK treatment. While tapering glucocoticoids, non-biologic immunosuppressive agents should be added to the treatment. LEF, MTX, AZA, or MMF could be chosen as the first -line immunosuppressive agents. If there is a treatment failure with first-line agents, switching to TNFi or TCZ should be considered. Despite an equal recommendation by EULAR recommendations after GCs plus IS failure in TAK, both ACR guidelines and our approach in our vasculitis clinic recommend a TNFi as the first-line biological due to a larger experience with TNFi.

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MUSCULOSKELETAL HEALTH IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS AND ITS ASSOCIATION WITH DISEASE ACTIVITY, MOBILITY, FUNCTIONALITY, AND QUALITY OF LIFE

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Abstract

Aim: Axial spondylarthritis (axSpA) patients present with symptoms such as the limitation of spinal mobility, loss in physical functions, pain, and fatigue. Due to the heterogeneity of symptoms, disease management should include a holistic approach and a broad variety of assessments. The purpose of the present study was to evaluate musculoskeletal health in patients with axSpA and to determine its association with spinal mobility, disease activity, functionality, quality of life (QoL).

Material and Methods: Forty-two patients with axSpA were included in this study. Demographic and disease-related data were recorded. The Musculoskeletal Health Questionnaire (MSK-HQ), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis QoL Questionnaire (ASQoL) were used to evaluate musculoskeletal health, spinal mobility, disease activity, functionality, and QoL, respectively. MSK-HQ, BASMI, BASDAI, BASFI, and ASQoL were also compared according to radiographic status and biological use.

Results: Forty-two axSpA patients (31 females and 11 males) were evaluated. MSK-HQ is significantly related to pain, BASDAI, BASFI, and ASQoL ($p<0.001$). Spinal mobility was better in the non-radiographic axSpA subgroup than in the radiographic axSpA subgroup ($p<0.001$). No other differences were found related to radiographic status or biological use ($p>0.05$).

Conclusion: Musculoskeletal health is impaired in patients with axSpA. Pain, functional capacity are closely related to musculoskeletal health. It seems that good disease management using appropriate treatment options may have a positive effect on the general health status of patients with axSpA.

Keywords: Axial spondyloarthritis, musculoskeletal health, disease activity, radiographic status, biologic use

INTRODUCTION

Axial spondylarthritis (axSpA) influences the sacroiliac joints and spine and is characterized by postural alterations, functional impairments, and inflammatory back pain (1,2). AxSpA includes two subsets of disease as radiographic axSpA (also known as ankylosing spondylitis) and non-radiographic axSpA (3). AxSpA patients present with symptoms such as limitation of spinal mobility, loss of physical functions, pain, and fatigue (4-6).

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These symptoms have adverse repercussions on Health Related Quality of Life (HRQoL), work productivity, and musculoskeletal health (7,8). Due to the heterogeneity of symptoms, disease management should include a holistic approach and a broad variety of assessments (9).

In recent years, it has become more important to assess the overall effect of the disease and the general condition of patients with axSpA. For these evaluations, clinicians use patient-reported results (PROs) that provide information about different subjective aspects of the disease (7). The Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), which are the most commonly used PROs in axSpA patients, evaluate physical function, disease activity, and HRQoL, respectively (10,11). Because axSpA presents with a variety of musculoskeletal manifestations at multiple sites in the body, a specific clinical tool should be used that provides a holistic view (8,9). The Musculoskeletal Health Questionnaire (MSK-HQ) was developed for patients with different musculoskeletal conditions. This scale evaluates physical symptoms, such as pain and fatigue, and the impact of the illness on psychological well-being (12).

In recently published studies, Norton et al. (12) used MSK-HQ in patients with inflammatory arthritis (including patients with ankylosing spondylitis). This study provided evidence that MSK-HQ is not disease specific and has high content validity in rheumatological conditions. In the same line, Akkubak and Anaforoğlu Külünkoğlu (8) suggested that the MSK-HQ is a reliable and valid questionnaire to evaluate musculoskeletal health in Turkish patients with axSpA. However, in the present studies, the factors related to musculoskeletal health in axSpA patients have not been investigated. Therefore, the main objective of the present study was to evaluate musculoskeletal health in patients with axSpA and to determine its association with spinal mobility, disease activity, functionality and HRQoL.

MATERIAL AND METHODS

Patients

Forty-two patients with axSpA were included between February-May 2022 from Necmettin Erbakan University Hospital, Rheumatology outpatient clinic. Patients were classified as axSpA according to the Assessment of Spondyloarthritis International Society criteria (3). Patients who failed to understand the commands, not being between 18 and 65 years old, being pregnant as hormonal changes may alter spinal mobility, and had advanced spinal limitation (bamboo spine) were excluded.

Study Design

This study, which was planned as an observational, cross-sectional, and single-center, was approved by the Necmettin Erbakan University Ethics Committee (decision no: 2021/3185, date: 02.04.2021), and each of the patients signed an informed consent to participate.

Variables Studied

Socio-demographic and disease-related variables, such as age, sex, human leukocyte antigen-B27 antigen positivity, radiographic status, use of biologics disease and symptom duration, were recorded for each patient.

For evaluating musculoskeletal health, MSK-HQ was used as the main variable. The MSK-HQ includes fourteen items, which are scored between 0 and 56. These items are related to the facets of musculoskeletal health, including pain/stiffness, fatigue, physical function, symptom interference, sleep, understanding of treatment and diagnosis, psychological well-being and self-efficacy. Higher scores indicate better musculoskeletal health condition (13).

The visual analog scale, which is a 10 cm horizontal line, was applied to evaluate the general pain level. It has two ends, where 0 indicates no pain and 10 indicates the worst pain imaginably (14).

For the evaluation of spinal mobility, Bath Ankylosing Spondylitis Metrology Index (BASMI), which contains measurements as modified Schober test, tragus to wall distance, intermalleolar distance, cervical rotations, and lumbar lateral flexions was performed. Each measurement is scored between 0 and 10, and the total BASMI score is calculated by summing the scores and dividing the sum to five. Higher scores indicate more severe impairment. Each measurement was scored between 0 and 10, and the total BASMI score was obtained by adding the scores and dividing by five. High scores indicate worse spinal mobility (15).

BASDAI was performed to assess disease activity. BASDAI contains six questions, which are back pain, peripheral joint pain/swelling, localized tenderness, fatigue, and severity and duration of morning stiffness. The first five questions were scored between 0 and 10, and the duration of morning stiffness was scored on a 10-point scale (0: 0 hours, 10: 2 hours). Values related to the severity and duration of morning stiffness were collected and divided into two. The resulting value is summed up with the values of the first four questions. The total score obtained is divided by five to obtain the total BASDAI score. Higher scores indicate higher disease activity (16).

BASFI, which contains ten questions and is scored between 0 and 10, was performed to assess the functional status. The total score is obtained by taking the arithmetic average of all items. 0 indicates no functional impairment and 10 indicates maximal impairment (17).

Finally, HRQoL was evaluated using the ASQoL. The ASQoL is a self-reported questionnaire that is scored between 0 and 18. Higher scores indicate worse HRQoL (18).

Statistical Analysis

SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) was used to analyze the data. Statistical significance level was considered as p≤0.05. Continuous data were presented as the means ± standard deviation, whereas categorical data were presented as frequencies and percentages.

First, the Pearson correlation test was performed to assess the presence of a linear correlation between different quantitative variables (related to musculoskeletal health, pain, spinal mobility, disease activity, functionality and HRQoL). The Pearson's correlation values were considered moderate, strong, or strong in the range of 0.40 and 0.69, 0.70 and 0.89, 0.90 and 0.99, respectively. Subsequently, Student's t-test was performed to calculate the differences in the means of the variables in different subgroups of patients (according to radiographic status, biological use).

RESULTS

Forty-two axSpA patients (31 females and 11 males) with a mean age of 37.05±7.43 yearsparticipated in the study. The most important descriptive data of axSpA patients are shown in Table 1. The mean time since symptom onset was 127.14±71.36 months, and the mean time since diagnosis was 78.57±53.08 months for axSpA patients.

The correlations between the data related to musculoskeletal health (MSK-HQ), pain, spinal mobility (BASMI), disease activity (BASDAI), functionality (BASFI), and quality of life (ASQoL) are given in Table 2. A strong positive correlation was found (p<0.001) between MSK-HQ and ASQoL (r=0.852). Significant (p<0.001) negative moderate correlations were obtained between MSK-HQ -BASDAI and MSK-HQ -BASFI (r=-0.660 and r=-0.681, respectively). Additionally, a negative moderate correlation (r=-0.445) of MSK-HQ and pain was obtained.

Musculoskeletal health, spinal mobility, disease activity, functionality, and quality of life of axSpA patients were also compared according to radiographic status (radiographic vs non-radiographic) and biological use (biologics + vs biologics-). Most patients were using biologics (54.8%) and 52.4% of patients had radiographic axSpA. No significant differences were identified related to radiographic status or the use of biologics (p>0.05, Table 3). However, spinal mobility was found to be better in non-radiographic axSpA than in radiographic axSpA (p<0.001, Table 3).

Table 1. Descriptive data of variables participated in the study (n=42)

		Mean (SD)
Gender (female), n (%)		31 (73.8)
Age (years)		37.05 (7.43)
BMI (kg/m^2)		27.02 (5.33)
HLA-B27 +, n (%)		30 (71.4)
Time since diagnosis (months)		78.57 (53.08)
Time since onset of symptoms (months)		127.14 (71.36)
Radiographic status, n (%)	Radiographic axSpA	22 (52.4)
	Non-radiographic axSpA	20 (47.6)
Biologics use, n (%)	Biologics +	23 (54.8)
	Biologics -	19 (45.2)
Pain level (VAS, cm)		5.43 (2.01)
Spinal mobility (BASMI, score)		2.61 (1.15)
Disease activity (BASDAI, score)		4.09 (1.74)
Functional status (BASFI, score)		3.24 (1.55)
Quality of life (ASQoL, score)		10.26 (3.54)
Musculoskeletal health (MSK-HQ, score)		32.93 (7.25)

BMI: Body mass index, HLA-B27: Human leukocyte antigen-B27, axSpA: Axial spondylarthritis, VAS: Visual analog scale, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire, MSK-HQ: The Musculoskeletal Health Questionnaire, SD: Standard deviation

Table 2. Correlations (Pearson's correlation coefficient) between musculoskeletal health, pain, spinal mobility, disease activity, functionality and HRQoL

MSK-HQ	r	p
Pain	-0.445	**0.003***
BASMI	-0.181	0.250
BASDAI	-0.660	**<0.001****
BASFI	-0.681	**<0.001****
ASQoL	0.852	**<0.001****

*p<0.05, **p<0.001, HRQoL: Health Related Quality of Life, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire, MSK-HQ: The Musculoskeletal Health Questionnaire

Table 3. Comparison of musculoskeletal health, spinal mobility, disease activity, functional status and QoL according to radiographic status, biologic use in axSpA patients

Radiographic status			
	Radiographic axSpA (n=22) mean (SD)	**Non-radiographic axSpA (n=20) mean (SD)**	**p value**
MSK-HQ	32.91 (6.84)	32.95 (7.86)	0.986
BASMI	3.18 (1.27)	1.98 (0.51)	**<0.001****
BASDAI	4.45 (1.93)	3.69 (1.46)	0.155
BASFI	3.24 (1.47)	3.24 (1.67)	0.997
ASQoL	10.18 (3.33)	10.35 (3.85)	0.881
Biologics use			
	Biologics + (n=23) mean (SD)	**Biologics - (n=19) mean (SD)**	**p value**
MSK-HQ	33 (7.1)	32.84 (7.53)	0.945
BASMI	2.8 (1.25)	2.38 (0.98)	0.230
BASDAI	4.28 (1.81)	3.86 (1.68)	0.443
BASFI	3.21 (1.4)	3.28 (1.75)	0.900
ASQoL	10.52 (3.47)	9.95 (3.70)	0.610

**p<0.001, axSpA: Axial spondylarthritis, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire, MSK-HQ: The Musculoskeletal Health Questionnaire, SD: Standard deviation

DISCUSSION

The main finding of this study was that musculoskeletal health, which was evaluated by MSK-HQ, deteriorated in patients with axSpA. In addition, deterioration of musculoskeletal health is significantly related to pain, functionality, disease activity, and HRQoL. Although musculoskeletal health, functionality, disease activity, and HRQoL did not differ according to radiographic status and the use of biologics, spinal mobility was found to be better in non-radiographic axSpA patients. To the best of our knowledge, this study is the first in the literature to investigate musculoskeletal health and the potential relationships between clinical characteristics in axSpA patients.

In the present study, the mean MSK-HQ was higher than the values documented in other studies, although the mean disease duration and disease activity were comparable (8,12). One possible explanation is that most the axSpA patients who participated in our study used biologics. On the other hand, the use of biologics may have a positive effect on disease management and inflammation control.

Our results suggest that worsening of MSK-HQ is significantly related to pain, BASDAI, BASFI, and ASQoL. A previously published study argued that deterioration of disease activity, loss of functionality, and worsening of ASQoL were independently associated with worsening of musculoskeletal health in axSpA patients (8,12). A possible reason for the strong correlation between MSK-HQ-BASDAI, MSK-HQ-BASFI, and MSK-HQ-ASQoL is that MSK-HQ includes measures of disease-related daily living activities, social functioning, self-efficacy, and psychological well-being. In addition, as some studies have shown, worsening of inflammatory lumbar pain and disease activity, loss in physical capacity may influence musculoskeletal health and the perception of welfare (19-21). However, spinal mobility as measured by BASMI is not associated with MSK-HQ, which indicates that patients may not perceive mobility restriction as a problem in their daily lives.

We hypothesized that radiographic status and use of biologics may affect musculoskeletal health, disease activity, functionality, and HRQoL before the study. However, according to our results, radiographic status and use of biologics do not play a role in musculoskeletal health, disease activity, functionality, or HRQoL. On the other hand, we found that radiographic status may negatively affect spinal mobility. Previous studies have shown that radiographic axSpA patients have more restricted spinal mobility than non-radiographic axSpA patients (22-25). A recent study reported that the formation of syndesmophytes in axSpA patients is mostly limited to patients with structural damage to their sacroiliac joints (26). We believe that the longer symptom duration of radiographic axSpA patients may negatively affect spinal mobility. The previously mentioned structural damage in the sacroiliac joints and syndesmophyte formation are associated with the function and mobility of the spine, which explains the spinal mobility limitation in radiographic axSpA patients, consistent with our results (26).

Study Limitations

The subjectivity of questionnaires used to evaluate the patient's condition and most of the patients were female, which may be considered study limitations. While radiographic axSpA is a predominantly male disease, non-radiographic axSpA is a predominantly female disease. We determined female-dominated patient groups for the study. Because there were more female patients in our study population.

CONCLUSION

Deterioration of musculoskeletal health in patients with axSpA was mainly related to disease activity, worsening of functionality,

and HRQoL. Radiographic status and use of biologics do not seem to influence disease activity, functionality and HRQoL. However, radiographic status may negatively affect spinal mobility. These results revealed that clinicians should be aware of the possible deterioration of musculoskeletal health, disease activity, functionality and HRQoL.

Ethics

Ethics Committee Approval: This study, which was planned as an observational, cross-sectional, and single-center, was approved by the Necmettin Erbakan University Ethics Committee (decision no: 2021/3185, date: 02.04.2021).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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EFFECTS OF EXERCISE USING A STRETCHING PLATFORM ON PAIN, PROPRIOCEPTION, BALANCE, AND MOBILITY IN PATIENTS WITH NON-SPECIFIC CHRONIC LOW BACK PAIN

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Abstract

Aim: Non-specific chronic low back pain (LBP) is defined as pain lasting more than 3 months, which is the first among musculoskeletal system diseases. This study aimed to examine and compare the effects of exercises applied with a stretching platform in addition to conservative treatment (CT) and CT only on pain, proprioception, balance, and mobility in patients with chronic LBP.

Material and Methods: Fifty five people with chronic LBP were included in the study and randomly divided into 2 groups. Group 1 was included in the CT, and group 2 was included in the exercise program applied with a stretching platform in addition to the CT. Pain intensity with visual analog scale (VAS), proprioception sense with the active re-creation of passive positioning method without extremity support, mobility with modified schober test (MST), hand finger-ground distance measurement (HFGDM) and trunk lateral bending measurement (TLBM), balance level with functional reach test (FRT), functionality with oswestry disability index (ODI), and quality of life (QoL) was assessed with the EuroQol Group 5D-3L.

Results: Statistically significant differences were observed between the results of pain, proprioception, MST, HFGDM and TLBM, FRT, ODI, and EuroQol Group 5D-3L in intragroup evaluations ($p<0.05$). In intergroup analysis, the VAS score during activity and 15° right ankle plantar flexion in proprioception evaluation were superior in group 2 compared with group 1 ($p<0.05$).

Conclusion: It was observed that CT and exercises applied with a stretching platform in the treatment of LBP had positive effects on pain, proprioception, mobility, balance, functionality, and QoL.

Keywords: Low back pain, exercise, balance, proprioception, mobility

INTRODUCTION

Non-specific chronic low back pain (LBP) is defined as pain lasting more than 3 months, which is the first among musculoskeletal system diseases, is located between the lower ribs and the gluteal line, can spread to the lower extremities (1). LBP, with a prevalence of 4-33%, is more common in females over 40 years of age (2,3). LBP that does not go away with rest, pain in the legs, numbness, and weakness, increased temperature in the pain areas, loss of sensation and tenderness, decreased proprioception sense in the lower extremity joints, lumbosacral joint and facet joints are common symptoms in chronic LBP (4).

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Medical, conservative treatment (CT), and surgical approaches are applied for treating LBP. CT approaches include thermotherapy, electrotherapy, exercise training, back schooling, and patient education (5). Thermotherapy is a treatment approach that generally includes hot applications in the chronic period to reduce pain and spasm (6). Electrotherapy is an application in which electrical currents are used to relieve pain and improve muscle function (7). Exercise training significantly reduces the level of pain and the possibility of recurrence of pain, and increasing flexibility by preventing pain-induced kinesiophobia (8). Patient education informs people about correct posture and ergonomics and offers suggestions that will enable people to cope with pain (9).

The reasons for preferring exercises with a stretching platform in our study are to increase the mobility of the lumbar region, reduce the fear of pain-induced movement, and improve the sense of proprioception and dynamic balance in the joints with the stretching effect that will occur in all joints from the lumbar region to the ankle.

Our primarily aim was to examine and compare the effects of exercises applied with a stretching platform in addition to CT in patients with chronic LBP and only CT on pain and secondarily on proprioception, balance, mobility, functionality and quality of life (QoL).

MATERIAL AND METHODS

Participants

Our study, which was designed as a randomized controlled prospective clinical trial (NCT05726955), was conducted in accordance with the Declaration of Helsinki. Ethics committee approval for this study was obtained from the İstanbul Okan University Ethics Committee with decision number (protocol no: 20.10.2021-14, date: 20.10.2021). The study included 55 participants aged 25-65 years, who had LBP for more than 12 weeks and whose pain intensity was greater than 3 on the 10 cm visual analog scale (VAS). Those who have structural deformity, circulatory disorder, and a disease that will prevent mobility in the columna vertebralis, those who have undergone surgery for the columna vertebralis and lower extremity in the last year, and those diagnosed with vertigo and osteoporosis were not included in the study. All volunteers participating in the study were given an informed consent form, and their signed consent was obtained.

Evaluations of pain, proprioception, mobility, balance, functionality and QoL were performed by a physiotherapist, while treatment programs were performed by another physiotherapist in this study. Physiotherapists were blind to each other. The face-to-face the interview method was used for data collection. A consultation was provided by the researchers when the patients had questions. It took about 30 min to complete all assessments.

Sample Size

The sample size of our study was made using PS Power analysis program. In the analysis, the number of samples was determined as 25 individuals in each group using the values of α=0.05, power: 0.80, minimal clinically important difference: 20 mm (VAS), standard deviation: 24.51. Considering the probability of 10% decrease in the participants, it was determined that 55 people should participate in the study (10).

Randomization

The participants were randomized via the "Research Randomiser" website (11). The numbers obtained because of randomization by entering the number of participants (n=55) and the number of groups (group 1 and group 2) were put into envelopes. Participants were assigned to groups according to the numbers on the envelopes they drew. Randomization was done in secret, blinding the groups and preventing the participants from meeting the other group.

Groups

Group 1 (n=27) were included in a CT program and group 2 (n=28) were included in an exercise training program applied with CT and a stretching platform 3 days a week for 6 weeks. Severity of pain, proprioception, mobility, balance, functionality, and QoL assessments of all participants were performed before and after the treatment. The participation status, assessments, and treatment methods applied to the participants were as shown in the flow diagram below (Figure 1).

Assessments

Demographic data including age, height, body weight, body mass index (BMI), previous diseases, and smoking habits of the participants who participated in the study were evaluated. To evaluate the severity of pain at night, at rest, and during activity, VAS was used, which digitizes the parameter values that cannot be measured numerically by numbering them from 0 to 10, where "0" is no pain and "10" is very severe pain (12).

In the method of actively recreating passive positioning without supporting the extremity, in which a goniometer is used to evaluate the proprioception sense, the extremity was passively moved to the target angle while the participant's eyes were closed, and the participant returned to the starting point after focusing on the position for 10 seconds. The participant tried to

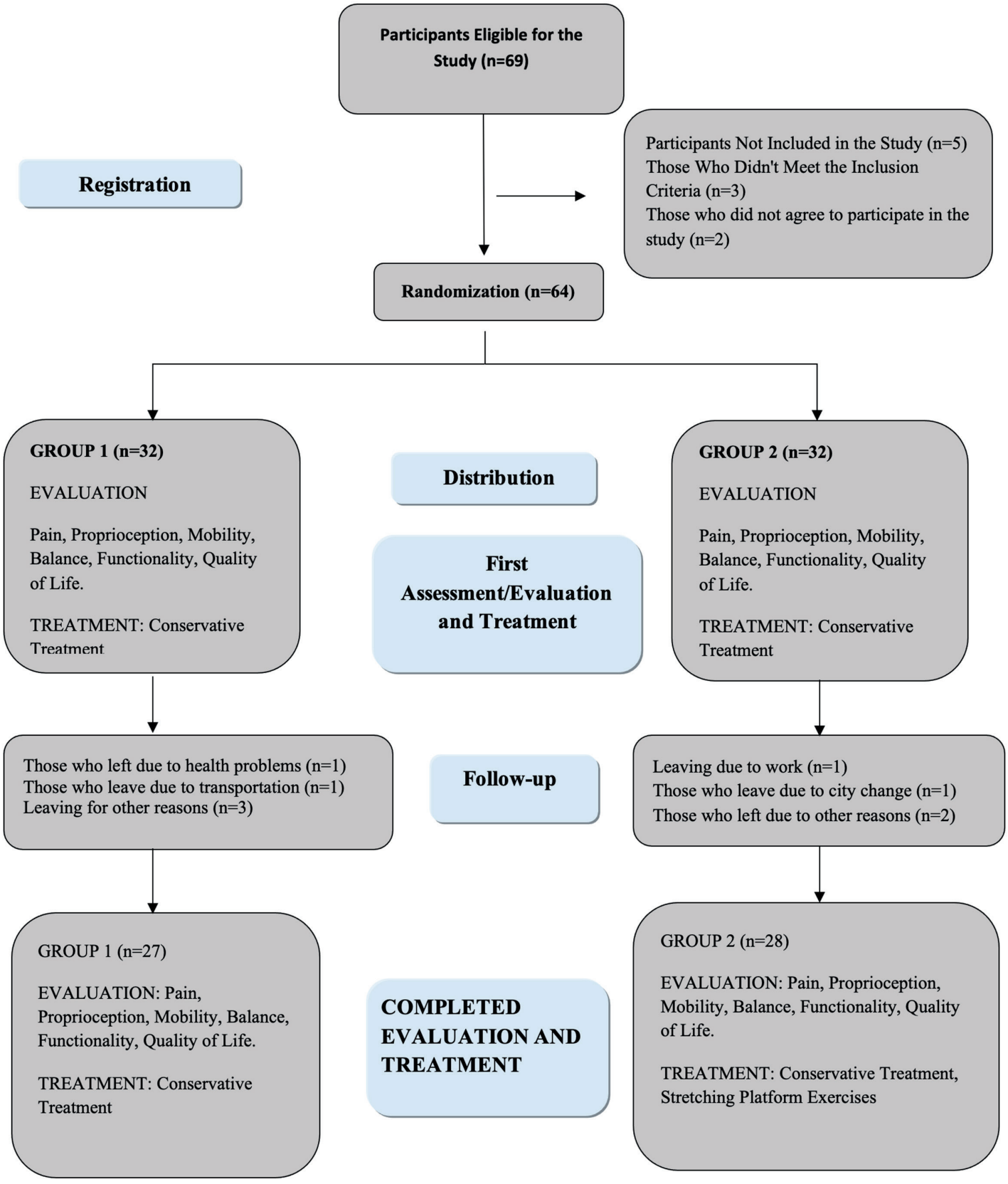

Figure 1. Working flow diagram

find the target angle by actively moving the same extremity, and the difference was recorded as the deviation angle (13).

Modified schober test (MST), hand finger-ground distance measurement (HFGDM), and trunk lateral bending measurement (TLBM) were used to evaluate the level of mobility. In the MST, 5 cm below and 10 cm above the line connecting the spinal iliaca posterior superior were marked with the help of a tape measure while the participant was in an upright position. While the participant was performing maximum trunk flexion, the distance between the two points was measured and 15 cm was subtracted from this measurement. If the difference is less than 5 cm, it is MST (+). This result indicates that lumbar region mobility decreases (14,15). In HFGDM, the participant is asked to bend forward and perform maximum flexion while in an upright position. In TLBM, the participant was asked to lean to the side with his arms on both sides of the body, with his shoulder and gluteal region resting against the wall. In both measurements, the distance between the third finger and the ground was measured with the help of a tape measure. Lumbar mobility increases as the distance between the finger and the floor decreases in TLBM and HFGDM (16).

Functional reach test (FRT) was used for balance assessment. The participant was positioned to stand sideways against the wall. The shoulder on the wall was brought to 90° flexion and the elbow to full extension, and the participant was asked to make a fist with the same arm. The alignment of the 3rd metacarpal head was marked on the wall. The participant reached forward with the knees fully extended and the level of the third metacarpal head was marked again. The difference between the two marks was measured using a tape measure. The average value was obtained after 3 trials. The same application was repeated with eyes closed. The greater the difference between the marked points in FRT, the better the balance (17,18).

The oswestry disability index (ODI) was used for functionality assessment. ODI is a scale that evaluates the degree of the loss of function in LBP between "0" and "100" points. As the score in ODI increases, the level of disability increases (19).

The EuroQol Group 5-dimension 3-level (EQ-5D-3L) QoL scale was used for QoL assessment. The 1st item of the parameters evaluated in the 1st part of the scale includes the expressions "no problem", the 2nd item "moderately severe problem" and the 3rd item "very severe problem". In scoring, '11111' represents complete well-being, and '33333' represents coma or death. Section 2 contains VAS, with 100 representing "excellent health" and 0 representing "very poor health" (20).

Treatment Program

All participants included in the study received CT 3 days a week for 6 weeks. CT included a 20-minute hot pack and conventional transcutaneous electrical nerve stimulation and William's flexion exercises applied to the lumbar region. The exercises performed on the stretching platform designed to stretch the lumbar, gluteal, and posterior parts of the lower extremity were applied only to the participants in group 2 for 3 days a week for 6 weeks after Williams flexion exercises (Table 1).

Statistical Analysis

The SPSS statistical package program was used to evaluate the data. For homogeneity of variances, which are prerequisites of parametric tests, "Levene test", the normality assumption "Shapiro-Wilk test", the differences between two independent groups "Student's t-test" and "Mann-Whitney U test", and the differences between the two dependent groups "Paired t-test" and the "Wilcoxon sign test" were used. Relationships between categorical variables were analyzed with Fisher's exact test and chi-square test. In the analysis of frequencies less than 20%,

Table 1. Exercises with stretching platform

Exercises with stretching platform	Purpose of the exercise	How to practice the exercise	Number of repetitions	Duration
1st exercise	Stretching the lumbal, gluteal, posterior part of the lower extremity	Leaning forward on the platform	3	30 sec/repeat
2nd exercise	Increasing the sense of proprioception and balance	Leaning forward on the platform with eyes closed	3	30 sec/repeat
3rd exercise	Stretching the gastrocnemius muscle, strengthening the ankle joint	Lean forward on the platform with the knees in the semiflexed position.	3	30 sec/repeat
4th exercise	Improving balance	Standing on one leg, leaning forward on the platform	3	30 sec/repeat
5th exercise	Strengthening the oblique muscles, stretching the iliotibial band	With right/left trunk rotation, leaning right/left on the platform	3	30 sec/repeat

evaluation was made with the "Monte Carlo simulation method". A $p<0.05$ level was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the participants are shown in Table 2. It was determined that the two groups were similar in terms of demographic and clinical characteristics ($p>0.05$), (Table 2).

In intragroup analysis, a statistically significant decrease was found in VAS scores at rest, night, and activity (Table 3), measurement of right and left TLBM, and a statistically significant increase was found in proprioception (Table 4), measurement of MST, HFGDM, FRT, and eyes-closed FRT (Table 5), ODI (Table 6), EQ-5D-3L, and EQ-5D-3L-GAS ($p<0.05$), (Table 6).

In intergroup analysis, the improvement in VAS activity and in 15° right ankle plantar flexion proprioception was found

Table 2. Comparison of demographics and clinical characteristics (n=55)

		Participant groups		Test statistics	P
		Group 1 (n=27)	Group 2 (n=28)		
Age		45.26±10.68	44.18±9.53	-0.464	0.643[1]
Height		167.63±9.17	160.61±30.07	-0.649	0.516[1]
Weight		70.93±17.75	78.36±15.73	-1.760	0.078[1]
BMI		25.58±4.24	28.25±5.19	-1.953	0.051[1]
Gender	Female	19 (70%)	18 (64%)	0.231	0.631[2]
	Male	8 (30%)	10 (36%)		
Smoking	Yes	16 (59%)	8 (29%)	4.089	0.053[2]
	No	11 (41%)	20 (71%)		

[1]Mann-Whitney U test (z), [2]Chi-square test, BMI: Body mass index
Summary statistics are given as the mean ± standard for numerical data and number (percentage) for categorical data.

Table 3. Intragroup and intergroups comparison of pain severity (n=55)

		Participant groups		Tİ[†] (group)			Tİ[&] (group x time)		
		Group 1 (n=27)	Group 2 (n=28)	Test statistics	p	ES	Test statistics	p	ES
VAS rest	First	5.30±3.12	4.61±3.35	-0.764	0.445	0.103	-0.234	0.815	0.032
	Last	3.37±2.39	2.75±2.43	-0.981	0.326	0.132			
Tİ[¥] (time)	Test statistics	-4.104	-3.939						
	p	**0.001**	**0.001**						
	ES	0.790	0.744						
VAS activity	First	7.00±2.53	6.64±2.00	-0.605	0.545	0.082	-2.359	0.018	0.318
	Last	5.33±2.15	4.14±1.96	-2.007	**0.045**	0.271			
Tİ[¥] (time)	Test statistics	-4.084	-4.582						
	p	0.001	0.001						
	ES	0.786	0.866						
VAS night	First	3.48±3.15	3.57±3.24	-0.052	0.959	0.007	-1.031	0.303	0.139
	Las	2.59±2.53	2.21±2.45	-0.456	0.648	0.061			
Tİ[¥] (time)	Test statistics	-3.223	-3.541						
	p	**0.001**	**0.001**						
	ES	0.620	0.669						

ES: Effect size, Tİ: Test statistics, First: First measure, Last: Last measure, VAS: Visual analog scale, z: Mann-Whitney U Test, z*: Willcoxon test, [†]Intergroup comparison, [¥]Intra-group comparison, [&]Intergroup difference between first and last scores comparison, summary statistics are given as mean ± standard deviation

Table 4. Intragroup and intergroup comparison of proprioception evaluation results (n=55)

		Participants		Tİ† (group)			Tİ& (group x time)		
		Group 1 (n=27)	Group 2 (n=28)	Test statistics	p	ES	Test statistics	p	ES
60° lumbal flexion	First	19.26±11.41	14.64±14.27	-1.372	0.170	0.185	-0.827	0.408	0.112
	Last	8.89±10.86	5.89±6.53	-0.717	0.473	0.097			
Tİ¥ (time)	Test statistics	-4.203	-3.536						
	p	**0.001**	**0.001**						
	ES	0.809	0.668						
60° hip flexion right	First	17.41±9.24	9.11±9.72	-3.041	0.002	0.410	-1.672	0.095	0.225
	Last	7.41±8.13	2.86±5.84	-2.260	**0.024**	0.305			
Tİ¥ (time)	Test statistics	-3.884	-2.909						
	p	**0.001**	**0.004**						
	ES	0.747	0.550						
60° hip flexion left	First	13.52±8.75	9.82±9.95	-1.501	0.133	0.202	-1.174	0.240	0.158
	Last	5.37±6.03	4.11±7.82	-1.289	0.198	0.174			
Tİ¥ (time)	Test statistics	-3.376	-3.15						
	p	**0.001**	**0.002**						
	ES	0.650	0.595						
30° hip abduction right	First	10.74±6.31	8.57±6.92	-1.258	0.208	0.170	-0.139	0.890	0.019
	Last	5.37±6.49	3.75±5.02	-0.901	0.368	0.121			
Tİ¥ (Time)	Test statistics	-3.020	-2.750						
	p	**0.003**	**0.006**						
	ES	0.581	0.520						
30° hip abduction left	First	10.19±6.58	9.64±8.04	-0.228	0.819	0.031	-0.624	0.532	0.084
	Last	4.81±6.58	3.21±6.27	-0.980	0.327	0.132			
Tİ¥ (time)	Test statistics	-3.228	-3.321						
	p	**0.001**	**0.001**						
	ES	0.621	0.628						
60° knee flexion right	First	21.85±40.65	11.43±12.16	-1.489	0.136	0.201	-1.247	0.213	0.168
	Last	7.04±6.54	6.79±9.05	-0.568	0.570	0.077			
Tİ¥ (time)	Test statistics	-3.237	-2.092						
	p	**0.001**	**0.036**						
	ES	0.623	0.395						
60° knee flexion left	First	10.56±5.77	10.89±11.55	-0.543	0.587	0.073	-0.432	0.666	0.058
	Last	5.74±6.00	6.07±8.32	-0.176	0.860	0.024			
Tİ¥ (time)	Test statistics	-2.714	-2.759						
	p	**0.007**	**0.006**						
	ES	0.522	0.521						
15° ankle plantar flexion-right	First	15.56±5.43	8.39±7.94	-3.610	0.001	0.487	-1.023	0.306	0.138
	Last	13.52±5.15	4.64±5.26	-4.897	**0.001**	0.660			
T/¥ (time)	Test statistics	-2.007	-3.077						
	p	**0.045**	**0.002**						
	ES	0.330	0.581						
15° ankle plantar flexion-left	First	15.93±5.89	7.5±7.64	-4.122	0.001	0.556	-0.592	0.554	0.080
	Last	12.22±4.87	4.82±6.31	-4.118	**0.001**	0.555			
Tİ¥ (time)	Test statistics	-2.843	-2.267						
	p	**0.004**	**0.023**						
	ES	0.547	0.428						

ES: Effect size, Tİ: Test statistics, First: First measure, Last: Last measure, z: Mann-Whitney U Test, z*: Willcoxon test, †Intergroup comparison, ¥Intra-group comparison, &Intergroup difference between first and last scores comparison, summary statistics are given as mean ± standard deviation

to be superior in group 2 compared to the group 1 ($p<0.05$), (Tables 3, 4). The improvement of 60° right hip flexion and 15° left ankle plantar flexion proprioception and TLBM were found to be superior in group 1 compared with group 2 ($p<0.05$), (Tables 4, 5).

DISCUSSION

In this study, we examined and compared the effects of exercises applied with a stretching platform in addition to CT and only CT in patients with LBP on pain, proprioception, balance, mobility, functionality and QoL.

Table 5. Intragroup and intergroup comparison of the mobility and balance evaluation results (n=55)

		Participants		Tİ† (group)			Tİ& (group x time)		
		Group 1 (n=27)	Group 2 (n=28)	Test statistics	p	ES	Test statistics	p	ES
Modified schober test	First	5.00±0.72	5.00±1.16	-0.465	0.642	0.063	-1.045	0.296	0.141
	Last	5.44±0.66	5.59±0.98	-0.788	0.431	0.106			
Tİ¥ (time)	Test statistics	-3.630	-3.581						
	p	**0.001**	**0.001**						
	ES	0.699	0.677						
Hand finger ground distance measurement	First	16.15±11.52	12.86±8.29	-1.104	0.269	0.149	-0.287	0.774	0.039
	Last	13.61±9.27	10.43±9.77	-1.412	0.158	0.190			
Tİ¥ (time)	Test statistics	-2.716	-2.093						
	p	**0.007**	**0.036**						
	ES	0.523	0.396						
Trunk lateral bending measurement right	First	38.37±10.79	45.16±9.08	-2.429	0.015	0.328	-0.838	0.402	0.113
	Last	32.30±9.94	39.07±11.63	-2.275	**0.023**	0.307			
Tİ¥ (time)	Test statistics	-4.374	-3.922						
	p	**0.001**	**0.001**						
	ES	0.842	0.741						
Trunk lateral bending measurement left	First	37.39±10.39	45.50±8.93	-2.942	0.003	0.397	-0.051	0.960	0.007
	Last	32.52±9.11	39.63±11.42	-2.435	**0.015**	0.328			
Tİ¥ (time)	Test statistics	-4.158	-3.135						
	p	**0.001**	**0.002**						
	ES	0.800	0.592						
Functional reach test	First	27.04±10.67	27.88±10.52	-0.379	0.704	0.051	-1.342	0.180	0.181
	Last	30.17±11.20	32.98±10.51	-1.315	0.189	0.177			
Tİ¥(time)	Test statistics	-3.416	-3.452						
	p	**0.001**	**0.001**						
	ES	0.657	0.652						
Eyes closed functional reach test	First	25.63±13.05	26.29±12.55	-0.076	0.940	0.010	-1.947	0.045	0.249
	Last	28.43±11.99	30.96±12.80	-0.708	0.479	0.095			
Tİ¥ (time)	Test statistics	-3.487	-3.229						
	p	**0.001**	**0.001**						
	ES	0.671	0.610						

ES: Effect size, Tİ: Test statistics, First: First measure, Last: Last measure, z: Mann-Whitney U test, z*: Willcoxon test, †Intergroup comparison, ¥Intra-group comparison, &Intergroup difference between first and last scores comparison, summary statistics are given as mean ± standard deviation

Table 6. Intragroup and intergroup comparison of the functionality and quality of life evaluation results (n=55)

		Participants		Tİ† (group)			Tİ& (group x time)		
		Group 1 (n=27)	Group 2 (n=28)	Test statistics	p	ES	Test statistics	p	ES
Oswestry disability index	First	46.67±19.94	41.93±14.48	-0.742	0.458	0.100	-1.066	0.283	0.142
	Last	36.00±17.51	28.86±12.71	-1.501	0.133	0.183			
Tİ¥ (time)	Test statistics	-4.336	-4.474						
	p	**0.001**	**0.001**						
	ES	0.834	0.846						
EQ-5D-3L	First	0.44±0.32	0.51±0.26	-0.591	0.554	0.080	-0.357	0.721	0.048
	Last	0.60±0.20	0.66±0.18	-1.220	0.223	0.164			
Tİ¥ (time)	Test statistics	-3.299	-3.504						
	p	**0.001**	**0.001**						
	ES	0.635	0.662						
EQ-5D-3L-GAS	First	76.30±16.0	72.86±19.22	-0.453	0.650	0.061	-0.291	0.771	0.039
	Last	83.30±13.30	80.00±16.33	-0.557	0.578	0.075			
Tİ¥ (time)	Test statistics	-3.275	-3.087						
	p	**0.001**	**0.002**						
	ES	0.630	0.583						

ES: Effect size, Tİ: Test statistics, First: First measure, Last: Last measure, z: Mann-Whitney U test, z*: Willcoxon test †Intergroup comparison, ¥Intra-group comparison, &Intergroup difference between first and last scores comparison, summary statistics are given as mean ± standard deviation, EQ-5D-3L: EuroQol Group 5-dimension 3-level

In previous studies, when the demographic characteristics of people with chronic LBP are examined, it is seen that the probability of chronic LBP is higher in people aged 40 and over, females, and people with a BMI of 25 kg/m^2 and above (21,22). In our study, the mean age of chronic LBP was 45.26±10.68 years in group 1 and 44.18±9.53 years in group 2. The mean BMI value was found to be 25.58±4.24 kg/m^2 in group 1 and 28.25±5.19 kg/m^2 in group 2. In addition, it was found that chronic LBP was more common in females compared to males with a rate of 70% in group 1 and 64% in group 2.

VAS is generally used for pain assessment in chronic LBP because of its easy application. In addition, in pain assessment, evaluating the pain according to its course during the day and its severity at rest and activity enables faster solutions to be developed by determining the causes of chronic LBP. In the studies conducted and in our study, it was determined that pain was felt most during activity in chronic LBP, while night pain was felt the least (23-25). We think that the reason why night pains are less is the decrease in the load on the bones, joints, ligaments and intervertebral disk in the column vertebralis compared to standing and sitting positions while lying down. When studies conducted to reduce pain and improve function in chronic LBP were examined, it was found that only stretching exercises were not effective on pain compared to other exercise training (26-29). In our study, the exercise program applied with a stretching platform was not found to be superior to the CT program in reducing the level of pain, and it was found that CT and exercises applied with a stretching platform were effective in reducing the pain score in chronic LBP. We think that the exercises performed with the stretching platform cause extra stretching in the calf group muscles, providing relaxation of the lower kinetic chain and relaxation of the lumbar region muscles, that the person feels less pain during the activity, and that our study may contribute to the literature thanks to this effect provided by the stretching platform.

There is a positive correlation between decreased proprioception sense and the loss of balance and function in people with chronic LBP (30). For this reason, the ability of exercise approaches to accelerate the proprioceptive response by improving the sensitivity of the spinocerebellar and dorsal lateral-medial lemniscal pathways is used (31). There is no study in the literature on the effect of stretching exercises on proprioception in people with chronic LBP. In our study, it was found that CT and exercises applied with a stretching platform improved the sense of proprioception in people with chronic LBP. We think that in addition to the stretching effect of the exercises and flexion

exercises performed with the stretching platform on the lumbar region and lower extremity muscles, the forward bending exercises with the eyes closed and the knees semi-flexed on the stretching platform increase the sense of joint position and the sense of joint movement in the joints of the lower extremity and lumbar region. It improves the sense of proprioception.

It is stated in previous studies that pain causes avoidance of movement in people with chronic LBP and therefore negatively affects mobility; therefore, adding different exercise approaches to exercise training programs for people with chronic LBP reduces pain levels as well as contributes to mobility and balance (10,26,32-35). In our study, MST, HFGDM, and TLBM methods were used to evaluate the mobility levels of people with chronic LBP. According to the data we have obtained, results that will contribute to the improvement of the level of mobility have emerged in both groups in MST, HFGDM, and TLBM methods. We think that the reason for this situation is that the exercises applied with the stretching platform and flexion exercises create a stretching effect on the lumbar and lower extremity muscles, and the hot pack application in the lumbar region causes an increase in the mobility of the lumbar region by relaxing the non-contractile tissues.

In people with chronic LBP, pain negatively affects balance and mobility. In general, exercise approaches positively affect balance by increasing the sense of joint position (31). When the studies in the literature are examined, it is seen that stretching exercises contribute the most to the development of balance among exercise approaches. However, we understand that only periods of 30 s or less improve balance, and therefore, the most important factor in the effect of stretching exercises on balance is the duration of stretching (32,35-37). According to the data we obtained in our study, FRT with eyes open and FRT with eyes closed increased in both groups, showing that the balance level of the participants improved. This result shows that forward bending exercises with one foot and eyes closed and the modified straightening exercise, which is one of the flexion exercises, applied with a stretching platform are directly effective in increasing the FRT scores. In addition, it is thought that the stretching effect of the exercises applied with the stretching platform and the stretching exercise applied to the hamstring muscle, which is one of the flexion exercises, on the lumbar region and lower extremity muscles triggers the development of balance by increasing the sense of joint position and joint movement.

In a study examining the functionality level of 225 people with LBP, it was reported that ODI is a reliable scale that evaluates chronic LBP in a multidimensional way (38). In our study, an increase in functionality was achieved in both groups according to ODI scores. This result suggests that exercises applied with a stretching platform are as effective as CT in improving the level of functionality in chronic LBP. We think that the stretching effect of the exercises applied with the stretching platform on the muscles of the lower extremities and lumbar region, as well as the stretching exercise for the hamstring muscle in the flexion exercises and the modified straightening exercise, and the diversification of these exercises by bending forward and sideways, standing on one leg, eyes closed, increased the functionality of the participants. Our study can contribute to the literature in this respect.

In the literature, it is seen that the use of the two scales together in chronic LBP yields more objective findings since the EQ-5D-3L scale is valid and reliable for QoL assessment and has a strong correlation with ODI (39-42). This result suggests that exercises applied on the stretching platform are as effective as CT in improving the QoL of people with chronic LBP. However, in the literature, there is no QoL assessment with the EQ-5D-3L scale for treating chronic LBP. In our study, an increase was observed in the QoL VAS score in both groups. This result suggests that exercises applied on the stretching platform are as effective as CT in improving the QoL of people with chronic LBP.

Study Limitations

The limiting factors of the study were the inability to examine the long-term effects of exercises due to the Coronavirus disease-2019 pandemic and the inability to use objective measurement methods because of existing clinical opportunities.

CONCLUSION

It was concluded that CT and exercises applied with a stretching platform in addition to CT in patients with chronic LBP reduce pain and increase proprioception, mobility, balance, functionality, and QoL. Since there is no consensus on the content of the exercises performed on the stretching platform, the duration of application, and the nature of passive or dynamic stretching, there is a need for studies that objectively evaluate the effectiveness of different types of exercise training using this exercise support and examine the long-term results.

Ethics

Ethics Committee Approval: Ethics committee approval for this study was obtained from the İstanbul Okan University Ethics Committee with decision number (protocol no: 20.10.2021-14, date: 20.10.2021).

Informed Consent: All volunteers participating in the study were given an informed consent form, and their signed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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EVALUATION OF EPICARDIAL FAT THICKNESS, A NEW INDICATOR OF THE CARDIOVASCULAR RISK FACTOR, IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Aim: Systemic lupus erythematosus (SLE) is a chronic autoimmune rheumatic disease with high cardiovascular mortality. Epicardial adipose tissue (EAD) is the visceral fat located between the myocardium and pericardium. EAD is recognized as an active metabolic and inflammatory tissue capable of producing and releasing various preatherosclerotic and proinflammatory hormones, cytokines. EAD is associated with coronary artery disease, metabolic syndrome, and subclinical atherosclerosis. In this study, we investigated the relationship between EAD and SLE patients.

Material and Methods: A total of 73 patients were recruited from the rheumatology department of a single center as a case-control study. The participants were divided into two groups: 73 patients with SLE (group 1) and 60 age- and sex- matched controls (group 2). Laboratory and radiological results were obtained from the electronic registration database. Data were analyzed and compared between the groups.

Results: There was no significant difference between the groups in terms of age, gender, height, weight, or body mass index (BMI). EAD was found to be significantly higher in SLE patients than in the control group. In the SLE group, EAD was found to be significantly higher in patients with low complement levels than in those without. There was a positive correlation between EAD and age, leukocytes, neutrophils, C-reactive protein (CRP), and BMI, but a negative correlation was found between SLE disease activity index.

Conclusion: Increased EAD was found in SLE patients compared with the control group. In addition, a correlation was found between increased EAD and low complement and CRP. EAD may be a measurable and modifiable potential therapeutic target associated with inflammation and cardiovascular risk in patients with SLE.

Keywords: Epicardial fat thickness, inflammation, systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune rheumatic disease of unknown cause that can affect almost every organ in the body. The reported prevalence of SLE in the United States is 20 to 150 cases per 100,000 (1). 65% of patients with SLE have the onset of the disease between the ages of 16 and 55 (2). Genetic, hormonal, immunological, and environmental factors are thought to play a role in the etiology of the disease (3). The clinical manifestations of SLE range from structural symptoms such as fever, sweating, weight loss, arthralgia, and rash to more severe organ involvement, including cardiovascular, central nervous system, and renal involvement. Cardiac disease is common among patients with SLE and may include the pericardium, myocardium, valves, conduction system, and coronary arteries (4). There is an increased prevalence of atherosclerosis in patients with SLE. Atherosclerosis is an inflammatory process that involves immune cell activation, plaque formation due to inflammation, and subsequent rupture (5). Systemic inflammation is thought to accelerate atherosclerosis (6,7). In mouse models of SLE, the degree of systemic inflammation correlates with the rate of atherosclerosis development. Dysfunctional proinflammatory high-density lipoprotein cholesterol, commonly found among patients with SLE, can accelerate low-density lipoprotein oxidation and atherosclerosis (8,9). The accumulation of immune complexes also stimulates the cholesterol deposition in atherosclerotic plaques (10). Type I interferon (IFN) promotes atherosclerosis by stimulating macrophage recruitment to atherosclerotic lesions in vitro, and type I IFN may have other effects on endothelium and atherogenesis (11,12). Epicardial adipose tissue (EAD) is a surrogate marker of visceral adiposity, and visceral fat may be an independent predictor of metabolic risk. Physiologically, EAD serves as an energy source for the myocardium by providing mechanical protection and plays a cardioprotective role by producing anti-inflammatory adipokines. Metabolically active EAD synthesizes and secretes bioactive molecules. These are transported to the adjacent myocardium via vasocrine and/or paracrine pathways. Recently, a meta-analysis revealed a correlation between EAD thickness and coronary artery disease (13-16). EAD measurement serves as a powerful potential diagnostic tool for assessing cardiovascular risk. The thickness of the EAD can be measured and evaluated using two-dimensional echocardiography, CT, or magnetic resonance imaging (MRI). Ultrasound requires experience, providing a linear measurement rather than a volumetric measurement. In addition, EAD located in the atrioventricular groove or elsewhere cannot be reached by ultrasound. Severely obese patients may have a weak acoustic window that does not allow for optimal visualization of EAD thickness. CT and cardiac MRI can provide a more accurate and volumetric EAD measurement (17). It has been reported that increased EAD measured using CT is associated with further progression of coronary artery calcification (18,19). Few studies have investigated the relationship between EAD and SLE. The aim of our study was to measure EAD thickness, which is known as a new indicator of atherosclerosis and a cardiovascular risk factor, with computed tomography (CT) in SLE patients and to compare it with the control group and to show its relationship with various variables such as demographic characteristics, clinical parameters, laboratory parameters, cardiometabolic risk markers, and disease duration.

MATERIAL AND METHODS

Study Population and Design

In this retrospective study, 73 patients over the age of 18 years and 60 controls, who applied to the rheumatology outpatient clinic of a tertiary hospital between January 2019 and January 2021, were diagnosed with SLE according to the 2012 Systemic Lupus International Collaboration Clinics criteria, were included in the study. Routine biochemical, whole blood samples, complete urinalysis and complement (C3-C4), antibodies against double-stranded DNA (dsDNA) levels, antinuclear antibody (ANA), and ANA profiles of SLE patients were retrospectively analyzed from the patient file. The laboratory and tomography results of the patients were retrospectively obtained by scanning the archives of the HBYS and PACS systems. Thorax CT images were analyzed at the workstation. SLE disease activity index (SLEDAI)-2K was used to evaluate the disease activity of patients with SLE. Patients who were the same age and gender as the patient group, had normal blood tests, had no known chronic disease, applied to the internal medicine outpatient clinic due to cough and dyspnea, underwent elective thoracic tomography, and had no pathological findings were selected as the control group. The radiological data of these patients were also scanned retrospectively from the PACS system archive. This single-center study was approved by the Sulçuk University Ethics Committee (decision no: 2021/320, date: 02.06.2021) and was conducted according to the principles. Written informed consent forms were obtained from all participants before the study.

Statistical Analysis

The Statistical Package for Social Sciences software was used for all procedures (IBM SPSS Statistics 21.0, IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normality distribution of the scale variables.

For continuous numerical variables, descriptive statistics are presented as mean standard deviation. Categorical variables are represented by the number of cases and percentage. The chi-square test was used to compare categorical variables, and the Student's t-test was used to compare continuous numerical variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate diagnostic performance. If the area under the curve (AUC) was found to be significant, the Youden index was used to determine the best cut-off point. The sensitivity and specificity of the diagnostic performance indicators were calculated. To determine the relationship between epicardial fat tissue and laboratory values, Pearson correlation analysis was used. Unless otherwise specified, the results were deemed statistically significant at p=;0.05.

RESULTS

The study included 73 patients with SLE, with 9.6% males and 90.4% females, a mean age of 47.58±10.98 years, and a mean disease duration of 7.52±5.68 years (range, 1-20 years). The control group included 60 age- and gender-matched healthy individuals. Tables 1 and 2 show the demographic and clinical characteristics of patients with SLE and the healthy control group. The groups did not differ significantly in terms of age, gender, height, weight, or BMI (p>0.05). Epipericardial fat tissue was found to be significantly higher in the SLE patient group than in the healthy control group (Table 1) (p=0.002). Within the SLE patient group, epipericardial fat tissue was significantly higher in patients with low complement levels than in those without (p=0.022). In addition, the renipericardial fat tissue did not differ significantly between SLE patients with anti-dsDNA positivity and comorbidity (p>0.05). The clinical characteristics and laboratory test results for the patients with SLE are shown in Table 2.

Table 1. Demographic and clinical characteristics of SLE patients and control group

	SLE patients	Healthy control	p-value
Gender (female)	n (%)* 66/73 (90.4)	51/60 (85.0)	0.425
Age, (years)**	47.58±10.98	49.78±11.99	0.270
Weight (kg)**	56.91±7.07	54.98±5.92	0.096
Height (cm)**	160.59±5.20	160.28±5.67	0.747
BMI**	22.17±3.38	21.52±3.07	0.253
Epipecardial fat tissue (cm^3)**	145.65±68.18	109.86±61.60	**0.002**

*Chi-square test's, data are presented as counts, with percentages in brackets, **Independent sample t-test, data are presented as mean ± standard deviation
SLE: Systemic lupus erythematosus, BMI: Body mass index

Table 3 shows the results of the ROC analysis. Epipericardial fat tissue demonstrated satisfactory diagnostic performance in differentiating SLE patients from healthy volunteers. The AUC was 0.662 (p=0.001), with a sensitivity of 75.3% and a specificity of 55.0% at a cut-off value of 96.95. Pearson correlation analysis was performed to determine the relationships between the epicardial fat tissue and laboratory values of patients with SLE (Table 4). There was a weak positive correlation between renipericardial fat tissue and age, leukocyte count, neutrophil count, and CRP (p=0.05). A strong positive correlation was found between epicardial fat tissue and BMI (p=0.001). However, in our study, healthy volunteers with BMI indices similar to those of SLE patients were included, and no significant difference in BMI was found (p>0.05). A weak negative correlation was found between epicardial fat tissue and SLEDAI (p=0.001).

DISCUSSION

SLE may present with clinical features ranging from mild joint and skin involvement to life-threatening renal, hematological, and central nervous system involvement. Heart disease is common among patients with SLE. There is an increased prevalence of atherosclerosis in SLE patients. Excessive oxidative stress in SLE increases inflammation, resulting in apoptotic cell

Table 2. Clinical characteristics of SLE patients (n=73)

Disease duration*	7.52±5.68
Additional disease**	29 (39.7)
HL**	4 (5.5)
ANA positivity**	73 (100)
Anti-DNA positivity**	11 (15.1)
Low complement levels**	44 (60.3)
Leukocyte (10^9/L)*	6.12±1.84
Hemoglobin (g/L)*	12.63±1.92
Platelet (10^9/L)*	239.18±82.17
PCT*	0.26±0.83
Neutrophile (10^9/L)*	3.61±1.43
Monocyte (10^9/L)*	0.47±0.16
Lymphocyte (10^9/L)*	1.76±0.65
Red cell distribution width (RDW) (%)*	14.94±2.32
Mean platelet volume (MPV) (FL)* SLEDAI *8.30±5.12	8.52±0.86
C-reactive protein (CRP) (mg/L)*	4.92±3.69
Erythrocyte sedimentation rate (ESR) (mm/h)*	24.52±16.23

*Data are presented as mean ± standard deviation, **Data are presented as counts, with percentages in brackets
SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, PCT: Platelets

Table 3. ROC analysis results of epipericardial fat tissue used for diagnosis of patients with SLE

	AUC (95% CI)	p-value	Cut-off	Sensitivity	Specificity
Epipericardial fat tissue	0.662 (0.568-0.756)	0.001	>96.95	75.3	55.0
Regression model (EAD, age and BMI)	0.757 (0.674-0.838)	<0.001	-	68.5	75.0

AUC: Area under the curve, 95% CI: 95% confidence interval, BMI: Body mass index, ROC: Receiver operating characteristic, EAD: Epicardial adipose tissue

Table 4. Correlation of epicardial fat tissue with disease activity, duration and laboratory findings in SLE patients (n=73)

	rs	p-value
Epicardial fat tissue - age	0.397	<0.001
Epicardial fat tissue - BMI	0.867	<0.001
Epicardial fat tissue - disease duration	-0.076	0.523
Epicardial l fat tissue - disease activity	-0.368	0.001
Epicardial fat tissue - hemoglobin	0.026	0.826
Epicardial fat tissue - leukocyte	0.267	0.022
Epicardial fat tissue - platelet	0.059	0.620
Epicardial fat tissue - neutrophile	0.250	0.033
Epicardial fat tissue - PCT	-0.080	0.499
Epicardial fat tissue - monocyte	-0.047	0.695
Epicardial fat tissue - lymphocyte	0.180	0.127
Epicardial fat tissue - RDW	0.010	0.935
Epicardial fat tissue - MPV	-0.145	0.219
Epicardial fat tissue - CRP	0.276	0.018
Epicardial fat tissue - ESR	0.018	0.877

rs: Pearson's rho correlation coefficients, BMI: Body mass index, MPV: mean platelet volume, RDW: Red cell distribution width, PCT: Platelets, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SLE: Systemic lupus erythematosus

death. Reactive species and free radical production in SLE and antiphospholipid syndrome are thought to contribute to chronic inflammation of tissues and lead to dyslipidemia and accelerated atherogenesis (20,21). A systematic review of 28 studies found that the risk of cardiovascular disease (CVD) among SLE patients was at least doubled compared to the general population (22). In a study, 105 patients with SLE and rheumatoid arthritis (RA) and 105 controls were compared (23). Coronary artery calcification was observed in 47.6 percent of SLE patients, 47.6 percent of RA patients, and 35.2 percent of controls. This increased frequency was strongly associated with inflammation, apart from other cardiac risk factors. EAD is a surrogate marker of visceral adiposity and it has been shown that visceral fat may be an independent predictor of metabolic risk. In the general population, EAD volume is independently associated with obstructive coronary artery plaque and noncalcified atherosclerotic lesions and is an independent predictor of ischemia (15,16). Mazurek et al. (24) compared epicardial and subcutaneous adipose tissue, and it was determined that epicardial tissue produced more inflammatory cytokines such as chemokines (monocyte chemotactic protein 1), leptin, interleukin-1B, interleukin 6 and tumor necrosis factor-alpha (TNF-α). In the light of these findings, they hypothesized that the presence of proinflammatory mediators such as TNF-α in the tissues surrounding the coronary arteries may lead to an increase in vascular inflammation and neovascularization via apoptosis (25). In our study, a weak positive correlation was found between EAD and leukocytes, neutrophils and CRP ($p<0.05$). This illustrates the link between EAD and inflammation. EAD is recognized as an active metabolic and inflammatory tissue capable of producing and releasing various proatherosclerotic and proinflammatory hormones, cytokines. There are studies in the literature showing its increase in autoimmune diseases. There are many studies showing increased EAD thickness in patients with RA. A cross-sectional study conducted with a cohort of 34 female RA patients and 16 controls matched for age and body mass index (BMI) showed greater EAD thickness in female patients with RA. Another age- and sex-matched cross-sectional study, including 76 patients with RA and 50 controls, reported a greater EAD thickness in RA patients (26,27). Increased EAD thickness is associated with endothelial dysfunction in spondyloarthritis (28). It suggests that EAD thickness is a candidate for atherosclerotic risk assessment in patients with systemic sclerosis without open heart disease (29). A systematic review and meta-analysis also shows that familial Mediterian fever patients have a higher risk of developing EAD than controls (30). In a study evaluating EAD thickness and total calcium score in sarcoidosis patients, EAD thickness calculated using thorax CT was found to be higher in sarcoidosis patients. The prognostic value of EAD measurements with CT: A systematic review of the literature also shows that most studies show that EAD quantification is significantly related to clinical outcomes and provides incremental prognostic value over coronary artery calcium scoring. Concerns with CT include the difficulty of integrating it into practice due to the radiation hazard, relatively high cost, and increased time required for measurements (31). A meta-analysis showed that EAD thickness was significantly higher in patients with metabolic syndrome (MetS) than in patients without (18). MetS is common among patients with SLE (32,33). In SLE, CVD risk factors (diabetes, hyperlipidemia, hypertension, family history of coronary heart

Table 5. Multivatiate analysis

	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Epipericardial_fat	-0.034	0.009	15.387	1	0.000	0.966	0.950	0.983
Gender (1)	-1.098	0.642	2.922	1	0.087	0.333	0.095	1.175
Age	0.043	0.020	4.734	1	0.030	1,044	1.004	1.086
BMI	0.438	0.171	6.604	1	0.010	1,550	1.110	2.166
Constant	-6.618	2.904	5.193	1	0.023	0.001		

EAD, age and BMI were found to be independent predictive parameters in SLE patients
SLE: Systemic lupus erythematosus, EAD: Epicardial adipose tissue, BMI: Body mass index, 95% CI: 95% confidence interval

disease, obesity, sedentary lifestyle and smoking), glucocorticoid use, disease duration and disease activity are associated with increased risk (34-36). Clinical factors associated with CVS in patients with SLE include: Higher disease activity, chronic nephritis, low serum C3 levels, anti-dsDNA, antiphospholipid antibodies, and high CRP (37). In our study, EAD in SLE patients was found to be significantly higher in patients with low complement levels (p=0.022).

In addition, EAT volume did not differ significantly in SLE patients with anti-dsDNA positivity and comorbidity (p>0.05). In addition, EAD predicted CVS events independent of conventional risk factors and BMI in the Multi-Ethnic Atherosclerosis Study MESA and another observational study (38). Lipson et al. (39) found increased EAD in SLE patients, similar to our study. However, the causes of increased EAD in SLE patients are still unknown. In our study, EAD was measured higher in SLE patients than in the control group, regardless of BMI. As noted above, inflammation is an important risk factor for atherosclerosis. This study also shows that increased EAD may be an independent risk factor for CVD in SLE patients (Table 5)

Study Limitations

Our study has limitations that must be acknowledged. First, due to its retrospective nature, it was impossible to standardize the point at which testing was performed in the natural history of the disease. The small number of patients, the fact that the study was conducted in a single center is another limitation of the study.

CONCLUSION

In our study, we observed increased EAD in patients with SLE compared with the control group. In addition, a correlation was found between increased EAD and low complement and CRP. EAD may be a measurable, modifiable potential therapeutic target associated with inflammation and cardiovascular risk in patients with SLE.

Ethics

Ethics Committee Approval: This single-center study was approved by the Sulçuk University Ethics Committee (decision no: 2021/320, date: 02.06.2021) and was conducted according to the principles.

Informed Consent: Written informed consent forms were obtained from all participants before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.H., S.Y., H.Ö., Ö.F.T., A.K., D.T., Concept: S.H., S.Y., D.T., M.K.K., Design: S.H., S.Y., H.Ö., Ö.F.T., A.K., D.T., Data Collection or Processing: S.H., S.Y., D.T., Analysis or Interpretation: S.H., H.Ö., Ö.F.T., A.K., M.K.K., Literature Search: S.H., D.T., Writing: S.H., S.Y., D.T., M.K.K.

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PATIENTS WITH INFLAMMATORY RHEUMATIC DISEASES HAVE HIGH CHRONOPHOBIA LEVELS DURING THE COVID-19 OUTBREAK

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Abstract

Aim: Coronaphobia during the Coronavirus disease-2019 (COVID-19) outbreak was commonly observed in the general population and in patients with chronic diseases. The study investigated chronophobia and its association with psychological parameters in patients with inflammatory rheumatic diseases.

Material and Methods: This cross-sectional study included 174 patients with rheumatic diseases, including fibromyalgia, connective tissue diseases (CTD) and spondyloarthropathies (SpA). Coronaphobia was evaluated using the COVID-19 Phobia Scale (C19P-S), and anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale. One-way ANOVA was used to calculate differences between diseases, and Pearson's correlation test was used for correlation analysis.

Results: The study was completed with 171 patients with rheumatic diseases [91 of them with CTD, 57 of them with SpA, and 23 of them with fibromyalgia syndrome (FMS)]. Significant differences were found in all subscales of C19P-S among FMS and inflammatory rheumatic diseases (CTD and SpA) ($p<0.05$). Significant correlations were found among anxiety, psychosomatic, and social subscales of C19P-S in both patients with CTD and SpA. No significant correlation was found between C19P-S, anxiety, and depression in FMS patients.

Conclusion: Higher chronophobia levels were found in patients with inflammatory rheumatic diseases than in those with non-inflammatory rheumatic diseases. Because it may be an additional reason for psychological problems, chronophobia should be considered in the management of inflammatory rheumatic diseases.

Keywords: Coronaphobia, COVID-19, rheumatic diseases

INTRODUCTION

Coronavirus disease-2019 (COVID-19), which emerged in Wuhan, China in 2019, has taken hold of the world in a short time. COVID-19 was first observed on March 10, 2020 in Turkey, and the World Health Organization declared the disease as pandemic on March 11, 2020 (1,2). Many governments have implemented various precautions and restrictions to minimize the spread of the pandemic and the risk of transmission (3). The importance of hygiene was emphasized within the scope of precautions against COVID-19 in Turkey. It was stated that the mask, curfew,

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and social distance were applied in necessary situations (4). Unfortunately, despite these precautions, COVID-19 was not brought under control in the world and death odds increased. Data about the negative effects of COVID-19 expanded rapidly among the general population through written, visual, and social media and caused anxiety and fear (5,6).

Phobia is defined as an anxiety disorder that causes an excessive and persistent reaction to an object, person, animal, activity, or situation (7). Coronaphobia is an overreaction to the fear of contracting coronavirus that may cause serious stress that can lead to physiological symptoms such as palpitations and tremors, personal and professional losses, and behavioral disorders that affect daily life. Disruptions may present in routine tasks such as meeting people, leaving the house, traveling, following the daily news, or going to work because of the fear of contracting the virus (7). Washing hands constantly, controlling vital organs, and self-medication are the results of fear and anxiety. Therefore, chronophobia may affect all daily living activities (8). The unending uncertainties (9), unforeseen reality (10), acquiring new practices and avoidance behavior (10), statements from international organizations (11), failure of powerhouses and lack of faith in health care facilities, leaders and famous celebrities contracting COVID-19 (12) and the relentless iodemia taking the shape of an infidelic (13) were accounted for as risk factors for coronaphobia. Mertens et al. (14) emphasized that chronophobia developed during the COVID-19 process was associated with increased social media exposure, fear of losing loved ones, and anxiety about their own life.

Patients with rheumatic diseases have a higher risk of infection than the general population because of their diseases and iatrogenic effects of immunosuppressive drugs (15). The mortality odds associated with COVID-19 in patients with rheumatic diseases was found 10.5%, which is higher than that in the general population in many countries. In addition, high disease activity, older age, male gender, comorbidities, and the use of immunosuppressive drugs, rituximab, and sulfasalazine were shown to be associated with death in patients with rheumatic diseases as well as in the general population (16). The rapid and uncontrolled spread of the COVID-19 pandemic outbreak may cause patients with rheumatic diseases to be more concerned. Psychosocial and physical changes were reported in a pandemic outbreak due to quarantine (17). Patients with rheumatic diseases may exhibit more phobic behavior against the coronavirus, considering that the depression and anxiety of these patients are higher than those of the general population, even under normal conditions (18). It was found that patients with fibromyalgia syndrome (FMS) had higher chronophobia levels than healthy controls (19). Toprak Celenay et al. (20) concluded that coronaphobia was higher in individuals who stayed at home except for compulsory situations for three months than in those who continued to work during the pandemic. The possible association of chronophobia with psychosocial factors will negatively affect the progression of the disease and complicate the treatment process. Therefore, determining the presence of chronophobia and related factors in these patients will guide health professionals working in clinics. To the best of our knowledge, no study has investigated the fear of coronavirus and its association with anxiety and depression in patients with inflammatory rheumatic diseases. The study investigated the coronaphobia level in patients with inflammatory and non-inflammatory rheumatic diseases. The secondary aim of the study was to investigate the relationship between chronophobia and the psychological status of the patients.

MATERIAL AND METHODS

This study was approved by the Fırat University Clinical Research Ethics Committee (number: 2020/15-23, date: 05.11.2020). Informed consent forms were obtained from the patients.

A total of 174 patients with rheumatic diseases were included in this study. Patients who were aged between 18 and 65 years, followed up in the Fırat University Rheumatology Department, and were literate were included in the study. Patients who were previously diagnosed with COVID-19 and had a pregnancy were excluded from the study. Patients who applied to the Fırat University Rheumatology Department outpatient clinic for 4 months between March 2021 and June 2021 and met the inclusion criteria were included in the study. Evaluations were done on the phone for patients who had routine control appointments but could not come to the hospital because of pandemic or any other reason.

Demographics were recorded, including age, gender, weight, length, education, marital status, occupation, and presence of other chronic diseases. All patients were asked to complete the COVID-19 Phobia Scale (C19P-S) to evaluate chronophobia and the Hospital Anxiety and Depression Scale (HADS) to evaluate anxiety and depression.w

Coronaphobia was evaluated using the C19P-S developed by Arpaci et al. (21) (Appendix 1). It consists of 20 items and four subscales including psychological, psychosomatic, economic, and social. Each item is scored with a 5-point Likert scale, where 1 means “strongly disagree” and 5 means “strongly agree”. The minimal score is 20 points and the maximal score is 100 points, where a higher score indicates a higher level of chronophobia (21).

The HADS, developed by Zigmond and Snaith (22), was used to assess anxiety and depression. It is a self-reported questionnaire consisting of 14 items that half of which evaluate depression and the other evaluate anxiety. All items are rated on a 4-point scale from 0 to 3. High scores indicate severe anxiety and depression levels.

Statistical Analysis

Statistical analysis was performed using IBM SPSS 21.0. Categorical measurements were expressed as numbers and percentages, and numeric measurements were presented as mean ± standard deviation. One-way ANOVA was used to calculate differences between means. The Pearson correlation test was used for correlation analysis. The chi-square test was used to compare categorical variables. A p-value of 0.05 was considered statistically significant.

RESULTS

This study was completed in 171 patients with rheumatic diseases. Three patients were excluded from the study due to not fulfilling the questionnaires. Twenty-three of the patients were diagnosed with FMS, 91 of them were diagnosed with connective tissue diseases (CTD) (66 of them were rheumatoid arthritis, 11 of them were systemic lupus erythematosus, 7 of them were Sjögren's syndrome and 7 of them were scleroderma) and 57 of them were diagnosed with spondyloarthropathies (SpA) (48 of them were ankylosing spondylitis and 9 of them were psoriatic arthritis).

Demographic measurements of the groups are summarized in Tables 1 and 2. Significant differences were found in all subscales of C19P-S among FMS and inflammatory rheumatic diseases (CTD and SpA) ($p<0.05$). In addition, a significant difference was found in anxiety between FMS and inflammatory rheumatic diseases (SpA and CTD) ($p<0.05$). In addition, significant differences were found in depression among SpA, CTD and FMS ($p<0.05$). However, no significant differences were found in the C19P-S and HADS anxiety subscale between CTD and SpA ($p>0.05$) (Table 2).

Significant correlations were found among all subscales of C19P-S in all groups ($p<0.05$). In addition, significant correlations were found between anxiety and psychosomatic and social subscales of C19P-S in patients with CTD and between anxiety and psychological, psychosomatic, and social subscales of C19P-S in patients SpA ($p<0.05$). In addition, there was a significant correlation between depression and psychosomatic and social subscales of C19P-S in patients with CTD and between depression and psychosomatic subscale of C19P-S in patients with SpA ($p<0.05$). No significant correlation was found between C19P-S and anxiety and depression in FMS patients ($p>0.05$) (Table 3).

DISCUSSION

This study is the first to investigate coronaphobia levels in inflammatory rheumatic diseases. Based on the results of the study, patients with CTD and SpA had high levels of chronophobia and low levels of anxiety and depression according to FMS patients. There were no significant differences between CTD

Table 1. Demographics and characteristic features for patients with fibromyalgia, connective tissue disorder and SpA

Characteristic or measurement		FMS group (n=23) n (%)	CTD group (n=91) n (%)	SpA group (n=57) n (%)	Chi-square	p
Gender	Male	2 (8.7)	20 (22)	23 (40.4)	10.356	**0.006**
	Female	21 (91.3)	71 (78)	34 (59.6)		
Smoking	Yes	9 (39.1)	26 (28.6)	21 (36.8)	2.034	0.730
	No	14 (60.9)	65 (71.4)	36 (63.2)		
Education level	Primary school	12 (52.2)	57 (62.6)	30 (52.6)	4.501	0.609
	High school	6 (26.1)	18 (19.8)	16 (28.1)		
	University	5 (21.7)	16 (17.6)	11 (19.3)		
Occupation	Yes	5 (21.7)	30 (33)	23 (40.4)	2.611	0.271
	No	18 (78.3)	61 (67)	34 (59.6)		
Occupation at pandemic	Yes	1 (4.3)	17 (18.7)	17 (29.8)	6.915	**0.032**
	No	22 (95.7)	74 (81.3)	40 (70.2)		
Accompanied other chronic diseases	Yes	7 (30.4)	25 (27.5)	9 (15.8)	3.232	0.199
	No	16 (69.6)	66 (72.5)	48 (84.2)		

FMS: Fibromyalgia syndrome, CTD: Connective tissue disorder, SpA: Spondyloarthropathies

Table 2. Characteristic features and measurements of patients with fibromyalgia, connective tissue disorder and SpA

Characteristic or measurement	FMS group (n=23) mean ± SD	CTD group (n=91) mean ± SD	SpA group (n=57) mean ± SD	p
Age (years)	45.04±7.89	44.93±11.71	41.67±12.13	0.210
BMI (kg/m^2)	26.87±4.99	26.57±4.27	26.45±4.56	**0.932**
Disease duration	4.49±5.54^A	9.08±8.15^B	8.59±5.47^B	**0.024**
Psychological subscale (C19P-S)	11.00±5.33^A	17.96±6.47^B	17.23±6.81^B	**0.000**
Pscyhosomatic subscale (C19P-S)	6.30±2.18^A	9.08±3.56^B	9.46±4.56^B	**0.003**
Economic subscale (C19P-S)	4.65±1.34^A	7.04±3.08^B	7.49±3.38^B	**0.001**
Social subscale (C19P-S)	9.30±5.16^A	13.96±5.12^B	13.19±5.68^B	**0.001**
Anxiety (HADS)	11.13±5.67^A	8.96±4.79^B	7.88±4.80^B	**0.029**
Depression (HADS)	9.39±4.73^A	8.42±4.62^A	6.89±4.22^B	**0.043**

^{A,B}Different letters indicate a statistically significant difference ($p<0.05$)
FMS: Fibromyalgia syndrome, CTD: Connective tissue disorder, SpA: Spondyloarthropathies, BMI: Body mass index, C19P-S: COVID-19 Phobia Scale, HADS: Hospital Anxiety and Depression Scale, SD: Standard deviation

and SpA patients in chronophobia and anxiety levels. In addition, significant correlations were found between psychological evaluations and chronophobia in patients with inflammatory rheumatic diseases.

The COVID-19 pandemic outbreak engulfed the world rapidly. Unforeseen reality and acquiring new practices and avoidance behavior cause anxiety and fear in the general population (14). Sixty-six percent of the public in the United States of America reported that coronavirus was a serious danger, and 56% of those were seriously worried about the spread of coronavirus (23). It was reported that odds of severe anxiety was 0.9%, moderate level was 2.7%, and mild level was 21.3% in a study including 7143 university students in China (24). Post-traumatic stress symptoms were found as 37%, anxiety level was found as 20.8%, depression was found as 17.3%, sleep disturbances were concluded as 37%, and perceived stress level was found as 21.8% in 18.147 people from Italy in a study investigating psychosocial health during pandemic and quarantine (25).

Considerable attention to hygiene, obligation to stay at home, curfew, and news of death due to the pandemic caused an increase in anxiety and depression in the general population. Fear developed with a pandemic outbreak may also negatively affect relationships with other people. In addition, psychosomatic and economic problems were brought along due to fear and anxiety. Therefore, we used the Turkish version of the C19P-S questionnaire, in which all these problems were evaluated (26). The C19P-S was demonstrated to be one of the few questionnaires to evaluate in detail the mental health associated with COVID-19 in a systematic review (27). The C19P-S questionnaire was tested to evaluate chronophobia in the general population and FMS patients (19,20,28).

The results of our study demonstrated that all subscales of chronophobia, including psychological, somatic, economic, and social, were higher in inflammatory rheumatic diseases than in non-inflammatory rheumatic diseases. Tzur Bitan et al. (29) concluded that patients with chronic diseases had higher levels of chronophobia than those without. It also determined that the presence of chronic disease was associated with the risk of severity and death during the COVID-19 process (30,31). High chronophobia levels in rheumatic diseases is an expected result because rheumatic diseases are chronic. Patients with rheumatic diseases should be more careful in terms of disease activity, comorbidities, and the risk of infection due to immunosuppressive treatment according to the general population (15). The death rate originating from COVID-19 was found to be higher in inflammatory rheumatic patients than in the general population (16). High or moderate dosage of glucocorticoid in chronic usage was found to cause hospitalization of severe COVID-19 (32). In addition, it was observed that viral diseases can cause disease activity in inflammatory rheumatic diseases that are in remission (33). Although FMS is also a chronic rheumatic disease, our results showed that inflammatory rheumatic diseases had higher chronophobia levels. The fact that FMS is not an inflammatory rheumatic disease and not used immunosupressive treatment may be the reason for the result. In addition, disease duration was higher in patients with inflammatory rheumatic diseases than in patients with non-inflammatory rheumatic diseases in this study. These factors may lead to increased fear in inflammatory rheumatic diseases compared with non-inflammatory diseases. Higher coronaphobia levels were found in FMS patients compared with

Table 3. Correlations between coronaphobia and psychological measurements

			Psychological	Pscyhosomatic	Social	Economic	HADS (anxiety)	HADS (depression)
FMS	Psychological	r	1	0.675**	0.812**	0.504*	0.345	0.330
		p	-	0.000	0.000	0.014	0.107	0.124
	Pscyhosomatic	r	0.675**	1	0.701**	0.864**	0.085	0.160
		p	0.000	-	0.000	0.000	0.701	0.467
	Social	r	0.812**	0.701**	1	0.576**	0.299	0.267
		p	0.000	0.000	-	0.004	0.165	0.219
	Economic	r	0.504*	0.864**	0.576**	1	0.126	0.080
		p	0.014	0.000	0.004	-	0.566	0.716
	HADS (anxiety)	r	0.345	0.085	0.299	0.126	1	0.632**
		p	0.107	0.701	0.165	0.566	-	0.001
	HADS (depression)	r	0.330	0.160	0.267	0.080	0.632**	1
		p	0.124	0.467	0.219	0.716	0.001	-
CTD	Psychological	r	1	0.461**	0.802**	0.346**	0.123	0.108
		p	-	0.000	0.000	0.001	0.246	0.308
	Pscyhosomatic	r	0.461**	1	0.473**	0.705**	0.295**	0.298**
		p	0.000	-	0.000	0.000	0.005	0.004
	Social	r	0.802**	0.473**	1	0.262*	0.238*	0.238*
		p	0.000	0.000	-	0.012	0.023	0.023
	Economic	r	0.346**	0.705**	0.262*	1	0.124	0.054
		p	0.001	0.000	0.012	-	0.242	0.611
	HADS (anxiety)	r	0.123	0.295**	0.238*	0.124	1	0.653**
		p	0.246	0.005	0.023	0.242	-	0.000
	HADS (depression)	r	0.108	0.298**	0.238*	0.054	0.653**	1
		p	0.308	0.004	0.023	0.611	0.000	-
SpA	Psychological	r	1	0.628**	0.812**	0.492**	0.378**	0.190
		p	-	0.000	0.000	0.000	0.004	0.158
	Pscyhosomatic	r	0.628**	1	0.674**	0.568**	0.380**	0.289*
		p	0.000	-	0.000	0.000	0.004	0.029
	Social	r	0.812**	0.674**	1	0.460**	0.458**	0.225
		p	0.000	0.000	-	0.000	0.000	0.092
	Economic	r	0.492**	0.568**	0.460**	1	0.211	0.119
		p	0.000	0.000	0.000	-	0.114	0.380
	HADS (anxiety)	r	0.378**	0.380**	0.458**	0.211	1	0.636**
		p	0.004	0.004	0.000	0.114	-	0.000
	HADS (depression)	r	0.190	0.289*	0.225	0.119	0.636**	1
		p	0.158	0.029	0.092	0.380	0.000	-

*p<0.05, **p<0.01
FMS: Fibromyalgia syndrome, CTD: Connective tissue disorder, SpA: Spondyloarthropathies, HADS: Hospital Anxiety and Depression Scale

healthy controls. The authors showed psychosocial disturbances observed in FMS as a reason for the result (19). Studies concluded high chronophobia levels in the general population in Turkey. Toprak Celenay et al. (20) concluded that higher chronophobia levels were observed in people who stayed home compared with people who continued to work. Psychological problems due to staying home might lead to high levels of chronophobia. In addition, Karaaslan et al. (28) found an association between high chronophobia levels and female gender, being married, having chronic diseases, staying at home, and sleep disturbances.

Ozamiz-Etxebarria et al. (34) demonstrated that individuals with chronic diseases had more emotional disturbances such as stress, anxiety, and depression. anxiety and depression are commonly observed in rheumatic diseases (35). Patients with FMS had higher levels of anxiety and depression than those with inflammatory rheumatic diseases in this study. Although patients with FMS had higher levels of psychological parameters, they had lower levels of coronaphobia. In addition, there was a correlation between psychosomatic and social subscales of C19P-S and psychological parameters, whereas no significant correlation was found between these parameters in patients with FMS. psychological disturbances are commonly seen in FMS patients (36) which is parallel with our study. However, the fact that psychological disturbances were not correlated with chronophobia in FMS patients may be due to low disease duration or because anxiety and depression might be affected disease-related factors more than COVID-19. Considering these results, depression and anxiety were found to be effective on chronophobia in inflammatory rheumatic diseases. Studies have demonstrated that chronophobia is associated with psychological disturbances such as hopelessness, suicide attempt, and coping problems (7).

Study Limitations

This study has some limitations. The low number of patients with non-inflammatory rheumatic disease and not including healthy controls are limitations of the study. In addition, not evaluating disease activity may be a limitation. However, obtaining significant difference despite the low number of patients with FMS is remarkable.

CONCLUSION

This study concluded that higher chronophobia levels were determined in patients with inflammatory rheumatic diseases than in those with non-inflammatory rheumatic diseases, although patients with inflammatory rheumatic diseases had lower levels of psychological disturbances. In addition, a positive correlation was found between chronophobia and psychological parameters. It should be considered that external factors such as COVID-19 may be effective in the psychology of these patients. Coronaphobia may be improved by psychological interventions in patients with rheumatic diseases. It is thought that this study will contribute to the literature. Further studies should include healthy controls and factors affecting chronophobia in patients with inflammatory rheumatic diseases.

Ethics

Ethics Committee Approval: This study was approved by the Fırat University Clinical Research Ethics Committee (number: 2020/15-23, date: 05.11.2020).

Informed Consent: Informed consent forms were 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., R.P.S., Analysis or Interpretation: R.P.S., Y.G., Literature Search: S.B.Y., Writing: S.B.Y.

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Appendix 1. COVID-19 Phobia Scale (C19P-S)
Below is a self-report questionnaire that is intended to measure individuals' different reactions during COVID-19 pandemic. Please read each item carefully and select the answer that best describe how you feel. Possible answers range from 1 to 5 (1 ¼ strongly disagree; 2 ¼ disagree; 3 ¼ agree; 4 ¼ generally agree; 5 ¼ strongly agree). Please answer all the questions honestly.
1. The fear of coming down with coronavirus makes me very anxious.
2. I experience stomach-aches out of the fear of coronavirus.
3. After the coronavirus pandemic, I feel extremely anxious when I see people coughing.
4. The possibility of food supply shortage due to the coronavirus pandemic causes me anxiety.
5. I am extremely afraid that someone in my family might become infected by the coronavirus.
6. I experience chest pain out of the fear of coronavirus.
7. After the coronavirus pandemic, I actively avoid people I see sneezing.
8. The possibility of shortages in cleaning supplies due to the coronavirus pandemic causes me anxiety.
9. News about coronavirus-related deaths causes me great anxiety.
10. I experience tremors due to the fear of coronavirus.
11. Following the coronavirus pandemic, I have noticed that I spend extensive periods of time washing my hands.
12. I stock food with the fear of coronavirus.
13. Uncertainties surrounding coronavirus cause me enormous anxiety.
14. I experience sleep problems out of the fear of coronavirus.
15. The fear of coming down with coronavirus seriously impedes my social relationships.
16. After the coronavirus pandemic, I do not feel relaxed unless I constantly check on my supplies at home.
17. The pace that coronavirus has spread causes me great panic.
18. Coronavirus makes me so tense that I find myself unable to do the thing I previously had no problem doing.
19. I am unable to curb my anxiety of catching coronavirus from others.
20. I argue passionately (or want to argue) with people I consider to be behaving irresponsibly in the face of coronavirus.
COVID-19: Coronavirus disease-2019

CASE REPORT AND LITERATURE REVIEW

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BEHÇET'S DISEASE WITH BILATERAL JUGULAR VEIN THROMBOSIS WHO RESPONDED TO MYCOPHENOLATE MOFETIL THERAPY

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Abstract

Behçet's disease (BD) is a systemic vasculitis that may progress with recurrent oral and genital aphthous ulceration and uveitis as well as locomotor, vascular, gastrointestinal, pulmonary, and neurological involvement. Although the rate of vascular involvement in BD varies from country to country, it varies between 1-38% in series. Venous involvement is more common than arterial involvement, and the most common form of involvement is lower extremity deep vein thrombosis; thrombosis may also cause occlusion in the superior and inferior vena cava. In this article, a case of BD presenting with bilateral jugular vein thrombosis is discussed.

Keywords: Behçet's disease, thrombosis, mycophenolate mofetil, jugular vein

INTRODUCTION

Behçet's disease (BD) is a chronic, multisystemic autoimmune disease with exacerbation and remission, which was first reported in 1937 by Prof. Dr. By Hulusi Behçet and defined as "triple symptom complex" consisting of recurrent oral, genital aphthous ulceration and hypopionic uveitis (1,2). In other studies, it has been shown that this triple symptom complex is accompanied by articular, pulmonary, gastrointestinal, urogenital, cardiac, vascular, and neurological symptoms (3). Although BD can be seen at any age, the average age of onset is within the third decade and is more severe and mortal, especially in young males (4). The vascular involvement rate in BD has been reported as 1-38% in some studies (5). Venous involvement is more common than arterial involvement, while the most common form of involvement is lower extremity deep vent thrombosis; thrombosis may cause occlusion in the superior-inferior vena cava and dural sinuses (6). Here, we present the case of a patient who was admitted to our emergency department with headache and neck swelling and was diagnosed with bilateral jugular vein thrombosis and BD.

CASE REPORT

A 23-year-old male patient was admitted to the emergency department with a sudden headache and bilateral swelling of the neck. The patient, who was found to have bilateral jugular vein thrombosis on cervical Doppler ultrasonography, was admitted to our rheumatology service for further examination after being consulted for cardiovascular surgery and after initiating low-molecular-weight heparin (LMWH) treatment.

The 23-year-old single male patient had no previous comorbidities. It was learned that the patient had oral aphthae 2-3 times a month, ulcers that healed by leaving scars in the genital area, and widespread acneiform lesions in the body. On admission, the patient's body temperature was 38.1 °C, blood pressure arterial 123/82 mmHg, and pulse 88. On skin examination, there were acneiform pustular lesions on the face and back

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and swelling in the bilateral anterior neck triangle. There were three active oral aphids on opharyngeal examination. Two healed genital ulcer scars were detected on the scrotum. There were no pathological findings in the respiratory system, cardiac system examination, gastrointestinal system, or musculoskeletal system examination. Detailed laboratory parameters are given in Table 1, and the C-reactive protein value at the patient's admission was found to be high at 234. There was no evidence of infection in the examination of the patient, and no growth was observed in the urine and blood cultures of the patient. The serology of human immunodeficiency virus and hepatitis was negative. Lupus anticoagulants, antiphospholipid-anticardiolipin antibodies, antithrombin III, protein C, and protein S levels were normal. While the anti-nuclear antibody test was positive at 1/100-320 titer (spotted), the extractable nuclear antigen panel was negative. The pathergy test was found to be negative. Bilateral jugular venous thrombosis was detected by cervical Doppler ultrasonography, and no other pathology was observed by other venous and arterial system imaging. No signs of active or sequelae uveitis were observed on eye examination. The patient was accepted as having BD according to the clinical and biochemical findings and the international diagnostic criteria for BD. LMWH treatment was discontinued, and acetylsalicylic acid (100 mg/day) and methylprednisolone (1 mg/kg) treatment were initiated. Cyclophosphamide treatment was recommended to the patient for treating vasculitis as a steroid-sparing agent, but the patient refused the treatment because of possible side effects. Thereupon, azathioprine treatment was initiated for the patient. After azathioprine treatment, there was a 3-fold increase in liver function test's. Azathioprine treatment was discontinued because of hepatotoxicity, and mycophenolate mofetil treatment was started. Under methylprednisolone and mycophenolate mofetil treatment, both clinical and biochemical responses were obtained. Recanalization of the jugular veins was observed by cervical Doppler ultrasonography, and the patient was discharged from the polyclinic.

Table 1. Laboratory findings

Parameters	Results
Complete blood count	
White blood cell, $\times 10^3$/mL	16.1
Neutrophil, %	94.1
Lymphocyte, %	2.2
Monocyte, %	3.2
Eosinophil, %	0.3
Hemoglobin, g/dL	11
Hematocrit, %	33.4
MCV, fL	82.7
MCHC, g/dL	33
Platelets, $\times 10^3$/mL	323
Blood biochemistry	
Glucose, mg/dL	143
Creatinine, mg/dL	0.77
Aspartate aminotransferase, U/L	13
Alanine aminotransferase, U/L	9
Alkaline phosphatase, U/L	99
Total protein, U/L	6.93
Albumin, g/L	3.6
LDH, U/L	135
Erythrocyte sedimentation rate, mm/hour	72
C-reactive protein, mg/L	234.6
Procalcitonin, ng/mL	0.34
Rheumatoid factor, IU/L	Negative
Anti-nuclear antibody	1/100-320 (spotted) positive
ENA panel	Negative
Thrombosis panel	No mutations
Spot urine protein	0.14
Coagulation	
INR	0.89
APTT, s	38
PT, s	11
Molecular nasopharyngeal swab (COVID-19 PCR)	Negative

ENA: Extractable nuclear antigen, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, INR: International normalized ratio, APTT: Activated partial thromboplastin time, PT: Prothrombin time, LDH: Lactate dehydrogenase

DISCUSSION

BD is a systemic vasculitis that can affect arteries and veins of all sizes. Perivascular infiltration of neutrophils and monocytes and endothelial dysfunction caused by immune-mediated vasculitis increase the risk of thrombosis (7). Venous involvement in BD can be seen as superficial and deep vein thrombosis. Recurrent thrombophlebitis is most commonly observed in lower extremity veins. Thrombosis may also be seen in the superior-inferior and dural sinuses of the vena cava, which have a worse prognosis (2,8). Our case is a case of BD that progressed with bilateral jugular venous thrombosis and responded to mycophenolate mofetil treatment.

Early initiation of steroid and immunosuppressive therapy is essential for prognosis in vascular involvement of BD. Glucocorticoids and immunosuppressives, such as cyclophosphamide, azathioprine, or cyclosporine, are recommended as the first choice for treating Behçet's disease venous thrombosis. It has been reported that monoclonal anti-tumor necrosis factor treatments can also be used in resistant cases (9). In different BD case reports, it has been reported that clinical response was obtained from mycophenolate mofetil treatment for treating cerebralsinus thrombosis (10,11). We also preferred methylprednisolone and azathioprine as the first choice for treating our patient, and clinical and biochemical responses were obtained in the patient, who was continued with mycophenolate mofetil treatment because of the development of hepatotoxicity under azathioprine treatment.

Anticoagulation is controversial for treating BD associated with venous thrombosis. Due to the possibility of aneurysm seen in BD, anticoagulant therapy is generally not recommended in BD, as thrombosis is firmly attached to the vascular wall and the possibility of embolism is low. However, in cases of life-threatening venous involvement such as Budd-Chiari and treatment-resistant cases, anticoagulant therapy can be administered after pulmonary artery aneurysms are excluded (12). In this study, anticoagulant treatment was administered during the first week during which the examinations continued. Anticoagulant treatment was discontinued after the diagnosis of BD was made and glucocorticoid and immunosuppressive therapy was initiated.

CONCLUSION

BD should also be considered in the differential diagnosis, especially when a young male patient comes across with venous thrombosis. The patient should be evaluated from this perspective.

Ethics

Informed Consent: Information of informed consent from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.D.Y., G.Ş., Design: T.D.Y., G.Ş., Literature Search: T.D.Y., G.Ş., Writing: T.D.Y., G.Ş.

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A DILEMMA IS WIDESPREAD BETWEEN RHEUMATOLOGY AND INFECTIOUS DISEASES, AS EVIDENCED BY A CASE

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multisystem organ involvement and various symptoms. Many diseases present with laboratory and clinical features similar to those of SLE, for example, malignancies and infections that are termed "lupus mimickers". This article presents a case of visceral leishmaniasis in which clinical characteristics and laboratory profiles imitated SLE in our hospital.

Keywords: Systemic lupus erythematosus, visceral leishmaniasis, splenomegaly

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease with a wide variety of clinical manifestations that predominantly affects women (1). Considering the variable manifestations of SLE, the differential diagnosis is broad. In this article, we share our case of visceral leishmaniasis (VL), which we considered a preliminary diagnosis of SLE.

CASE REPORT

A 23-year-old female patient with no history of disease was examined for diffuse myalgia, arthralgia, and fever. She was referred to our clinic because of anti-nuclear antibody (ANA) positivity, pancytopenia, high acute phase reactant, and splenomegaly (Table 1). In the examination of the patient, it was determined that splenomegaly, which was 170 mm, was detected incidentally; her complaints had increased gradually for three months; and she lost nearly ten percent of her body weight in this process. It was learned that the patient had been evaluated in terms of hematological malignancies before but could not get any diagnosis. At the physical examination, her body temperature was 38.5 °C, her arterial blood pressure was 90/60 mm/Hg, and her heart rate was 110 beats/min. She had hepatosplenomegaly (19 cm hematometry and a palpable spleen 9 cm from the left costal border). She had no lymphadenopathy or skin lesions. The most frequent infectious diseases were eliminated, including leptospirosis, tuberculosis, human immunodeficiency virus, Epstein-Barr virus, and viral hepatitis B and C. Laboratory tests revealed pancytopenia, elevated levels of C-reactive protein, and sedimentation (Table 1). Abdominal tomography confirmed splenomegaly, with the spleen on its largest axis measuring 24.6 cm. Laboratory results showed ANA 1/320-1000 dilution with a speckled pattern, pancytopenia with lymphopenia, and polyclonal hypergammaglobulinemia (Table 1). The diagnostic hypothesis at that time was an autoimmune disease or hematological malignancy. No atypical cells were detected in the peripheral smear, and bone marrow aspiration and biopsy were performed. In the infectious examinations of the patient, leishmaniasis enzyme-linked immunosorbent assay: Positive

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Table 1. Laboratory findings

Tests	Results	Normal range
Hemoglobin, g/dL	6.9	12-16
Leukocytes/(10^3/uL)	1.1	4-10.3
Lymphocytes/(10^3/uL)	0.4	1-3.5
Platelets, (10^3/uL)	120	156-373
Aspartate aminotransferase, µ/L	28	0-35
Alanine aminotransferase, µ/L	17	0-50
Creatinine, mg/dL	0.62	0.6-1.1
Rheumatoid factor, IU/mL	10↓	-
C-reactive protein, mg/L	68	0.2-5
Sedimentation rate (mm/h)	25	-
Anti-nuclear antibody	1/320-1000 speckled	Negative <1/100< titer
Anti-dsDNA	Negative	1/10< titer
Hematuria	Negative	-
Urine protein	Negative	-
Complement C3, mg/dL	64	90-180
Complement C4, mg/dL	23	10-40
Protein electrophoresis	Hypergammaglobulinemia	-

(serum was studied at 1/100 dilution) and leishmaniasis indirect fluorescence antibody test: 1/256 positive were detected. A bone marrow biopsy was reported as having polytypic staining with more plasma cells close to each other with kappa and lambda in the appearance found in myelodysplastic syndrome (MDS) cases and thought to be reactive. After clinical information, sections were also evaluated for leishmania, but no specific findings were observed. In the patient's history, VL was diagnosed due to multiple mosquito contacts during her stay in Manisa, all other anamneses, physical examination, laboratory, and leishmaniasis serology positivity. From the time of diagnosis, treatment with intravenous liposomal amphotericin B on 3 mg/kg/day was initiated on days 0-5,14, and 21. The clinical and laboratory findings improved. The patient's splenomegaly decreased, and she was discharged with an improved general condition.

DISCUSSION

When diagnosing rheumatologic disease, it is always important to distinguish between mimicrs. This dilemma is very common in rheumatology and infectious diseases. There are reports in the literature that leishmaniasis can mimic or trigger an autoimmune disease such as SLE and rheumatoid arthritis (2). Because of the clinical heterogeneity of SLE and the lack of pathognomonic testing, it can usually be diagnosed after alternative diagnoses have been excluded (3). VL, or kala-azar, is a systemic disease that is potentially fatal to humans. Infection caused by a protozoan of the genus *Leishmania* causes death in 95% of cases if left untreated (4). Our country is reported as an endemic region for cutaneous leishmaniasis by the World Health Organization, but VL is sporadically seen in the Aegean region (4). Fever, myalgia, arthralgia, and pancytopenia are common in VL cases, and the diagnosis of SLE was investigated when clinically combined with the ANA positivity detected in our case. The mechanisms involved in the pathophysiology of autoantibody production are not yet fully understood (5). However, a negative anti-dsDNA test, normal levels of C3 and C4 complement proteins, and massive splenomegaly made the diagnosis of infection stronger. In areas endemic to VL, SLE diagnosis can be a clinical dilemma. At the same time, VL may present as an opportunistic disease in immunocompromised patients with SLE, and thus, this differential diagnosis should be considered (6). In addition, pancytopenia is remarkable in patients with VL. Clinicians usually encounter VL as an opportunistic infection in patients with cell-mediated immunosuppression or, because the clinical presentation is not specific, in the differential diagnosis of myeloproliferative diseases. Recent advances, for example, in manipulation of the PI3K/Akt/HIF1 axis, which may contribute to the MDS features of VL, have enhanced our understanding of the role of the liver, spleen, and bone marrow microenvironments in shaping host-parasite interactions and their defining effect

on clinical expression and infection outcome (7). In this study, early diagnosis of VL and initiation of treatment prevented misdiagnosis and inadequate treatment.

Ethics

Informed Consent: Information of informed consent from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.D.Y., E.E., G.Ş., Data Collection or Processing: T.D.Y., E.E., G.Ş., Literature Search: T.D.Y., E.E., G.Ş., Writing: T.D.Y., E.E., F.Ö.

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CASE REPORT AND LITERATURE REVIEW

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INTRAVENOUS IMMUNOGLOBULIN THERAPY IN A CASE OF INTERSTITIAL LUNG DISEASE ASSOCIATED WITH DERMATOMYOSITIS

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Abstract

Idiopathic inflammatory myopathy is a systematic autoimmune disease characterized by chronic muscle inflammation. Dermatomyositis (DM) is an idiopathic inflammatory myositis characterized by muscle pain, muscle weakness, and skin rash. It is important to screen patients with DM for an underlying malignancy. Interstitial lung disease is a major prognostic determinant that increases morbidity and mortality in these patients. Here, we present the successful treatment of a 51-year-old case of DM with interstitial lung involvement with intravenous immunoglobulin. The patient had a history of surgery due to a mass in the rectum and was admitted with complaints of weight loss, muscle weakness, skin rash, and shortness of breath at follow-up.

Keywords: Dermatomyositis, intravenous immunoglobulin, interstitial lung disease

INTRODUCTION

Idiopathic inflammatory myopathy (IIM) is a heterogeneous group of systematic autoimmune diseases characterized by chronic muscle inflammation. Dermatomyositis (DM) is an idiopathic inflammatory myositis characterized by muscle pain, muscle weakness, and rash. It is seen that it peaks between the ages of 45 and 60 in adults (1).

Patients with DM are more likely to have an underlying malignancy. In DM patients over 50 years of age, 30% develop cancer during their clinical course. DM is considered as a part of the paraneoplastic syndrome mediated by cancer-associated secretions and antibodies (2).

Interstitial lung disease (ILD) is a common condition (20-65% of patients) in patients with DM, similar to other connective tissue diseases. Some antibodies thought to be associated with ILD have been identified. ILD is a major prognostic determinant that causes an increase in morbidity and mortality. Severe pulmonary involvement was demonstrated in the presence of anti-MDA5 antibodies. It is a condition that should be screened for with the diagnosis of disease (3).

In this presentation, in a case referred to us for differential diagnosis with complaints of weight loss, muscle pain, weakness, skin rash, and shortness of breath, we wanted to underline the rare simultaneous DM and ILD after being followed up for a mass in the colon.

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CASE REPORT

A 51-year-old male patient was referred to our rheumatology clinic with complaints of weight loss, muscle pain, weakness in the upper and lower extremities, skin rash, and shortness of breath. The patient, who developed general muscle weakness such as inability to stand up about 1 month ago, had an erythematous rash on the upper arm and trunk in the last 10 days. The patient's history revealed that he had been operated on in an external center 2 years ago for a mass in the rectum, and the resected tissue pathology was compatible with squamous cell carcinoma. Tumor markers were found to be normal as a result of malignancy scans performed afterward, and no pathology was observed in the imaging of the patient.

In his physical examination, the manual muscle test revealed 3-/5 strength. In the upper extremity and 3+/5 in the hip flexors in the lower extremity. Deep tendon reflexes were normoactive, and sensory examination was normal. Dermatological examination revealed erythema on the extensor surfaces of the arms and erythematous maculopapular lesions on the anterior and posterior trunks. DM was considered in the foreground, and routine tests were performed. In the laboratory examination, acute phase reactants slightly increased as C-reactive protein was 14 mg/dL (normal range: 0-5 mg/dL), sedimentation was 31 mm/h (normal range: 0-20 mm/h), and aspartate aminotransferase (AST) was 59 U/L (0-40), and lactate dehydrogenase (LDH) was 619 U/L (135-225). Baseline creatine kinase (CK) levels were increased to 574 U/L (0-200). In the rheumatological examinations requested for differential diagnosis, anti-nuclear antibody (ANA) was stained in a 1:160 µmoL positive spotted pattern. In the ANA panel, anti-dsDNA, SS-A, SS-B, and anti-Jo-1 were normal. Rheumatoid factor, anti-cyclic citrulized peptide, and anti-neutrophil cytoplasmic antibodies (P-ANCA, C-ANCA) were negative.

In terms of internal organ involvement, chest X-rays, pulmonary function tests, high-resolution computed tomography, echocardiography, electrocardiography, abdominal ultrasonography, and tumor markers were requested. Electromyography of the patient revealed findings consistent with myogenous involvement. There were dense consolidated areas in the right side of the chest radiograph (Figure 1). While vital capacity was normal in the respiratory function test, the 6-min walk test distance was measured at 340 meters. Thorax tomography was performed, and the right lung upper lobe anterior segment and lower lobe superior segment were dominant; scattered ground glass densities showed nodulation in places; and a fine reticular density increase was detected (Figure 2). It was evaluated by bronchoscopy in terms of malignancy and infection, and no neolasic changes were observed because of the biopsy. Magnetic resonance imaging of bilateral lower extremity muscles showed patchy edematous areas in the quadriceps muscle (rectus femoris, vastus lateralis, and semitendinosus). Based on these clinical, laboratory, and imaging findings, we concluded that the patient had DM with prominent ILD involvement.

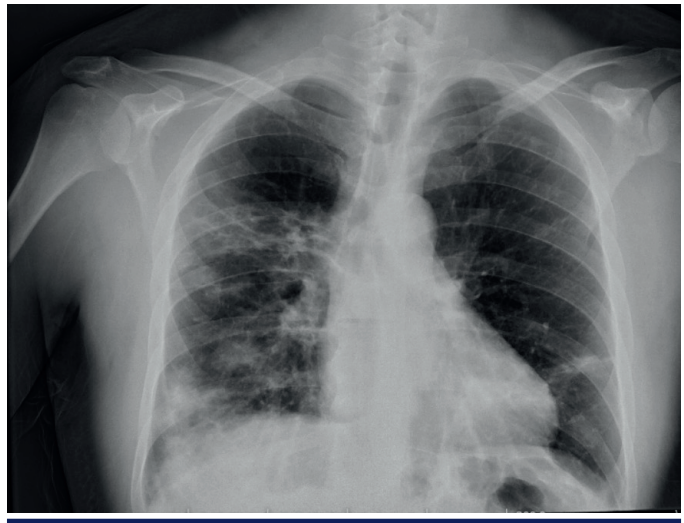

Figure 1. Dense consolidated areas in the right lung

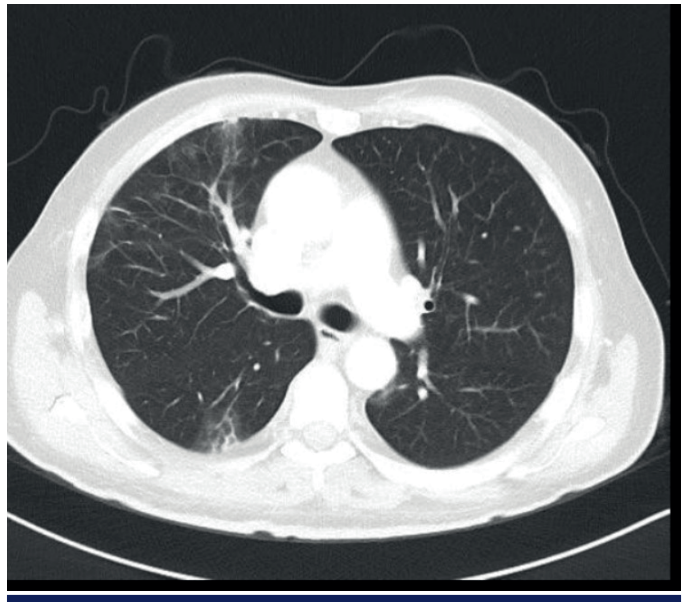

Figure 2. In the evaluation of the lung parenchyma areas, ground glass densities and fine reticular density increases are observed, which is more prominent in the lower lobes of both lungs

Systemic corticosteroid (1 mg/kg/day) treatment was initiated. On the 3rd day of treatment, intravenous immunoglobulin (IVIG) treatment (at 2 g/kg for 5 days) was administered for

lung involvement. On the 7th day of treatment, CK: 142 U/L and LDH: 219 U/L were in the normal range. Clinically, at the end of the 10th day, the patient had regression of skin lesions and increased muscle strength (3+/5, hip flexors 4/5). The steroid dose was gradually reduced. IVIG treatment was continued for 3 months, once a month. At the end of three months, no side effects related to IVIG treatment were observed. In the thorax tomography of the patient, regression was observed in the ground glass areas (Figure 3). The patient's skin lesions did not recur. The exercises for the patient whose muscle strength was 4/5were continued. After IVIG, maintenance treatment was continued with methotrexate (10 mg/week) and steroids (8 mg/day).

Written and verbal consent was obtained from the patient and his relatives.

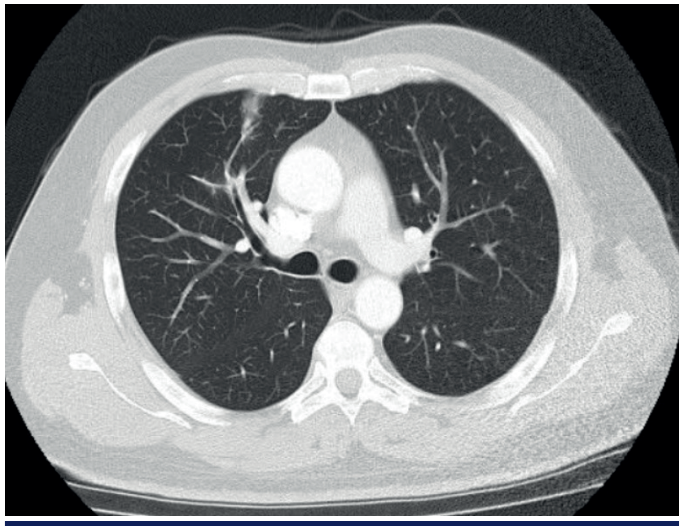

Figure 3. The findings observed in the upper lobe in the tomography taken after the treatment were evaluated as regressed

DISCUSSION

DM is an extremely rare IIM that often presents with progressive, symmetrical, proximal muscle weakness and characteristic cutaneous findings. Skin manifestations may also develop in the absence of muscle disease. It is characterized by pink-purple papules (gottron papules) on the interphalangeal and metacarpophalangeal joints and pink-purple erythema (heliotropic rash) with or without edema involving the periorbital skin (4).

The diagnosis of DM is made by combining characteristic cutaneous findings, muscle weakness, and laboratory evidence of myositis. However, a biopsy should be performed in the absence of clinical signs of muscle disease and in patients presenting with vague skin findings (5).

In this study, bilateral lower and upper extremity muscle weakness and rashes on the arms and trunk supported the clinical diagnosis of DM.

CK, LDH, aldolase, AST, and alanine aminotransferase are muscle enzymes that can be elevated in patients with inflammatory myopathy and other muscle disorders (6). Our patient had high initial CK and LDH levels, which contributed to the diagnosis in the laboratory.

The presence of an underlying malignancy in cases of DM requires age- and gender-appropriate screening, particularly in the first three years. The risk of malignancy increases in patients with severe skin involvement (especially shawl signs or skin necrosis) and high sedimentation. In addition to its association with malignancy in many organs, including the ovary, breasts, stomach, colorectum, lungs, and prostate, non-Hodgkin lymphomas can also be seen (7). Paraneoplastic DM has been reported, particularly in the elderly and men. DM may occur simultaneously with cancer, either before or after cancer (8). Our patient had a history of surgery due to a rectal tumor two years ago.

ILD is a feature of myositis, mostly in association with anti-Jo-1, but rapidly progressive ILD is associated with pulmonary failure and death, most commonly MDA5-related DM. In anti-MDA5-related DM, it is critical to identify patients who may benefit from close monitoring of their pulmonary status (9). Our patient also had symptomatic pulmonary involvement, and ANA was positive, whereas anti-Jo-1 and anti-MDA5 were negative.

Our patient also had symptomatic pulmonary involvement, and ANA was positive, whereas anti-Jo-1 and anti-MDA5 were negative. The cornerstone of initial therapy for DM is the use of glucocorticoids. If ILD is present, it is usually resistant to glucocorticoid monotherapy; therefore, combination therapy with glucocorticoids and immunosuppressants is recommended as the initial therapy. However, ILD associated with DM, including amyopathic DM, is considered an important condition because it often causes death despite intensive treatment with high-dose corticosteroids and immunosuppressive agents (10).

IVIG is a plasma product consisting mainly of monomeric IgG. In the last few decades, the indications for the use of IVIG have expanded to include the treatment of various autoimmune diseases. The standard dose of IVIG therapy is 2 g/kg in two to five daily doses, usually lasting 3-6 months (11). Although IVIG therapy appears to have rarely been used as first-line therapy in DM, it has been shown to be beneficial in glucocorticoid-

resistant conditions as initial therapy in selected patients with progressive muscle weakness or severe dysphagia at risk for aspiration. In these situations, IVIG may have a faster onset of action than glucocorticoids. IVIG has been shown to be effective in most DM patients with lung and esophageal involvement. In some patients, IVIG may reduce the dose of corticosteroid required for maintenance, which is the most effective steroid-sparing effect (12).

In a double-blind study in patients with resistant DM, IVIG combined with corticosteroids significantly improved muscle strength and decreased serum CK levels compared with placebo (13).

Other treatment options for DM include rituximab, a chimeric anti-CD20 monoclonal antibody targeting B cells. In a retrospective analysis of seven patients with ILD refractory to first-line therapy, RTX showed that clinical signs and pulmonary functions improved and uptake on CT regressed (14). However, greater clinical experience with this agent is required before firm conclusions can be drawn.

Azathioprine and methotrexate are both widely used for treating connective tissue disease because of their favorable safety profiles. No prospective studies of DM controlled using methotrexate have been conducted; however, in a few studies, it has been found that it can be used in maintenance therapy in cases where glucocorticoids fail initially (15). In this case, steroid use was gradually reduced after IVIG and methotrexate were added to the treatment, and the disease remained stable at follow-up.

CONCLUSION

IIM is a rare disorder of the muscles. In this case, we aimed to draw attention to the rare inflammatory myositis-associated interstitial lung involvement. If the diagnosis is made quickly and effective treatment is initiated, the results are satisfactory.

Ethics

Informed Consent: Written and verbal consent was obtained from the patient and his relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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IMAGE ARTICLE

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SACROILIITIS, PSORIASIS, OTOIMMUNE HEPATITIS AND LEUKOCYTOCLASTIC VASCULITIS IN FAMILIAL MEDITERRANEAN FEVER

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Keywords: Familial Mediterranean fever, vasculitis, psoriasis

Familial Mediterranean fever (FMF) is characterized by recurrent attacks of fever and serositis or erysipelas-like erythema. Most patients with FMF experience their first attack in early childhood (1).

A 27-year-old male patient, diagnosed with FMF, has been followed up with colchicine treatment for 15 years. Four years ago, sacroiliitis (Figure 1) was detected and adalımumab treatment was added. During follow-up, the patient had widespread papulosquamous rashes on the palms, soles and scalp and biopsy results were compatible with pustular psoriasis. Adalimumab treatment of the patient who was thought to have paradoxical psoriasis was stopped and secukinumab was switched. The liver biopsy of the patient with elevated transaminases was compatible with autoimmune hepatitis and azathioprine was added to the treatment. The patient presented with diffuse palpable purpura in the lower extremities and the biopsy result was compatible with leukocytoclastic vasculitis (Figures 2, 3). Immunofluorescence examination revealed no immune complex deposits (IgA, C3). The patient who could not tolerate anakinra added to the treatment was controlled with canakinumab.

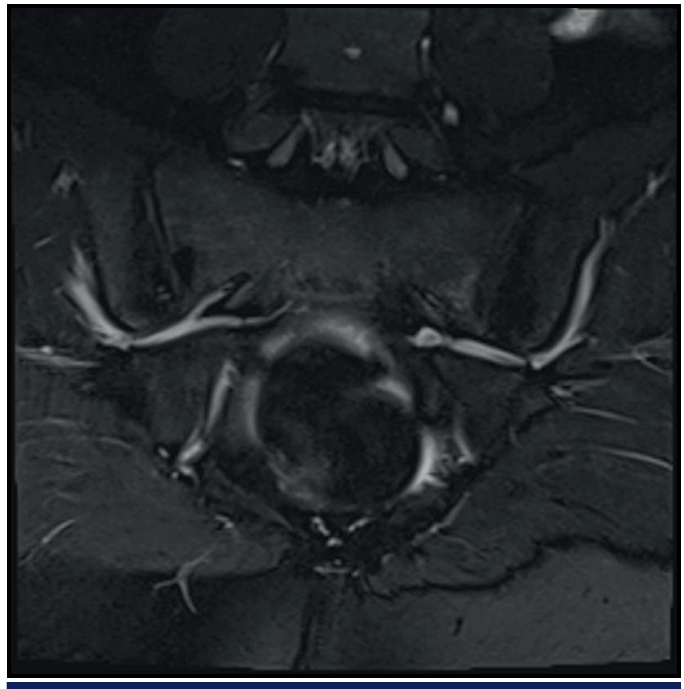

Figure 1. Osteitis on both joint surfaces on sacroiliac MR T2 image
MR: Magnetic resonance

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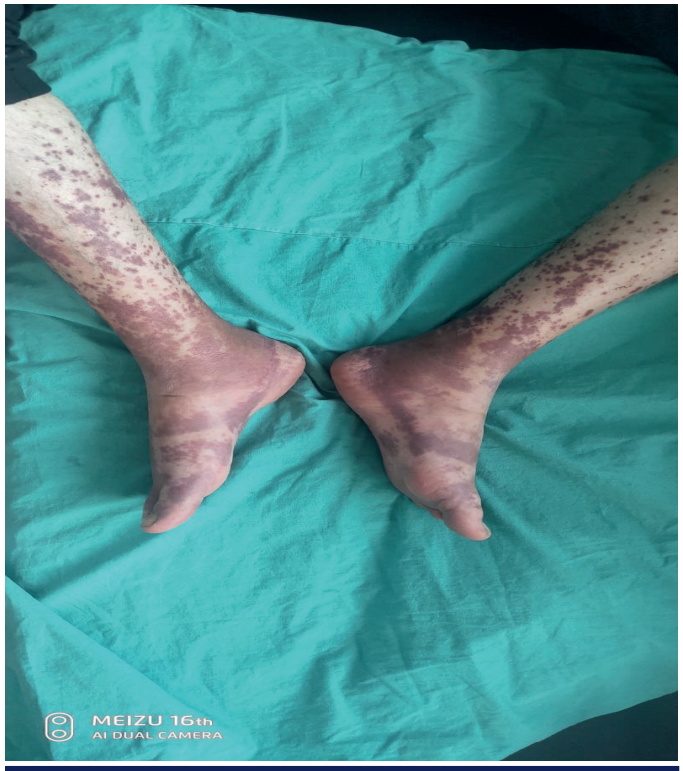

Figure 2. Palpable purpura in the lower limbs

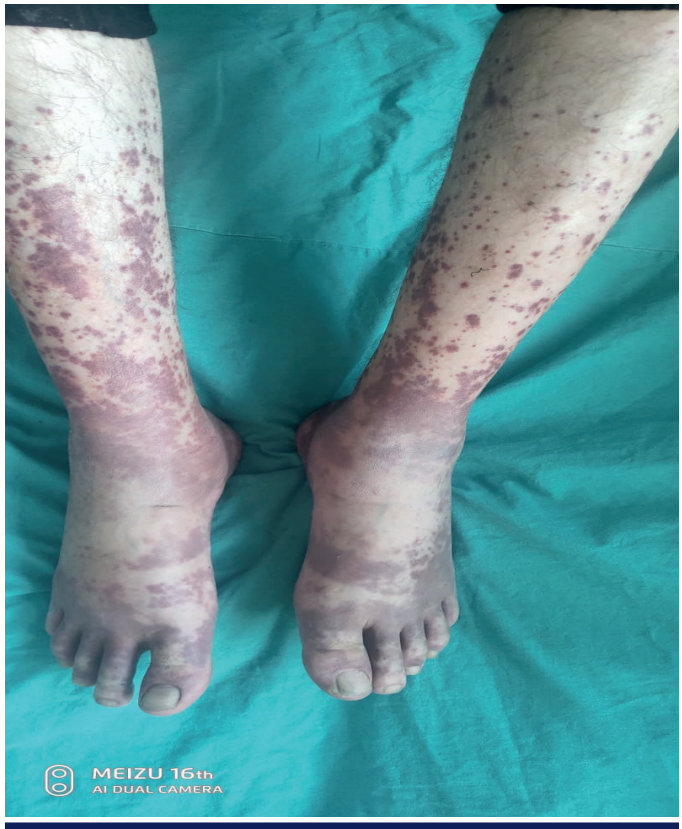

Figure 3. Palpable purpura in the lower limbs

Ethics

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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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