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RHEUMATOLOGY QUARTERLY

RQ
Rheumatology Quarterly

galenos yayınevi

December
2023

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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AIMS AND SCOPE

Advertisers are responsible for ensuring that their advertisements comply with applicable laws regarding deceptive and/or offensive content and ethical issues.

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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

INSTRUCTIONS TO AUTHORS

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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- ✓ **Lasting REMISSION over 5 years[7]**
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*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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▼ This medicinal product is subject to additional monitoring. This triangle will allow quick identification of new safety information. Healthcare professionals are encouraged to report suspected adverse reactions to TÜFAM (Turkish Pharmacovigilance Center).

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

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

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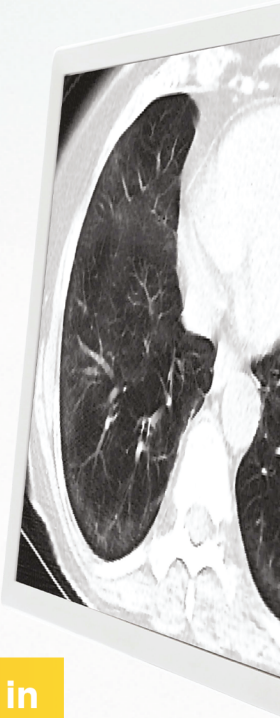

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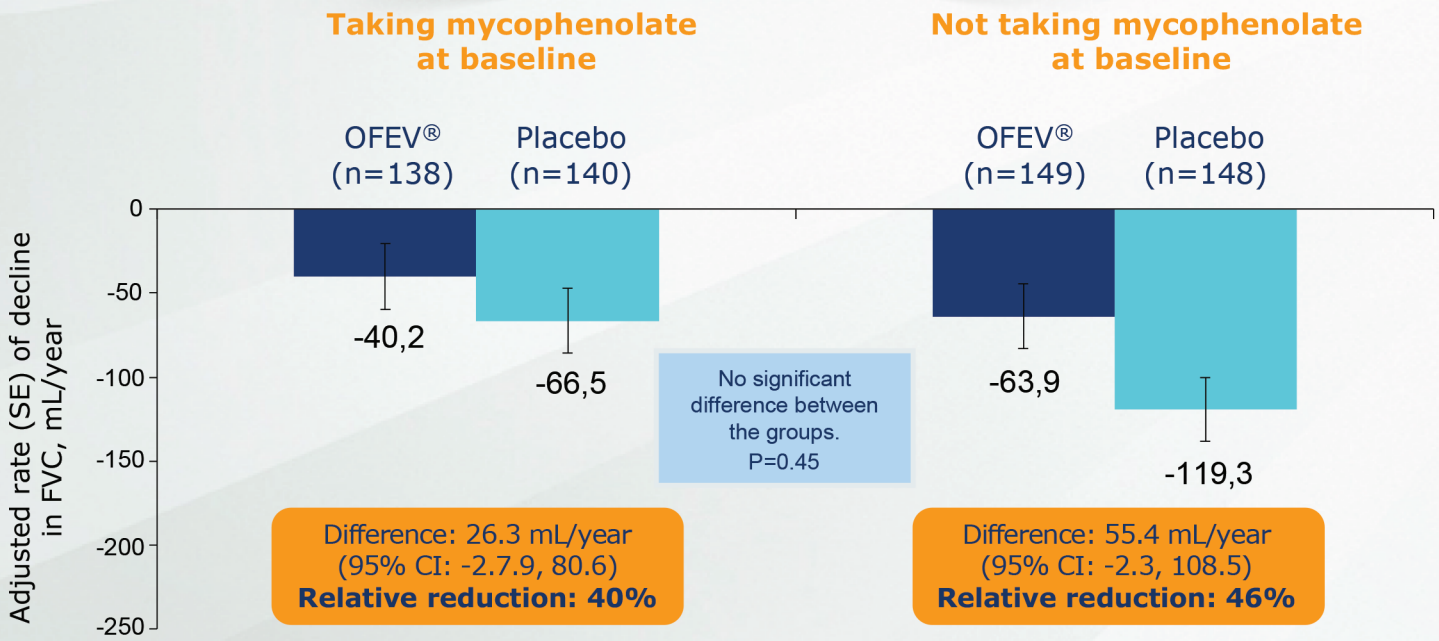

PC-TR-102515

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3. Distler O, et al. N Engl J Med. 2019;380:2518-2528. **4.** Richeldi L, et al; for the INPULSIS®Trial Investigators. N Engl J Med. 2014;370(22):2071-2082.

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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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1. Burmester GR et al. Adv Ther 2020 37, 364-380 2. Saurat JH et al, Br J Dermatol 2008.;158(3):558-66

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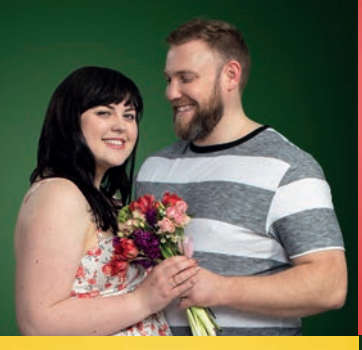
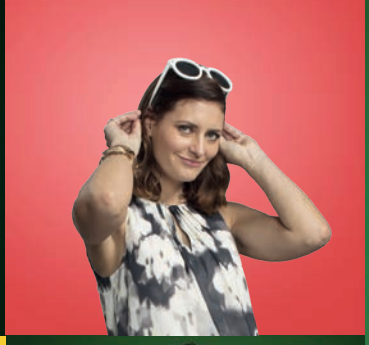

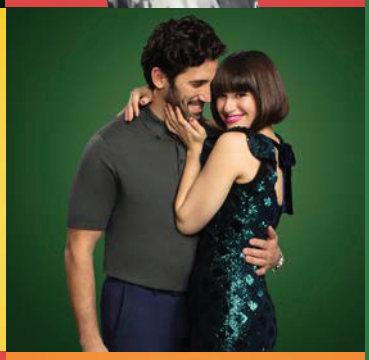
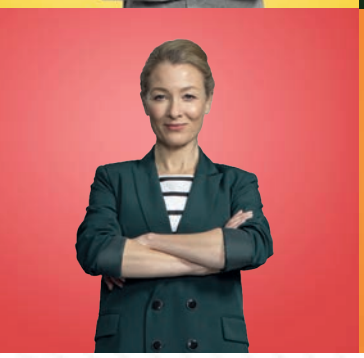
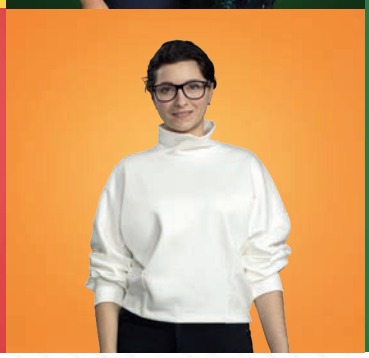

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patient-years of worldwide cumulative exposure across previously approved indications[2c]

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.

▼This medicine is subject to additional monitoring. The triangle will allow quick identification of new safety information. Healthcare professionals are required to report any suspected adverse reactions to TÜFAM. (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99).

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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- Low immunogenicity and a favourable tolerability profile[1-4]
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▼ 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: 0312218 35 99) and/or related pharmaceutical company officials.

*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]

References: 1. Matucci-Cerinic M, et al. RMD Open 2018;4:e000757 & Supplementary material. **2.** Jaworski J, et al. Arthritis Res Ther. 2019;21(1):130. **3.** Griffiths CEM, et al. Br J Dermatol. 2017; 176:928-38 & Supplementary data. **4.** Gerdes S, et al. J Eur Acad Dermatol Venerol. 2018;32:420-27. **5.** Colaci M, et al. Ann Rheum Dis. 2021;80:1135. **6.** Schmalzing M, et al. Ann Rheum Dis. 2021;80:540. **7.** Schmalzing M, et al. Presented at EULAR 2022 Virtual Congress. Abstract 1110. **8.** Paul C, et al. J Eur Acad Dermatol Venereol. 2015;29(6):1082-1090. **9.** Nash P, et al. Arthritis Res Ther. 2018;20(1):47. **10.** Schmalzing M, et al. German Society for Rheumatology (DGRh) 2020.

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INVITED REVIEW

Rheumatology Quarterly

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Rheumatology Quarterly 2023;1(4):130-39

SKIN MANIFESTATIONS OF RHEUMATOLOGICAL DISEASES

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Abstract

Rheumatic diseases have very heterogeneous manifestations and diagnostic criteria. Rheumatic diseases have a wide range of involvement, including systemic (joints and internal organs), as well as skin, mucosa, hair, and nails. Some of these symptoms can cause severe comorbidities and significantly impair the quality of life. Skin findings are critical for early recognition or reinforcing the diagnosis of rheumatic diseases. At the same time, some skin lesions have particular importance as they may be the first and/or most serious comorbid symptom of the disease. Although most of these findings are not specific for rheumatic diseases (such as facial telangiectasia in scleroderma or nonscarring alopecia seen in systemic lupus) some findings may be disease-specific (e.g. discoid lesions in discoid lupus, malar rash in systemic lupus, and Gottron papules in dermatomyositis). Thanks to the contributions of dermatology, the skin findings of rheumatic diseases have become clearer in recent years, thus enabling the classification, phenotyping, and early treatment of rheumatic diseases. Considering all these, each dermatological finding should be taken into consideration and evaluated on a case basis in terms of suspected condition, diagnosis, treatment, and management of post-treatment comorbidities. In conclusion, both rheumatologists and dermatologists have a great responsibility in detailed anamnesis and dermatological examination for detecting the condition, classifying and phenotyping as when necessary, and developing early treatment options.

Keywords: Rheumatology, dermatology, lupus erythematosus, scleroderma, dermatomyositis, Sjögren's disease, morphea

INTRODUCTION

Rheumatic diseases have very heterogeneous manifestations and diagnostic criteria. Skin findings are critical for early recognition and reinforcing the diagnosis of rheumatic diseases (1). Thanks to the contributions of dermatology, skin findings of rheumatic diseases have become clearer in recent years, thus enabling the classification, phenotyping, and early treatment of rheumatic diseases. A detailed clinical observation of the skin is also essential in rheumatic diseases (2). Here we discuss the skin findings of lupus erythematosus (LE), dermatomyositis (DM), scleroderma (SCL), and Sjögren's disease.

1. Lupus Erythematosus

LE is a chronic, inflammatory, autoimmune rheumatological disease that can cause multiple organ involvement, various comorbidities, and mortality (3-5).

The etiology of LE is not yet fully known, but it is thought to be polygenic, with multifactorial factors involved (4). The key risk factor for LE is gender: a female-male incidence ratio of 7:1 in adults and 4:1 in children has been determined. Even in patients with isolated cutaneous lesions, the female-male ratio is 3:1 (5).

LE has a broad spectrum, including localized CLE on one side and systemic LE with severe involvement on the other (2-4). Of these, cutaneous lupus erythematosus (CLE) can be examined under

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three subheadings, i.e., acute, subacute, and chronic cutaneous lupus erythematosus (CCLE), from skin involvement, diagnostic, prognostic, and therapeutic perspectives (1-3). Chronic CLE, on the other hand, covers discoid lupus erythematosus (DLE), lupus profundus (LEP), chilblain LE, and LE tumidus (LET) (3,5). Apart from these, there are less common variants such as lupus panniculitis, bullous LE, hypertrophic/verrucous discoid LE, mucosal discoid LE, and lichenoid CLE (5).

To classify by clinicopathological involvement, LE lesions can be divided into dermo-epidermal, dermal, and subcutis subtypes (1).

Acute Cutaneous Lupus Erythematosus

Acute cutaneous lupus erythematosus (ACLE) can be both localized and generalized, mostly associated with active subacute lupus erythematosus (SLE), and its exacerbations may co-exist with systemic involvement (3,5). Generally, ACLE occurs in the third decade (3). Antinuclear antibodies and anti-dsDNA antibodies are elevated in laboratory tests in most patients. Although ACLE lesions usually heal without scarring, post-inflammatory pigmentation disorder can sometimes be observed (1,5).

Possible skin findings in ACLE are as follows:

- Malar rash/butterfly rash is typical in ACLE and is a congestive erythema involving the cheeks and dorsum of the nose while sparing the nasolabial folds and eyelids. Reversible and sensitive to sunlight, these lesions can sometimes be observed on the forehead and front of the neck (1,5).
- Mild edema or red-purple discoloration, sometimes accompanied by papules
- Poikiloderma
- Telangiectasias
- Dyspigmentation
- Widespread hair thinning
- Mucosal ulcerations
- Photosensitive lupus dermatitis/maculopapular lupus rash:

They are itchy, light-sensitive, symmetrically located maculopapular lesions that spread to the neck, and this rare form of ACLE may resemble drug rashes (3,5) (Figure 1). They are called inverse Gottron because, although the involvement of these lesions, especially those on the hands, is similar to DM, it does not affect the distal interphalangeal joint, proximal interphalangeal joint, and metacarpophalangeal joints that DM affects (3,5).

- Cuticle hypertrophy
- Reduced peripheral vascularity
- Erythema and dilated vessels are other rare nail findings (3).

Subacute Cutaneous Lupus Erythematosus

Its common points with SLE are that it mainly affects the young/middle-aged female population and causes light sensitivity (1,3). The lesions affect the areas exposed to the sun upon exposure, but interestingly, the scalp, mid-face area, and lower waist are generally spared. Subacute cutaneous lupus erythematosus (SCLE) has two forms: papulosquamous and annular, but sometimes both forms can co-exist. The annular type is in the form of erythematous, annular polycyclic plaques that tend to merge and form a polycyclic arrangement. (Figure 2). The papulosquamous type presents as psoriasiform papulosquamous without induration. As with some SLE skin lesions, it tends to heal, leaving only dyspigmentation and/or telangiectasis without atrophy, tissue hardening, and scarring. Immunologically, anti-RO (SS-A) positivity was found to be higher in this type, unlike others. Therefore, it will likely overlap with Sjögren's syndrome or be seen in primary Sjögren's patients (1,3,5).

Chronic Cutaneous Lupus Erythematosus

CCLE includes DLE, LEP, CCLE, and LET. Among these, the most common cutaneous lesions of CCLE are DLE (3).

Discoid Lupus Erythematosus

DLE usually occurs during the 4th and 5th decades, a decade later than SCLE (3). DLE has a better prognosis than other chronic subtypes, and DLE lesions have localized and generalized forms, of which the generalized form is relatively more likely to progress

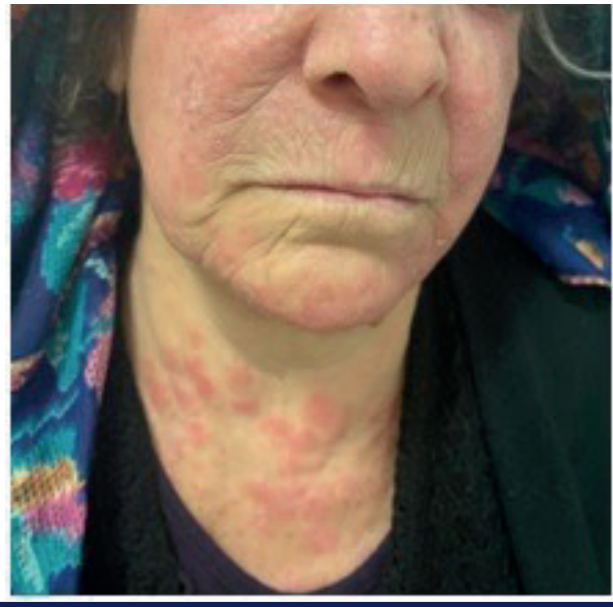

Figure 1. Itchy, photosensitive, symmetrically located drug rush-like maculopapular lesions in an elderly female patient with a generalized form of ACLE
ACLE: Acute cutaneous lupus erythematosus

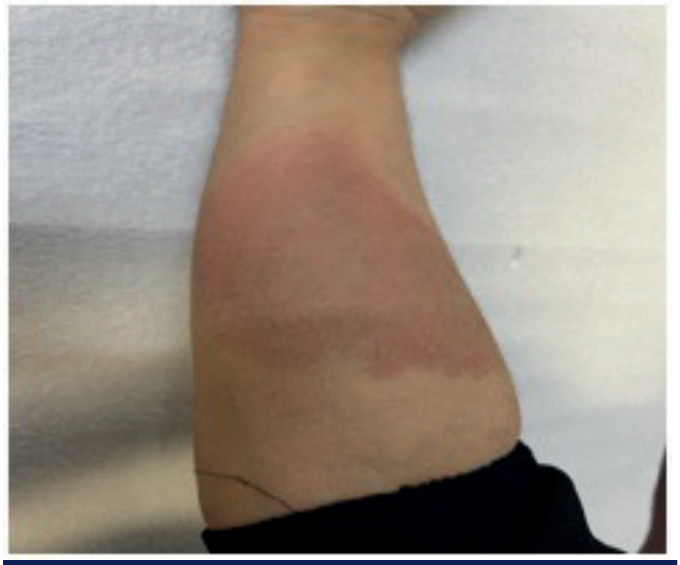

Figure 2. SCLE on the flexor of the right arm of a female patient
SCLE: Subacute cutaneous lupus erythematosus

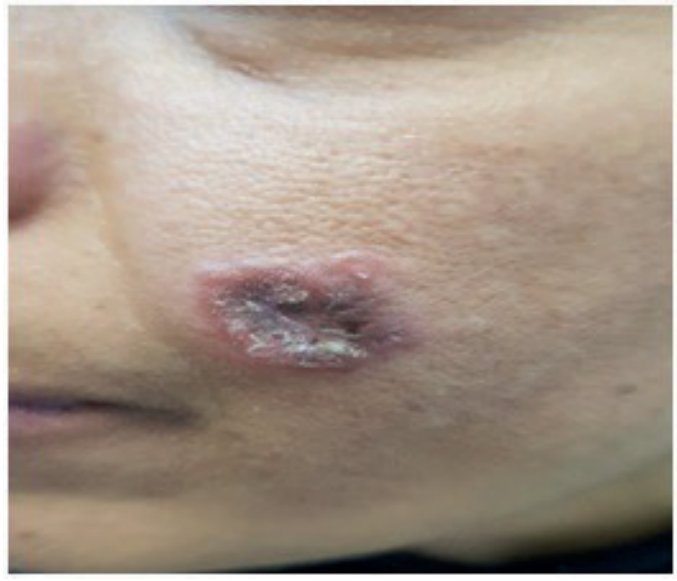

Figure 3. Atrophic hyperkeratotic plaque on the face of a female patient with discoid lupus erythematosus

to DLE (1,3). In addition to sun-exposed areas such as the head, neck, scalp, ears, extensor surfaces of the extremities, and hands, mucosal involvement can also be observed, including genitals, conjunctiva, oral, nasal, and genital mucosa protected from sunlight (3,5) (Figure 3). DLE plaques tend to specifically involve the hair follicle, and scarring alopecia may develop due to a chronic course. Lesions that can be triggered by sun, heat/cold exposure, infection, thermal burn, and trauma have erythema, follicular hyperkeratosis, atrophy, hyperpigmentation at the periphery, and discoid plaques with hypopigmentation in the center (1,3,5).

Buccal Mucosal Discoid Lupus Erythematosus

It may mimic lichen planus in the affected areas and lesion type but can be distinguished by erythematous, centrally located white papules and lesions in the form of plaques or erosion with white radial lines extending from there (3,5).

Verrucous/Hypertrophic Discoid Lupus Erythematosus

Usually on the extremities and face, lesions in the form of hypertrophic, hyperkeratotic, or papulonodules, similar to keratoacanthoma and hypertrophic lichen planus in some points, are observed (3,5). Because there is a risk of developing squamous cell carcinoma in long-term DLE lesions, especially mucosal lesions, it is essential to closely monitor the lesions (3,5).

Lupus Profundus or Lupus Panniculitis

It is generally seen in the 3rd-4th decades. Although it especially affects areas with a fat build-up, such as the extremities, face, and chest, the extremity distal is generally preserved. Painful hard subcutaneous nodules, deep scars that sometimes progress to lipoatrophy with a discoid plaque on the overlying skin, often appear as ulcerations in depressed tissue (1,3,5).

Chilblain Lupus Erythematosus

It is a rare subtype of CCLE with clinical features similar to those of frostbite. Lesions, which can be itchy or painful, appear mainly on the fingers, toes, nose, ears, and sometimes on the heels and knees exposed to cold. Erythematous swellings, purplish erythematous papules, plaques, and nodules, as well as central erosion and ulcerations developing from these lesions, can be observed (3,5).

Lupus Erythematosus Tumidus

It is a CCLE subtype with a relatively male gender bias compared with other CLE subtypes. It is generally expected to have a benign course, and relapses occur with sun exposure. It presents as erythematous, edematous, urticaria-like polycyclic plaques with a raised edge or smooth surface, with no squaring and follicular plug (3,5). Lesions generally appear on the face, neck, and trunk exposed to sunlight (5).

Bullous Lupus Erythematosus

It is a rare form found in 5% of SLE patients. Although the lesions, which are not itchy and are generally not expected to leave a scar, prefer sun-exposed areas such as the face, chest, and extremities, they can also be located on the vermillion border or oral mucosa

(5). To manage treatment, it is important to distinguish bullous LE from lupus subtypes with other cutaneous findings showing epidermal separation, especially the toxic epidermal necrosis (TEN) variant of LE (5).

Toxic Epidermal Necrosis Variant of Lupus Erythematosus

It is similar to severe cutaneous adverse reactions of Steven-Johnson syndrome and TEN, with extensive erythematous skin lesions showing epidermal separation. Although they are difficult to distinguish, histopathological findings, preservation of mucosal barriers/minimal focal involvement, and lesions affecting areas with significant light exposure may clinically support lupus diagnosis (5).

2. Sjögren's Syndrome

Sjögren's syndrome is a chronic, inflammatory, autoimmune rheumatological disease that may cause the involvement of exocrine glands, including the oral mucosa, salivary glands, and lacrimal glands in the orbit, especially the nose, ear, skin, vagina, respiratory, and gastrointestinal tract, and various comorbidities (6-10).

The etiology of Sjögren's syndrome is controversial, and its etiology pathogenesis, and risk factors are still not fully elucidated. However, polygenic factors and multifactorial factors that may cause chronic lymphocytic infiltration in the exocrine glands are thought to play a role (7-10). Although it can affect anyone, an exceptionally high female dominance rate of 9:1 was observed. In women, the disease is particularly prominent during the menopausal period, i.e., the 4th and 5th decades (7-10). It also peaks in the 2nd-3rd decades (10).

Because many immunological and clinicopathological features of Sjögren's syndrome are similar to those of other connective tissue diseases, diagnosis may be challenging (7,8). Sjögren's syndrome is classified as primary or secondary, depending on whether there is any accompanying autoimmune disease. While there is no other accompanying systemic autoimmune disease in primary Sjögren's syndrome, the most common autoimmune diseases accompanying secondary Sjögren's syndrome are rheumatoid arthritis, followed by other connective tissue diseases such as SLE, SCL, and DM (7,8,10).

Although symptoms related to the involvement of the salivary and lacrimal glands, i.e., "keratoconjunctivitis sicca", are the prominent clinical symptoms, skin findings may occur long before the specific findings of Sjögren's syndrome. The most common of these are xerosis, Raynaud's phenomenon, cutaneous vasculitis, localized nodular amyloidosis lesions on the skin, and annular erythema (7-11).

Skin findings that can be seen in Sjögren's syndrome are as follows (7-11):

- Xerosis cutis (seen in approximately half of the patients with primary Sjögren's syndrome, but its etiology is not fully known).
- Although cutaneous vasculitis presents with different types of vasculitis (such as cryoglobulinemic vasculitis, urticarial vasculitis, Waldestrom's cutaneous leukocytoclastic vasculitis or hypergammaglobulinemic purpura), the leukocytoclastic vasculitis type (small vessel vasculitis) is more common and prefers the lower extremities.
- Purpura and cutaneous ulcerations (vasculitis findings vary depending on the size of the involved vessel).
- Raynaud's phenomenon.
- Urticarial papules and plaques.
- Transient macular or papular purpura (mostly presenting as concentric circular purpuric rings).
- Annular erythema (ring-shaped/doughnut-like or polycyclic-shaped erythema that may be accompanied by papulosquamous lesions, as in subacute cutaneous lupus).
- Pruritus.
- Granuloma annulare.
- Oral candidiasis.
- Erythema multiforme and persistent lesions.
- Nodular amyloidosis localized to the skin (rarely in the genital area, other than that, single or multiple nodules of different sizes, which are primarily seen in the trunk, extremities, tongue, face, breast, glandular structures and internal organs).
- Angular cheilitis (Perleche).
- Erythema elevatum diutinum.
- Livedo reticularis.
- Subcorneal pustular dermatosis.
- Tongue depapillation (secondary to xerostomia).
- Vaginal xerosis.
- Erythema nodosum, granulomatous panniculitis, and other types of panniculitis.
- Sweet syndrome (acute febrile neutrophilic dermatosis)
- Oral mucosal erosion and ulcerations (secondary to xerostomia).
- Photosensitivity (especially on the face and upper extremities exposed to the sun).
- Pernio.
- Anetoderma.
- Xerotic cracked tongue and lips (secondary to xerostomia).

•Signs of other autoimmune skin diseases, such as psoriasis, lichen planus, vitiligo, and alopecia.

3. Dermatomyositis

DM is a multisystemic, idiopathic inflammatory myopathy primarily affecting the skeletal muscles and skin, with heterogeneous cutaneous and systemic findings (12-15). Its etiopathogenesis is not fully known, as in many inflammatory rheumatic diseases, but it is thought to be multifactorial, with microangiopathy and autoantibodies affecting the skin and muscles involved in the pathogenesis (15). Mostly affecting women, with a male-female ratio of approximately 2:1, this disease can also be seen in children and adults (16-19). This myopathy can occur at any age and has different juvenile and adult sub-forms with onset at ages 5-15 and 40-60 years (13,19).

It is classified as classical, amyopathic, and myopathic DM according to the coexistence of muscle and skin involvement, and there is also paraneoplastic DM, which accompanies paraneoplastic conditions, especially internal organ malignancies (13,17,19). Apart from these known subtypes, different subtypes, such as DM sinus dermatitis, hypomyopathic DM, and post-myopathic DM, have also been defined (13). While both skin findings and muscle involvement can be seen together in classical DM, distinct skin findings without or before significant muscle involvement are observed in amyopathic and, even more recently, skin-predominant DM. In the myopathic type, which has a smaller percentage, typical muscle involvement is observed without skin lesions (13,17,19).

The pathognomonic skin findings of DM are as follows (13,17,19):

•Gottron papules: These are flat purple-violet papules and plaques that cover the dorsal or dorsolateral surface of the interphalangeal and/or metacarpophalangeal joints, to which slight pressure can be applied and may be accompanied by telangiectasis. DM lesions are generally itchy and sensitive to sunlight and may cause dyspigmentation, atrophy, and scarring during healing.

•Gottron's sign: Symmetrically located violet maculae/plaques that may be accompanied by squads and edema covering the dorsal surface of the interphalangeal and/or metocarpophalangial joints, olecranons, medial malleoli, and patellas, i.e. the extensor surfaces of the extremities. They may also be accompanied by erythema and telangiectasia.

•Heliotropic rash: Violet erythema, which may be accompanied by edema in the eyelids and periorbital tissue, significantly affects the upper eyelids and may also affect the nose and cheeks.

The characteristic nail findings of DM include (12,13,17):

•Dystrophic cuticles and diffuse periungual changes.

•Prominent periungual telangiectasias without a dystrophic cuticle.

•Haemorrhagic nail fold and infarcts.

•Distorted nail fold capillaroscopy findings (showing a SCL pattern: low-density capillaries, irregular giant ring-shaped capillaries, and microhemorrhages).

Other skin findings that can be observed in DM (12,13,17,19):

•"V" neck sign/shawl sign: Purple-colored or diffusely erythematous symmetrical maculae/patches on the posterior shoulders, deltoids, neck, upper back, and additionally on the proximal lateral aspects of the upper extremities create this appearance by affecting the front neck in a "v" shape. They even form the poikilodermic "sheath sign" with its symmetrical placement on the lateral thighs and thighs. All these lesions can be exacerbated by UV/sunlight exposure.

•Poikiloderma/poikiloderma vasculare atrophicans/poiklodermatomyositis (coexistence of hypopigmentation, hyperpigmentation, superficial atrophy and widespread telangiectasia) usually occurs in the lateral upper arms and upper chest area.

•Walker's foot: Hyperkeratotic lesions that stimulate callosity on the plantar surface of the feet and fingers.

•Machinist's hand.

•Mechanic's hand sign: Chronic irritant dermatitis-like painful fissures on the palmar surface of the hands and hyperkeratotic lesions located on the lateral side of the palmar surface of the hands and fingers.

•Sunburn symptom: Bright red diffuse facial inflammatory erythema and subsequent post-inflammatory hyperpigmentation that affects the light-sensitive areas on the forehead, cheeks, nose, and chin, as defined in hispanic DM, but does not go beyond the nasolabial folds.

•Sunbed sign: Erythematous patch or plaque-shaped lesions where intertriginous areas and transverse skin folds are preserved; previously described in other diseases and now used in DM.

•Angel wing sign: Generalized erythema over the lumbar region and shoulders, typically separating the area around the scapulae.
Apart from these, some less common or more nonspecific skin findings are as follows:

•Vascular/vasculopathic changes (e.g., cutaneous vasculitis).

•Vesiculobullous and necrotic lesions.

•Skin erosion and ulcerations (e.g., in the digital pulp, periungual area).

•Erythroderma.

•Panniculitis and subsequent calcification lipodystrophy, sometimes simultaneously .

•Inverse Gottron and ulcerated Gottron papules.

•Photosensitivity and pruritus.

•Raynaud's phenomenon (episodic vasospasm in the fingers and toes resulting from exposure to cold).

•Painful calcinosis cutis (in the form of white papules and nodules in bone spurs and infection areas).

•Diffuse hair loss (may cause mild to moderate non-scarring alopecia).

•Koebner phenomenon positivity.

•Petechiae, palpable purpura.

•Oral mucosal changes (gingival telangiectasis, leucoplakia, erosion and ulcerations, oval palatal patches).

•Painful palmar papules.

•Whiplash erythema (linear erythematous maculae and patches on the back).

•Palmar hyperkeratosis.

•Psoriasiform plaques.

•Follicular hyperkeratosis [Pitriasis rubra pilaris (PRP)-like hyperkeratotic papules on the extensor surfaces, especially in Wong type DM].

•Contractures.

4. Systemic sclerosis/scleroderma

Systemic sclerosis (SSc) is an autoimmune, multifactorial, and multisystemic chronic inflammatory connective tissue disease in which microvascular damage and excessive fibrosis are pronounced (18,19). Differential diagnosis includes many immune-mediated, inflammatory, toxic, drug-induced, genetic, vascular, and paraneoplastic conditions with abnormal accumulation, which can be confused with SSc because they cause cutaneous sclerosis (CS) (14).

SSc is a condition whose etiology is not fully known, in which microvascular damage is observed, especially in the skin and internal organs, resulting in excessive collagen accumulation (14). A very small portion of SSCs have a pediatric onset, most of which typically occurs in the 3rd-5th decades (14).

SSc is evaluated in three subcategories based on the intensity and distribution of CS: localized CS (Morphea), limited cutaneous SSc (Crest Syndrome), and generalised cutaneous SSc. Because CS manifests itself with oedema that does not leave pits on the skin, swollen, puffy fingers, and a decrease in facial wrinkles are observed (14,19). Depigmentation and hypopigmentation, which may resemble vitiligo but with the perifollicular area is preserved and generalised, sometimes follicular hyperpigmentation, which is more dominant in sun-exposed areas, and a typical finding, the "salt-pepper sign", forms. In addition, cutaneous appendages, such as sweat glands, other than the hair follicle in shiny and hard skin diminish/disappear (14,19).

Skin thickening and hardening, starting symmetrically and extending proximally from the metacarpophalangeal joints of both hands, may tend to spread to the extremities, face, and trunk, but involvement of the entire skin is rare. Again, progressive nail folding and nail changes constitute the "SCL pattern" in capillaroscopic examination (14,18,19). Dyspigmentation, telangiectasis, cutaneous ulceration, calcification, purpura, and atrophic deep scars in the form of ice picks that are difficult to heal caused by progressive vasculopathy can be expected in the involved skin (14,19). The characteristic cutaneous findings in limited cutaneous SSc are limited to the hands, upper extremities, and face, whereas in diffuse SSc, spread, albeit slowly, to the upper extremities, the face, as well as the lower extremities, and trunk, can be observed (14,18,19). Cutaneous calcifications can progress to affect the fingers, forearms, elbows, and knees (14). The main findings of limited cutaneous SSc, also known as Crest syndrome, include calcinosis, Raynaud's phenomenon, esophageal motility disorder, sclerodactyly, and telangioctasias (14,18,19). Among these, Raynaud's phenomenon is usually bilateral and severe and can involve acral areas, such as the fingers, earlobe, tongue, toes, nose, and ear, and can be encountered in the early stages (14). An ischemic phase, which begins as blanching upon exposure to cold, is followed by the asphyctic phase, which is a painful phase in which the purplish color predominates and is followed by widespread erythema that occurs as a result of revascularisation (Figure 4) (14). Raynaud's phenomenon, which has primary/idiopathic and secondary forms that are important for early diagnosis and treatment, can progress to digital ulceration and gangrene, and autoamputations (resorption of the terminal phalanges) along with sclerodactyly (thinning and tapering of the fingertips secondary to developing deformities) can be observed in the same primary site (14,18,19).

In patients with systemic SCL, changes are also detected in the nail fold and nail bed, and these are defined as an SCL-type pattern (large avascular areas hemorrhages curled giant capillaries, capillary abnormalities in the nail fold, capillary branching, irregularity in microvascular alignment, fibrosis) in capillaroscopy/dermatoscopy. Other nail findings that can be observed in SCL are as follows (14,18,19):

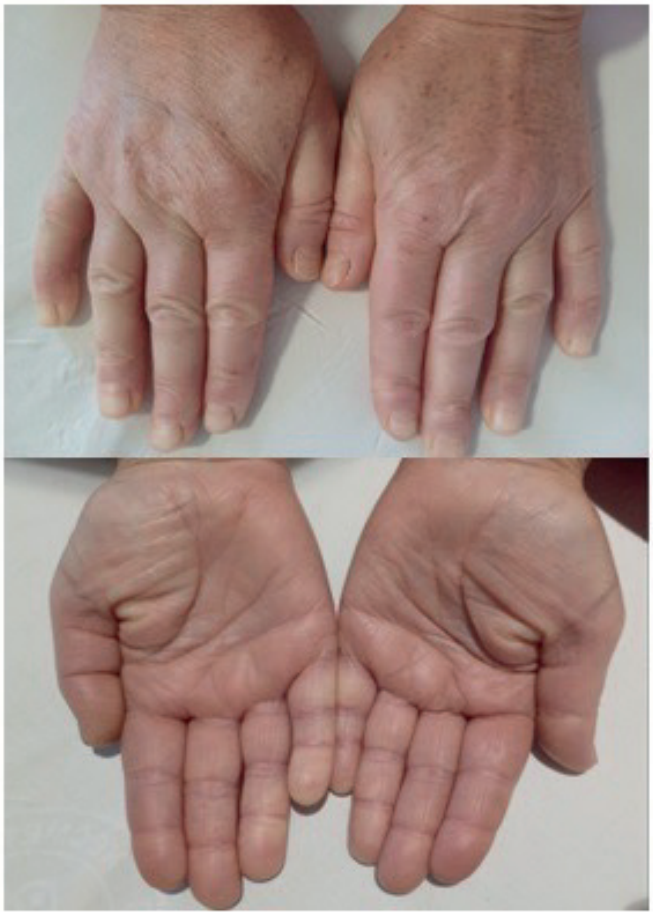

Figure 4. Raynaud's phenomenon in a female systemic sclerosis patient

- Trachyonychia (longitudinal protrusions),
- Sclero-onycholysis,
- Brachyonychia,
- Thickening of the nail,
- Hyperkeratosis in the hyponychium,
- Pterygiumversum unguis,
- Protruding, thickened, and distorted cuticles,
- Parrot beak appearance,
- Leukonychia,
- Red lunula,
- Dyschromia,
- Clubbing,
- Warping in the longitudinal axis,
- Splinter haemorrhages.

CS, with an initial phase in the form of pitting edema has three phases: indurative and atrophic (14). Because of recurrent ischemic attacks, the skin becomes shiny as it stretches and hardens, and its appendages disappear, taking on a wax-like appearance and progressing proximally, resulting in flexion contractures, ankylosis, and the complete disappearance of skin folds, giving the appearance of a claw hand (14).

Because of the involvement of the perioral soft tissue in CS, mouth opening decreases and microstomia develops, while vertical wrinkles begin to appear on the upper lip and a typical facial appearance occurs (Figure 5) (14,18,19). In the oral mucosa, increased tooth pocket openings and xerostomia lead to increased candidal and periodontal infections (14). Cutaneous telangioctasias are dermally located dilated capillaries that can be seen on the neck, palmar and dorsal surfaces of the hands, shoulders, face, thighs, abdomen, breasts, lips, and oral mucosa (14,18,19).

Calcinosis cutis appears as symmetrical white papules and subcutaneous nodules, which are their harder-consistency forms, mainly on the extremities and sometimes on the trunk (14,18,19).

Localized Cutaneous Scleroderma/Morphea

It is a connective tissue disease with fibrosis, where exogenous multifactorial causes and genetics are blamed, but its etiology is unknown. It primarily affects the skin and subcutaneous tissues, sometimes involving the bones, face, and head, and may also involve the central nervous system (14,20). There is a female dominance of 2-4.2:1 in the prevalence of the disease, and especially the white race is affected. The prevalence in children (highest incidence in 2-14 years) and adults (highest incidence in the 5th decade of life) was found to be similar, and the most common subtypes are linear-type and plaque-type morphea, respectively (14,20).

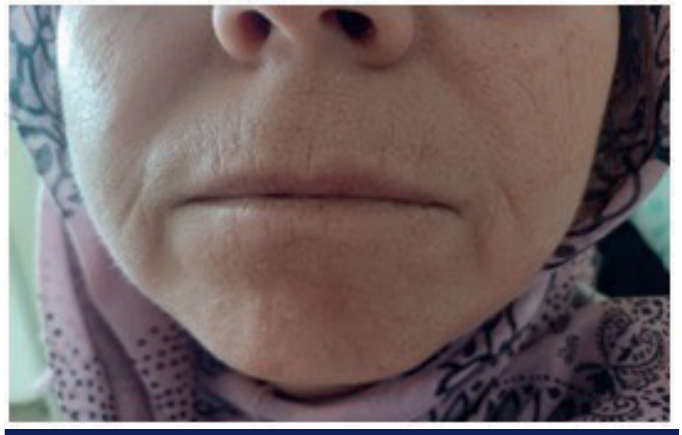

Figure 5. Perioral soft tissue involvement in a female patient with systemic sclerosis typical facial involvement (microstomy, vertical upper lip wrinkles)

Classification of morphea according to the most common classification (14,20):

•Plaque morphea /"en plaque" morphea (including gutta morphea, Pasini and Pierini atrophoderma, keloidal/nodular morphea, and lichen scleroatrophicus)

•Generalized morphea (more than two areas involved)

•Bullous morphea

•Linear SCL (including extremity involvement and en coup de saber)

•Progressive facial hemiatrophy, deep morphea (including morphea profunda, subcutaneous morphea, and eosinophilic fasciitis), and pansclerotic morphea.

Plaque Morphea/"En Plaque"Morphea

This type is generally located on the proximal part of the trunk and extremities and is the type most frequently encountered in adults (14,20). While it affects the dermis and above, the number of plaques often appearing in the pressure areas of clothing due to the Koebner phenomenon usually does not exceed three (14). In the early period, purple-colored, well-defined erythematous patches/plaques of various shapes become white in color with a sclerotic structure over time and are surrounded by a purple-colored inflammatory border called a lilac ring, which gradually expands and eventually disappears (14,20). When the fully active phase of the lesion ends, it appears as sclerotic plaques accompanied by post-inflammatory hyperpigmentation and as anhydrous and smooth as skin appendages such as hair follicles and sweat glands disappear (Figure 6) (14).

Guttate Morphea

It is a subform of plaque morphea with sharper borders but less induration, mostly seen on the upper body and above (14).

Keloidal/Nodular Morphea

In this rare type, which is also a subform of plaque morphea, nodular lesions resembling keloids are observed, unlike other forms (Figure 7) (14).

Pasini-Pierini Atrophoderma

It has sharp borders, is brown, and has a smooth surface. It is mainly located proximal to the trunk. Owing to the round-shaped atrophy, it is flattened compared with the skin, and when multiple lesions come together, it creates the appearance of "Swiss cheese" or "footprints in the snow" (14). Unlike others, structures such as hair follicles and tissue elasticity are preserved because it occurs before inflammation develops and does not reach the threshold of sclerosis (14).

Deep Morphea/Subcutaneous Morphea/Morphea Profunda

As its name suggests, it is the morphea form in which subcutaneous tissues are involved in addition to the dermis, and it is mostly depressed compared with the surrounding area and tightly connected to the underlying tissue, but the overlying skin may be normal, atrophic, or sclerotic (14).

Linear Morphea

There are three different variants depending on the location: head variant, extremity/trunk variant, and progressive

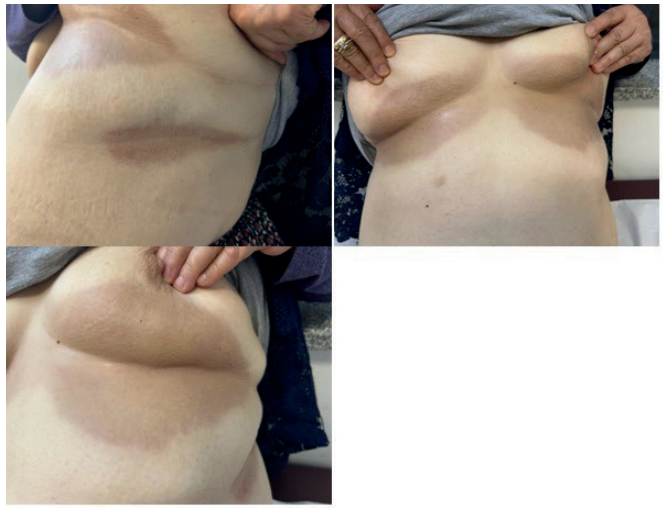

Figure 6. Sclerotic plaques accompanied by postinflammatory hyperpigmentation in a female patient with plaque morphea

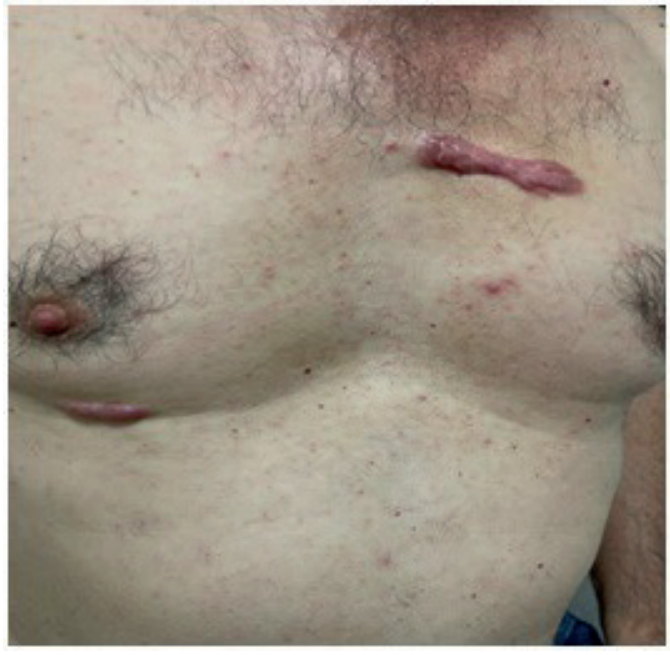

Figure 7. Keloid-like raised nodular lesions on the chest in a male patient with keloidal moraea

hemifacial atrophy, specifically named "en coup de sabre" and "Parry-Romberg syndrome" (14,20).

Lesions following Blascko's lines contain a linear cutaneous induration line extending into the subcutaneous tissue (14,20). The last variant is mostly seen in children and adolescents and is the most common morphea subtype in the pediatric population (14,20).

In linear morphea, which affects both genders, the lesions appear as an inflammatory erythematous linear line or a morphea plaque and adhere to the subcutaneous tissues with the effect of sclerosis, disrupting growth and development, and movements of the extremities (14,20).

''En Coup De Saber" Type of Linear Morphea

It is a subtype of linear morphea affecting the scalp, forehead, and paramedian of the forehead and can sometimes progress to the lips and gums, including the malar-nasal areas. It generally occurs at the age of 13 years, has a high rate of occurrence at menarche, and is more common in girls (14,20). In addition to the atrophic but smooth, hard, and unilateral linear plaque on the face, it may be accompanied by alopecia that leaves scars on the scalp (14,20).

Parry-Romberg Syndrome/Progressive Hemiatrophy

This syndrome mainly presents with unilateral involvement of the subcutaneous tissue of the dermatomes belonging to the trigeminal nerve and its branches and the elements of the musculoskeletal system, and ultimately unilateral atrophy. It exhibits clinical findings similar to En Coup De Saber and appears at the age of 13 (in the 1st-2nd decades), but unlike En Coup De Saber, it affects girls more commonly (14,20). The syndrome has a slow and progressive course but is self-limiting, and its etiology is still unknown (20).

In this syndrome, in which the periorbital skin is frequently affected, dyspigmentation and sclerosis may be observed in the affected skin, and the skin may maintain its normal structure but may be accompanied by ophthalmic and neurological complications (14,20).

Generalised Morphea

It manifests as four or more plaques located in more than one body part and/or plaques larger than 3 cm in size (14,20).

This type of morphea rarely involves the subcutaneous tissues and is mainly limited to the dermis; however, it has a progressive course covering the entire body surface and is relatively more common in women (14,20).

Although involvement in the hands has similar clinical manifestations as SCL, it can be differentiated by the absence of additional findings, such as other nail and vascular findings accompanying SCL (14,20).

Bullous Morphea

It is a rare subtype of Morphea, with tense, subepidermal localization on Morphea plaques and with contents varying from serous to hemorrhagic (14,20).

Mixed Variant Morphea

It is a Morphea subtype in which two or more Morphea subtypes are combined to different degrees (14).

Conclusion

Rheumatic diseases have several involvement, including systemic (joints and internal organs) and skin, mucosa, hair, and nails. Some of these symptoms can cause severe comorbidities and significantly impair quality of life. At the same time, some skin lesions are of particular importance as they may be the first and/or most serious comorbid symptom of the disease. Although most of these findings are not specific for rheumatic diseases (such as facial telangiectasia in SCL or nonscarring alopecia seen in systemic lupus), some findings may be disease-specific (e.g., discoid lesions in discoid lupus, malar rash in systemic lupus, and Gottron papules in DM). Considering all these, each dermatological finding should be considered and evaluated on a case basis in terms of suspected condition, diagnosis, treatment, and management of post-treatment comorbidities (21). In conclusion, both rheumatologists and dermatologists have a great responsibility in detailed anamnesis and dermatological examination for detecting the condition, classifying and phenotyping when necessary, and developing early treatment options.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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FREQUENCY OF AUTOIMMUNE THYROID DISEASE AND THYROID DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS AND ITS RELATIONSHIP WITH CLINICAL FINDINGS

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Abstract

Aim: Thyroid dysfunction (TD) and autoimmune thyroid disease (AITD) are frequently reported in patients with systemic lupus erythematosus (SLE). The relationship between SLE disease activity and thyroid disease is controversial. In this study, we aimed to investigate the frequency of TD and AITD in patients with SLE and their relationship with clinical findings and disease activity.

Material and Methods: Two hundred SLE patients between the ages of 18 and 75 years, who were followed in the rheumatology outpatient clinic and met the revised 1997 American College of Rheumatology (ACR) SLE classification criteria, were included in the study. Demographic, clinical, and laboratory data of the patients were obtained from patient files and hospital databases. The SLE Disease Activity Index (SLEDAI)- 2 K was used to evaluate SLE disease activity, and the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index was used to assess damage.

Results: AITD was detected in 18.5% of patients with SLE, and 26.5% had TD. Neurological involvement (p=0.017), lymphopenia (p=0.016), hemolytic anemia (p=0.006) and direct coombs positivity (p=0.034) were found to be higher in patients with TD. Female gender (p=0.005), hemolytic anemia (p=0.001), antiphospholipid antibodies (aPL) (p=0.032) and direct coombs positivity (p=0.023) were more common in patients with AITD. When the risk factors were examined, it was determined that neurological involvement [odds ratio (OR)= 6.5], hemolytic anemia (OR= 4.6) and direct coombs positivity (OR= 2.2) increased the risk of TD, whereas aPL positivity and low complement decreased the risk. It was observed that the risk of AITD increased 5.2-fold in the presence of hemolytic anemia. A borderline significant increase in disease activity was observed in patients with TD (p=0.049). When a limit 6 was used for the SLEDAI score, activity was found to be higher in patients with TD (p=0.036).

Conclusion: Neurological involvement, hemolytic anemia, and direct Coombs positivity are risk factors for the presence of TD and AITD in SLE.

Keywords: Systemic lupus erythematosus, thyroid dysfunction, autoimmune thyroid disease

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease with multisystem involvement. SLE affects many organs, including the skin, joints, kidneys, nervous system, lungs and cardiac system (1). SLE is a multifactorial disease whose etiology is not well known, and genetic, hormonal, immunological and environmental factors play a role in its etiology.

Thyroid hormones may affect clinical findings in SLE, and conversely, SLE may cause changes in thyroid function. The relationship between SLE and thyroid diseases was first described in 1961 by White et al. (2) and Hijmans et al. (3). Studies have shown that the presence of thyroid dysfunction (TD) is more common in SLE patients than in the general population (4).

Most studies in the literature show that the prevalence and incidence of hypothyroidism and autoimmune thyroiditis are high in patients with SLE, especially in women. A limited number of cases of Graves' disease have also been reported in patients with SLE (5).

Studies have investigated whether there is a relationship between TD and different clinical findings of SLE, but most have reported that there is no significant relationship between TD and thyroid autoimmunity and the clinical and serological features of SLE (5). The results of studies evaluating TD and SLE are controversial.

The presence of TD in SLE patients may be due to euthyroid sick syndrome due to underlying systemic disease or the effects of drugs such as corticosteroids and immunosuppressives. Because both SLE and autoimmune thyroid disease (AITD) are seen in similar populations, it is a matter of debate whether SLE is an independent risk factor for TD or whether it is an incidental finding (6).

This study aimed to investigate the frequency of TD and AITD in patients with SLE and their relationship with clinical findings and disease activity.

MATERIAL AND METHODS

Four hundred patients aged 18-75 who were followed up in the rheumatology outpatient clinic between 2002 and 2022 and were diagnosed with SLE according to revised American College of Rheumatology (ACR) criteria were included in the study (7). Two hundred of these patients were excluded from the study according to the exclusion criteria. Demographic data, clinical findings, laboratory data, and medications of the patients included in the study were recorded in preprepared patient forms from the patients' clinic follow-up filesand hospital database. Patients without sufficient data due to lack of follow-up, who were pregnant when their thyroid functions were checked, and those without a thyroid function test were excluded from the study.

Patients with abnormal thyroid function tests and those who used levothyroxine (LT4) due to AITD and had normal thyroid function tests were classified as the TD group. Ten patients who were diagnosed with AITD based on ultrasonography findings and thyroid antibody positivity, who did not use LT4 and had normal thyroid function tests, were not included in the group of patients with TD. Disease activity scores at the time of thyroid function tests were calculated using the SLE Disease Activity Index (SLEDAI)-2K (0 inactive, 1-5 mild, 6-10 moderate, 11-19 high, >20 very highly active) (8). Laboratory parameters included in the disease activity score were obtained from patient examinations within the last month. The Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index was used to calculate damage (maximum 47 points) (9). Study protocol was approved by Kocaeli University Local Ethics Committee (ethics approval number: GOKAEK-2019/22.08)

Statistical Analysis

Statistical evaluation was performed using SPSS 20.0 (IBM Corp, Armonk, NY, USA) package program. Compliance with normal distribution was determined by the Kolmogorov-Smirnov test. Since the normal distribution assumption could not be met, numerical variables were given as median (25^{th}-75^{th} percentile). Categorical variables are given as the frequency (percentage). Differences between groups were determined by the Mann-Whitney U test. Relationships between categorical variables were determined using chi-square analysis. Binary logistic regression analysis was used to determine the factors affecting the outcome variable. In the hypothesis tests, $p<0.05$ was considered sufficient for statistical significance.

RESULTS

Of the 200 SLE patients included in the study, 175 were women (87.5%), and the age of the patients was 48.57±13.27 (minimum-maximum: 21-75). Demographic data of the patients are given in Table 1.

Mucocutaneous involvement was detected in 71.5% of the patients, joint involvement in 62%, serositis in 23%, kidney involvement in 43.5%, neurological involvement in 11%, hematological involvement in 87%, and immunological involvement in 73.5%. Antinuclear antibody was positive in all patients, 125 (62.5%) had low complement and 79 (39.5%) had direct Coombs positivity. In addition, antiphospholipid syndrome (APS) was detected in 20.5% of the patients, heart valve disease in 51%, pulmonary arterial hypertension in 6%, and avascular

Table 1. Demographic characteristics and clinical findings of the patients

n (%)	n=200
Gender (woman)	175 (87.5)
Age (years) mean ± Std (median; 25-75)	48.57±13.27 (49; 39-57.75)
Age of disease onset (years) mean ± Std (median; 25-75)	35.49±13,32 (34.5; 25-44)
Disease duration (years) mean ± Std (median; 25-75)	13.09±8.46 (12; 6-18)
Follow-up duration (years) mean ± Std (median; 25-75)	9.27±5.35 (8; 5-13)
Mucocutaneus Photosensitivity Malar rash Discoid rash	143 (71.5) 75 (37.5) 96 (48) 29 (14.5)
Joint involvement	124 (62)
Serositis	46 (23)
Neurological involvement	22 (11)
Kidney involvement	87 (43.5)
Hematological involvement Leukopenia Lymphopenia Hemolytic anemia Thrombocytopenia	174 (87) 124 (62) 138 (69) 13 (6.5) 78 (39)
Immunological involvement Anti-dsDNA Anti-Smith	147 (73.5) 130 (65) 24 (12)
Lung involvement	9 (4.5)
Antiphospholipid syndrome Anticardiolipin antibody Anti-β2 glycoprotein Lupus anticoagulant	41 (20.5) 36 (18) 26 (13) 31 (15.5)
Heart valve disease Aortic regurgitation Mitral regurgitation Tricuspid regurgitation	102 (51) 26 (13) 56 (28) 73 (36.5)
Pulmonary arterial hypertension	12 (6)
Avascular necrosis	27 (13.5)
Comorbidite Diabetes Ischemic heart disease Malignancy	32 (16) 20 (10) 8 (4) 8 (4)
Treatment Hydroxychloroquine Corticosteroid Mycophenolate mofetil Azathioprine Cyclophosphamide Cyslosporine Methotrexate Rituximab	 174 (87) 156 (78) 65 (32.5) 72 (36) 4 (2) 2 (1) 2 (1) 10 (5)

Std: Standard

necrosis in 13.5% (Table 2). When the thyroid function tests of the patients were performed, the median SLEDAI was calculated as 4 (Q1-Q3=0-6) and SLICC was calculated as 3 (Q1-Q3=1-4).

Thirty-seven (18.5%) SLE patients had AITD, 34 (17%) had Hashimoto thyroiditis, and 3 (1.5%) had Graves disease. According to laboratory results, TD was detected in 35 patients [high thyroid stimulating hormone (TSH) in 29 patients and low TSH in 6 patients]. Apart from these patients, 18 patients were using LT4 due to AITD (17 Hahimoto, 1 Graves patient), and the thyroid function tests of these patients were normal. There were no patients with T3 or T4 abnormalities. As a result, 53 patients were considered to have TD. Anti-thyroid peroxidase (anti-TPO) was positive in 31 (15.5%) patients, anti-thyroglobulin (anti-TG) was positive in 36 (18%) patients, and both antibodies were positive in 19 (9.5%) patients. Anti-TSHR antibody was tested in only 23 patients, and 7 (30%) of them were positive (Table 2). In addition, 13 (6.5%) patients had non-autoimmune hypothyroidism.

When the disease activities were examined according to SLEDAI at the time when the thyroid function tests of the patients were examined, it was observed that 58 (29%) patients were in remission. Mild activation was observed in 85 (42.5%), moderate in 50 (25%), high in 6 (3%) of the patients and very high in only one patient. When the damage index of that period was examined, no damage was detected in 18 (9%) of the patients, whereas the damage index was below 10 in all the remaining patients (score 1-2 in 38%, 3-4 in 40%, 5-6 in 11%, and 7-8 in 2%).

Table 2. Laboratory findings and diagnoses of patients regarding thyroid function

n (%)	n=200
High TSH	29 (14.5)
Low TSH	6 (3.0)
High T3	6 (3.0)
High T4	6 (3.0)
Anti-TPO positivity	31 (15.5)
Anti-TG positivity	36 (18.0)
Anti-TSHR positivity	7 (3.5)
Thyroid dysfunction	53 (26.5)
Hashimoto thyroiditis	34 (17)
Graves' disease	3 (1.5)
Multinodular goiter	5 (2.5)
LT4 usage	45 (22.5)

TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, Anti-TPO: Antithyroid peroxidase, Anti-TG: Anti-thyroglobulin, LT4: Levothyroxine

94.3% of the patients with TD and 85% of those without TD were female (p=0.130). When compared in terms of clinical involvement of SLE, no significant difference was found between those with and without TD in any involvement other than neurological involvement (20.8% vs. 7.5%; p=0.017, respectively). In terms of laboratory findings related to SLE, lymphopenia (83% vs. 63.9; p=0.016, respectively), hemolytic anemia (15.1% vs. 3.4%; p=0.006, respectively), and direct Coombs positivity (54.7% vs. 36.5%; p=0.034, respectively) were observed to be higher in the TD group. While no difference was detected in the SLICC score, a borderline increase in the SLEDAI score was detected in those with TD (median 4 vs. 3; p=0.049). When the SLEDAI score was grouped as <6 and ≥6, activity was found to be higher in those with TD (22.4% with SLEDAI <6, 36.8% with ≥6; p=0.036).

All 37 patients diagnosed with AITD were female (100% vs. 85%; p=0.005). When comparing patients with and without AITD in terms of SLE-related clinical findings, no significant difference was detected in any involvement. There was no significant difference in laboratory findings except for hemolytic anemia (19% vs. 3.6%; p=0.001), direct Coombs positivity (56.7% vs. 35.5%; p=0.023), and aPL (10.8% vs. 27.6%; p=0.032) positivity. In addition, it was observed that the activity and damage scores were similar in the groups with and without AITD.

When the factors associated with TD in patients with SLE were examined, only neurological involvement, APS, hemolytic anemia, direct Coombs positivity, and low complement were found to be significant. Among these factors, it was found that APS reduced the risk by 5.29 times (p=0.035), and low complement decreased the risk by 3.75 times (p=0.002). It was shown that neurological involvement [odds ratio (OR)=6.5; p=0.005), hemolytic anemia (OR=4.6; p=0.037) and direct coombs positivity (OR= 2.2; p=0.038) increased the risk of TD. When factors related to AITD were evaluated in SLE patients, only the presence of hemolytic anemia was found to be significant. It was determined that hemolytic anemia increased the risk of AITD by 5.29 times (p=0.026) (Table 3).

Table 3. Factors associated with thyroid dysfunction and autoimmune thyroid disease

	OR (95% confidence interval)	p value
Thyroid dysfunction		
Antiphospholipid syndrome	0.189 (0.04-0.88)	0.035
Neurological involvement	6.525 (1.78-23.81)	0.005
Hemolytic anemia	4.660 (1.09-19.75)	0.037
Low complement	0.266 (0.11-0.61)	0.002
Direct Coombs positivity	2.277 (1.04-4.95)	0.038
Autoimmune thyroid disease		
Hemolytic anemia	5.296 (1.22-22.92)	0.026

OR: Odds ratio

DISCUSSION

The frequency of AITD and TD in SLE patients and their relationship with SLE findings have been examined in various studies, and conflicting results have been reported. In this study, we aimed to investigate the frequency of AITD and TD and the factors associated with them in our patients.

Thyroid disease is frequently reported in SLE, and it is stated that SLE patients with thyroid disease have a higher risk of serious complications such as renal and neurological involvement. It has been emphasized that the frequency of thyroid disease is significantly higher, especially in those who have another autoimmune disease (overlap syndrome) along with SLE (10,11). The most commonly reported TD is overt and subclinical hypothyroidism. Hypothyroidism is 5 times more common than SLE in the general population. In a meta-analysis, it was reported that hypothyroidism was higher in SLE patients than in the control group (OR= 2.93), and this difference was greater in subclinical hypothyroidism patients (OR= 5.67) (12).

While the frequency of autoimmune hypothyroidism is reported to be 15.4%, the frequency of non-autoimmune hypothyroidism is reported to be 0.3-28.6% in different studies (10,13). In another study, TD was reported at a rate of 36%, and half of these patients were reported to have AITD and the other half had non-AITD (6). In our study, TD was detected in 26.5% of patients, and 55% of these patients were associated with AITD, whereas 45% had non-AITD. Our frequency of TD was found to be compatible with the rates reported in the literature.

In the study of Liu et al. (10) (n=2800), it was reported that renal involvement (35.6% in those with thyroid disease, 27.9% in those without; p=0.024) and neurological involvement (respectively 21.7%, 14.2%; p<0.0001) were detected more frequently in SLE patients with thyroid disease. In our study, neurological involvement (respectively 20.8%, 7.5%; p=0.017), lymphopenia (respectively 83%, 63.9%; p=0.016) hemolytic anemia (respectively 15.1%, 3.4%; p=0.006), and direct Coombs positivity (respectively 54.7%, 36.5%; p=0.034) were found to be higher in patients with thyroid dysfunction. When the risk factors were examined, it was determined that neurological involvement (OR =6.5) hemolytic anemia (OR =4.6), and direct coombs positivity (OR =2.2) increased TD, whereas APS and low complement decreased it. This difference may be due to our small sample size.

AITD affects 5% of the general population and is reported in 1-60% of patients in studies conducted in the SLE group. It is known that more than one autoimmune disease may occur simultaneously in SLE and Sjogren's syndrome (SjS). In the presence of more than one autoimmune disease, AITD usually accompanies these diseases. The frequency of AITD in SLE has been reported at different rates in different countries, with the lowest rate reported in Brazil (1%) and the highest rate in India (60%). A study from Colombia reported this rate as 12% (13). In our study group, the frequency of AITD was 18.5% and was found to be similar to the rates in the literature.

Female gender, advanced age, smoking, rheumatoid factor (RF) positivity, presence of SjS, and skin and joint involvement are reported as factors associated with AITD in SLE (13). It has been reported that RF positivity and the presence of SjS are more common in SLE patients with AITD (14). In the study by Wei et al. (14), 38 SLE patients with AITD were compared with 190 SLE patients without AITD, and it was found that serositis increased the risk of AITD by 3.64 times (p=0.00), anti-dsDNA positivity (p=0.01) and low C3 (p=0.02) has been reported to reduce the risk (15). In this study, although a relationship was found between female gender, presence of hemolytic anemia, aPL and direct Coombs positivity, and AITD, regression analysis showed that only hemolytic anemia increased the risk of AITD by 5.2 times.

Hashimoto thyroiditis is the most common thyroid disease in patients with SLE and has been reported to be 2.68-12.6% in studies (16-18). Additionally, euthyroid sick syndrome has been reported in 47.8% of patients with SLE (16). It has been reported that mor anti-Smith positivity (p=0.04) was detected in SLE patients with Hashimoto thyroiditis (17). In our patients, in the AITD group, all patients had Hashimoto thyroiditis (17%) except three patients. There was no patient with euthyroid sick syndrome. Similar to the AITD group, a relationship was found between Hashimoto thyroiditis and female gender, presence of hemolytic anemia, aPL, and direct Coombs positivity.

Antithyroid antibody positivity is observed in patients with SLE. In a systemic literature review, it was reported that 1.5-100% of SLE patients had anti-TPO positivity and 0.9-82.3% had anti-TG positivity (6,13,19,20). In our SLE group, 15.5% of the patients were anti-TPO positive and 18% were anti-TG positive, which was consistent with these rates.

The results of studies evaluating the relationship between SLE activity and thyroid disease are controversial. TD and euthyroid sick syndrome in patients with SLE may be due to the effects of systemic disease or medications such as corticosteroids and immunosuppressives. Because both diseases are seen in similar populations, it is a matter of debate whether SLE is an independent risk factor for TD or whether it is an incidental finding (6). The relationship between hypothyroidism or AITD and SLE clinical activity has been described in a few studies (16). The SLEDAI score was higher in SLE patients with sick euthyroid syndrome (mean SLEDAI score was 10.11 in those with euthyroid syndrome, 6.69 in those without; p=0.03). Also, there was no difference in terms of disease duration (6). In a study in which the SLEDAI score was considered <6 or ≥6, it was stated that there was no difference between the two groups in terms of antithyroid antibody positivity and hypothyroidism frequency (14.8% vs. 6.6%, p=NS) (21). In our study, a borderline significant increase in the SLEDAI activity index was observed in patients with TD (p=0.049). There was no difference in activity and damage indices between the groups with and without AITD.

Study Limitations

The retrospective design of our study is one of our limitations. Although our number of patients is high compared with many studies conducted on this subject, our sample size is another limitation.

CONCLUSION

As a result, TD was detected in 26.5% of our patients, and AITD was detected in 18.5% of our patients. A positive relationship was found between TD and neurological involvement, direct Coombs positivity, and hemolytic anemia, and a negative relationship with APS and low complement. A positive relationship was found only between AITD and hemolytic anemia. When evaluated in terms of activity and damage, a borderline significant increase in the SLEDAI activity index was observed only in those with TD. Consequently, larger controlled, prospective studies are needed to elucidate the causal relationships between TD.

Ethics

Ethics Committee Approval: Study protocol was approved by Kocaeli University Local Ethics Committee (ethics approval number: GOKAEK-2019/22.08)

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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EVALUATION OF CARDIAC INVOLVEMENT THROUGH TRANSTHORACIC DOPPLER ECHOCARDIOGRAPHY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Aim: Rheumatoid arthritis (RA) is a chronic inflammatory disease found to cause the cardiovascular disease risk. We aimed to evaluate cardiac involvement through transthoracic echocardiography (ECHO) in RA patients and its relationship with age and comorbidities.

Material and Methods: By analyzing the records of follow-up RA patients in outpatient clinics of rheumatology, 200 patients who had ECHO (female/male: 155/45, age range: 57.12±12.08 years, average duration of disease: 108.57±115.99 months) were examined.

Results: The frequency of RF and anti-CCP were 67.2% and 58.4%, respectively, and 40% of patients had other accompanying. According to the ECHO findings, 6% of patients had systolic dysfunction, 4.5% pericardial effusion, 68.1% diastolic dysfunction (DD), 14% valvular disease, and 20.5% pulmonary hypertension. In addition, 81% of patients had an increased left ventricular mass, 33.5% hypertrophy in the left atrium and 11% in the right ventricular area. There was no correlation between seropositivity and ECHO findings, except between anti-CCP and decreased deceleration time (p=0.0013, r=0.214). Left atrial hypertrophy, left ventricular hypertrophy and DD were identified more frequently in patients ages ≥55 years and in patients with accompanying diseases. Pulmonary hypertension was identified more frequently in patients ages ≥55 years.

Conclusion: According to ECHO results, many cardiac involvements, especially DD, were observed in a significant number of RA patients. Factors such as age, autoantibody status, and concomitant diseases may influence the cardiovascular risk. Close monitoring and consideration of cardiovascular interventions can contribute to the prevention of RA-related cardiovascular complications.

Keywords: Rheumatoid arthritis, doppler echocardiography, cardiovascular risk

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that affects many organs including cardiac ones. Several forms of cardiac involvement have been described in RA, and the most common involvement is pericardial effusion and pericarditis (1). In autopsy studies, it was reported a high incidence of involvement of all cardiac structures (myocardial, endocardial and pericardial) in RA patients (2). Myocardial lesions may cause myocardiopathy, conduction defects, structural abnormalities, and cardiac dysfunctions. In RA, the risk of death caused by

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cardiovascular disease was considered to be two-fold higher compared with normal population, which is not explained by traditional cardiovascular risk factors (3,4). The pathological mechanism leading to development of cardiac failure is generally either systolic or diastolic dysfunction or both. It has been demonstrated that diastolic dysfunction is directly related with structural changes in the left ventricle (5). Recent studies have reported the presence of diastolic dysfunction in RA patients which may be clinically silent for years (6-8). It was also confirmed that there is a correlation between left ventricular (LV) diastolic dysfunction and disease duration or the presence of extra-articular manifestations of RA (4).

Easy to use Doppler echocardiography (ECHO) is a non-invasive and sensitive method for detecting systolic and/or diastolic dysfunction and other cardiac abnormalities. However, this conventional method has several limiting factors, such as the effects of changes in preload-afterload and arrhythmia on the method. The purpose of this study was to evaluate the cardiac involvement such as diastolic dysfunction by standard ECHO in patients with RA and compare the findings in terms of age and presence of concomitant disease.

MATERIAL AND METHODS

The study was designed as a retrospective study. Two hundred of 425 patients with RA diagnosed by the revised American College of Rheumatology classification criteria (9) who had ECHO, were recruited from the rheumatology outpatient department. Those who had an ECHO taken at another center were not included, because it was performed by a different echocardiographer and there was missing data. All ECHO was performed in our center, and at that time only one person used it.

Medical records of RA patients were used to extract the data on demographic information, clinical and laboratory findings. The results of ECHO were analyzed with regard to problems with valves, internal chamber size quantification, and systolic and diastolic functions.

ECHO Assessments

Transthoracic M-mode, 2-dimensional and Doppler ECHO was performed with a Toshiba SSA-390A ultrasound machine using a 2.0-3.7 MHz broadband transducer. The left and right ventricles and left atrium measurements were obtained from a parasternal long-axis view in accordance with the American Society of ECHO recommendation. LV mass was calculated using the Penn-convention method and indexed to body surface area. Left ventricular ejection fraction (LVEF) was determined using the modified Simpson's rule in the apical 2- and 4-chamber views. Trans-mitral flow velocity pattern was evaluated from the apical 4-chamber view with pulsed-wave Doppler placing the sample volume at the tips of mitral leaflets during diastole. Early filling deceleration time (DT), atrial (A) and early (E) peak wave velocities, the E/A ratio, and isovolumic relaxation time (IVRT) were measured on three consecutive beats and averaged (10).

Diastolic dysfunction was defined by determination of relaxation abnormality on mitral flow, and it was defined as an E/A ratio <1 or DT >240 ms in patients ages <55 years and an E/A ratio <0.8 and DT >240 ms in patients ages ≥55 years. IVRT measurement, available for all patients, was >90 ms in all patients with abnormal relaxation. According to these definitions, patients were divided into groups with normal or abnormal diastolic function (10).

Statistical Analysis

Statistical analysis was performed by SPSS for Windows 20.0 version. The normal distribution of numerical variables was evaluated with the Kolmogorov-Smirnov test. Besides descriptive statistical methods (median, min-max, mean ± standard deviation), the independent t-test or Mann-Whitney U test were used for continuous variables in comparison of groups. Chi-square test and Fisher's exact test were used for categorical variables. To find the relationships between variables, Spearman correlation analysis was performed. $p<0.05$ was considered sufficient for statistical significance for testing two-sided hypotheses.

RESULTS

By analyzing the records of follow-up patients with RA in the clinics of rheumatology, 200 patients with ECHO (female/male: 155/45, age range: 57.1±12.1 years, average duration of disease: 108.6±116.0 months) were analyzed. It was found that 67.2% of patients had RF positivity, 58.4% had anti-CCP positivity, and 40% (80 patients) of patients had other accompanying diseases (of these comorbidities, 35.5% was hypertension, 5% was ischemic heart disease, and 14.1% was diabetes).

According to the ECHO findings, a significant proportion of RA patients exhibited cardiac involvement; 12 patients (6%) had systolic dysfunction, 9 (4.5%) had pericardial effusion, 128/188 (68.1%) had diastolic dysfunction, 41 (20.5%) had pulmonary hypertension, and 28 (14%) had valvular disease (mitral regurgitation in 17, tricuspid in 15, aortic in 10, and pulmonary only in one patient were identified). There was spontaneous ECHO contrast in two patients with heart valve prostheses. In addition, increased LV mass, left atrium hypertrophy and right ventricular hypertrophy were found in 162 (81%), 67 (33.5%) and 22 (11%) patients, respectively, and there was no correlation between

these parameters and diastolic dysfunction (p>0.05). Moreover, there was no significant correlation between seropositivity and all ECHO findings, except between anti-CCP and decreased DT (r=0.214, p=0.0013). The comparison of demographic findings by age is given in Table 1.

When the ECHO findings were compared by age (58% were above 55 years old) increased LV mass, left atrial hypertrophy, decreased EF, diastolic dysfunction and pulmonary hypertension were identified more frequent in patients ages ≥55 years (Table 1). Although these increased frequencies of ECHO findings in elderly patients, there was no significant difference in terms of presence of accompanying diseases (Table 2). There was significant increase in frequency of diastolic dysfunction, left atrial and LV hypertrophy in patients with accompanying diseases under 55 years old, as it expected. However, the frequency of diastolic dysfunction and LV hypertrophy were 37.3% and 67.2% in patients without accompanying diseases under 55 years old, respectively (Table 3). In addition, there was no significant difference between the two genders, except the frequency of LV hypertrophy in female patients (female: 71%, male: 46.7%; p=0.003).

When we evaluated the correlation between ECHO findings and demographic features, there was significant correlation between

Table 1. The comparison of echocardiographic findings in terms of ages

n (%)	<55 years old (n=84)	≥55 years old (n=116)	p
Age (mean ± std) (min-max; median)	45.8±6.7 (26-54; 47.5)	65.3±7.7 (55-89; 64)	**0.000***
Gender (female)	62 (74.1)	93 (80)	0.288
Disease duration (mean ± std) (min-max; median)	86.1±93.7 (3-476; 42)	124.7±127.6 (4-602; 85)	**0.009***
Concomitant diseases Diabetes mellitus Hypertension Ischemic heart disease	23 (27.4) 6 (7.1) 21 (25) 2 (2.4)	57 (49.1) 22 (19) 50 (43.1) 8 (6.9)	**0.002*** **0.017*** **0.008*** 0.197ξ
Decreased ejection fraction	1 (1.2)	11 (9.6)	**0.015***
Diastolic dysfunction	37/81 (45.7)	91/107 (85.0)	**0.000***
Left atrial hypertrophy	19 (22.4)	48 (41.7)	**0.006***
Right ventricular hypertrophy	6 (7.1)	16 (13.9)	0.138
Left ventricular hypertrophy	62 (57.6)	100 (71.3)	**0.027***
Pulmonary hypertension	8 (9.4)	33 (28.7)	**0.001***
Deceleration time (minute) (mean ± std)	206.4±35.2	229.0±40.5	**0.000***
LVEF (%) (mean ± std)	69.8±6.7	66.0±12.9	**0.052**
LV mass index (g/m^2) (mean ± std)	146.1±44.6	163.4±62.7	**0.031***
Left atrium (cm) (mean ± std)	3.7±0.4	4.0±0.6	**0.000***
Right ventricles (cm) (mean ± std)	2.3±0.3	2.4±0.3	**0.032***
Pulmonary artery pressure (mmHg) (mean ± std)	27.7±7.7	32.6±10.5	**0.006***

Std: Standard deviation,*: p<0.05, ξ: Fisher's exact test was used, LVEF: Left ventricular ejection fraction

Table 2. The effect of presence of concomitant diseases on echocardiographic changes in patients ages ≥55 years

	Concomitant diseases		
n (%)	With (n=57)	Without (n=59)	p
Gender (female)	48 (84.2)	45 (76.3)	0.745
Decreased ejection fraction	7 (12.3)	4 (6.8)	0.312
Diastolic dysfunction	47/53 (88.7)	44/54 (81.5)	0.297
Left atrial hypertrophy	24 (42.1)	24 (40.7)	0.876
Right ventricular hypertrophy	9 (15.8)	7 (11.9)	0.540
left ventricular hypertrophy	49 (85.9)	51 (86.4)	0.941
Pulmonary hypertension	20 (35.1)	13 (22.0)	0.119

Table 3. The effect of presence of concomitant diseases on echocardiographic changes in patients ages <55 years

	Concomitant diseases		
n (%)	With (n=23)	Without (n=61)	p
Gender (female)	19 (82.6)	43 (70.5)	0.260
Decreased ejection fraction	1 (4.3)	0 (0)	0.274
Diastolic dysfunction	15/22 (68.2)	22/59 (37.3)	0.013*
Left atrial hypertrophy	9 (41.3)	10 (16.4)	0.026*
Right ventricular hypertrophy	2 (8.7)	4 (6.6)	0.734
Left ventricular hypertrophy	21 (91.3)	41 (67.2)	0.025*
Pulmonary hypertension	1 (4.3)	7 (11.5)	0.321

*: p<0.05

decreased EF and age (r=0.17, p<0.014), presence of diabetes mellitus (r=0.22, p=0.002) and disease duration time (r=0.26, p=0.000), and between diastolic dysfunction and age (r=0.41, p=0.000), presence of concomitant diseases (r=0.29, p<0.001) and disease duration time (r=0.18, p=0.016).

DISCUSSION

It has been reported increased mortality rate due to cardiovascular events in RA patients, and many of these patients did not experience clinical cardiac symptoms (1,3,5,11,12). This study evaluated the cardiac involvements by standard ECHO such as valvular diseases, diastolic dysfunction and compared the findings in terms of age and presence of concomitant disease in patients with RA. In our study, diastolic dysfunction was detected in 68.1% of all patients, and was found to be significantly higher in patients over 55 years of age (p=0.00). Moreover, 8.5% of patients had valvular dysfunction, 6% had systolic dysfunction, and 4.5% had pericardial effusion. The prevalence of pulmonary hypertension in our study was found to be 20.5%, similar to a previous study (21-27.5%) (13).

Chronic inflammation causes microvascular and endothelial dysfunction, causing myocardial remodeling and fibrosis, and it is thought that LV dysfunction results from this (14). The prevalence of diastolic dysfunction (detected as relaxation abnormalities during LV filling) in the general population has been reported to be 11-34.7%, and increases with age. It has been defined as one of the important causes of heart failure (6,15-17). Diastolic dysfunction has been demonstrated in many studies at a rate of 55-66% in patients with RA without clinical symptoms (3,5,8,18-20). Dal Piaz et al. (20) published a prospective study analyzing the occurrence of diastolic dysfunction in asymptomatic patients with RA followed for one year. Diastolic dysfunction has been found in 26% of RA patients at baseline, and in an additional 24% after one year, for a total of 60% without cardiac symptoms (20). This finding shows how important close monitoring for diastolic dysfunction is in routine practice. Although, it has been reported that LV wall thickening, high LV mass index, and increased left atrial size are associated with diastolic dysfunction (5,7), in the present study we did not find any correlation between diastolic dysfunction and ventricular and atrial hypertrophy. The sample size of the present study was larger than others [in Arslan et al. (7) study' n=52, in Gonzalez-Juanatey el al. (3) study' n=47], and all patients in these studies were ≥55 years old. It is thought that the current difference may be due to this.

In the study, which included 145 RA patients (83% women), the increase in LV muscle mass was found to be significantly higher in women in the follow-up ECHO. They concluded that women with RA had the strongest association with LV hypertrophy, regardless of the presence of CVD risk factors or RA-specific features (21). In the present study, similar to this study, increased LV mass was detected more in female patients in our study (female: 71%, male: 46.7%; p=0.003).

In a study of eighty RA patients under 55, lower ejection fraction and LV diastolic dysfunction have been found to be more common among the anti-CCP positive patients (p=0.01 and p=0.034, respectively) (22). In another study published in 2016, it was noted that inflammation and anti-CCP status in the assessment of cardiovascular mortality in patients with RA may influence the dynamic changes in LV function over time (12). However, in our study, a significant relationship was detected only between anti-CCP seropositivity and the decrease in DT (r=0.214, p=0.0013).

Unlike other studies, in this study, the patients were also compared according to age groups. It is well known that diastolic dysfunction develops with increasing age (12), and in the present study, the increase in LV mass, left atrial hypertrophy, and diastolic dysfunction were detected more frequently in patients aged ≥55 years. However, there were no differences between with and without comorbidities in ECHO findings such as diastolic dysfunction in this patient group. On the other hand, in the presence of comorbidities, there was a significantly increased frequency of diastolic dysfunction, left atrial hypertrophy, and LV mass in patients under 55. This showed that young patients should be closely monitored for cardiovascular complications, especially in the presence of comorbidities.

Study Limitations

This study had some limitations, including small sample size, the lack of a control group and retrospective design. ECHO is not routinely examined for RA patients in the outpatient clinic. Since ECHO is routinely performed on patients hospitalized during disease diagnosis or disease activation, the patients included in the study generally consisted of this group of patients. This can be considered as another limitation.

CONCLUSION

This study highlights the complexity of cardiac involvement in RA patients and the need for meticulous cardiovascular monitoring, irrespective of autoantibody status. The influence of age, along with the presence of comorbid conditions, underscores the necessity for a holistic approach to the care of RA patients. Considering these multifactorial aspects, timely interventions are essential for mitigating the risk of RA-associated cardiovascular complications. Detecting diastolic dysfunction may help reduce cardiovascular mortality in patients with RA without clinical symptoms.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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INACTIVITY BEHAVIOR AND EXERCISE BARRIERS IN PATIENTS WITH BEHÇET DISEASE

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Abstract

Aim: Impaired quality of life, aerobic capacity, respiratory function and life satisfaction, sleep disorders, depression, anxiety, and fatigue are commonly seen in patients with Behçet disease (BD), similar to other rheumatic diseases. Considering that regular physical activity affects the survival of patients and healthy people, it is important to determine the factors affecting physical activity level and exercise barriers. The purpose of this study was to investigate physical activity levels and exercise barriers in patients with BD.

Material and Methods: Fourty five patients were included in the study. Physical activity level, exercise barriers, fatigue, depression, pain, quality of life, and aerobic capacity were evaluated using the International Physical Activity Questionnaire (IPAQ), Exercise Barriers and Benefits scale, Fatigue Severity Scale, Beck Depression inventory, Behçet Disease Quality of Life Questionnaire (BDQoL), visual analog scale, and 6-min walk test, respectively. Spaerman's correlation coefficient was used to investigate the relationships between exercise barriers and other parameters.

Results: Physical activity levels significantly correlated with both exercise benefits (rho =0.320) ($p>0.05$) and exercise barriers (rho =-0.345). BDQoL scores also correlated significantly with exercise barrier scores (rho =0.338) ($p<0.05$). No significant relationships were observed for the other parameters. Additionally, IPAQ demonstrated that 22 (48.8%) patients had low levels of physical activity.

Conclusion: Considering the negative effects of physical inactivity, patients with BD should be encouraged to exercise. In addition, the reasons for physical inactivity should be investigated.

Keywords: Behçet disease, physical activity level, exercise barriers

INTRODUCTION

Behçet disease (BD) is a chronic, inflammatory, rheumatic disease that is characterized by oral aphthous ulcers and major organ involvement, including the ocular, musculoskeletal, gastrointestinal, and central nervous systems. Gender and the type of organ involvement may affect the prognosis of the disease. While papulopustular lesions and ocular and vascular involvement are more common in male patients, genital ulcers and erythema nodosum are more frequent disease

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manifestations in female patients. BD has a more aggressive course in male patients with early onset of the disease (1).

BD has negative effects on the physical and mental health of patients, resulting in impaired quality of life. When compared with the healthy population, it was observed that fatigue, depression, and anxiety were more frequent in BD patients (2,3). Bodur et al. (4) reported that quality of life, life satisfaction, and psychological well-being were impaired in patients with BD.

Physical activity can be described as all body movements that require energy expenditure over basal metabolism and contraction of the skeletal muscle. Promoting physical activity level is one of the major goals in the management of patients with rheumatic diseases because of the negative impact of sedentary lifestyle due to disease (5). Physical inactivity is a general health problem and a risk factor for some diseases such as coronary artery disease, type II diabetes mellitus, hypertension, and obesity (6). A decrease in the physical activity level in patients with rheumatic diseases has been observed in previous studies. Additionally, reasons for physical inactivity were investigated in these studies and some disease-related and general factors were concluded to reduce physical activity (7-9). Clinical symptoms associated with rheumatic diseases, such as periodic pain, chronic fatigue, depression, and decreased aerobic capacity, are reported to be responsible for physical inactivity (10). Non-disease-related symptoms, such as lack of time, motivation, and family responsibilities, are also responsible for physical inactivity and exercise barriers (11). Individuals with several rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and systemic lupus erythematosus (SLE) were found to be physically inactive due to general barriers as well as fatigue, depression, pain, and morning stiffness (7,8,12). However, to the best of the author's knowledge, no study has investigated physical activity levels and exercise barriers in patients with BD.

Impaired quality of life, aerobic capacity, respiratory function, life satisfaction, sleep disorders, depression, anxiety, and fatigue are commonly seen in patients with BD as in other rheumatic diseases (4,13,14). Because of these symptoms, it is possible and expected that patients with BD have low physical activity levels. The World Health Organization declared that physical inactivity is the fourth most common cause of global mortality and is responsible for three million deaths per year. Considering that regular physical activity affects the survival of patients and healthy people, it is important to determine the factors affecting physical activity level and exercise barriers. Therefore, the aim of this study was to investigate the physical activity level and exercise barriers in patients with BD.

MATERIAL AND METHODS

This study was approved by Gazi University Clinical Research Ethics Committee, referenced 25. An informed consent form was completed by the participants.

Patients: This study included 45 patients who were being followed up at Gazi University Faculty of Medicine, Department of Rheumatology with BD who met the diagnostic criteria proposed by the International Study Group of BD. All patients were in the age of 18-65 years. Patients who were illiterate, pregnant, diagnosed with malignancy, accompanied by any other rheumatic diseases except for fibromyalgia, had changed medical treatment in the last 3 months, and had dysfunction that limited physical activity such as severe neurological impairment, immobility, or cooperation deficits were excluded from the study.

Outcomes: Age, body mass index, vocation, smoking/alcohol habits, drug use, duration of the disease, personal background, and family histories were recorded. Whether patients had an exercise habit or not was also recorded. Physical activity level, exercise barriers, fatigue, depression, disease activity, pain, quality of life, sleep disorders, and aerobic capacity were evaluated in this study.

Physical Activity Level: Physical activity level was assessed using the Turkish version of the International Physical Activity Questionnaire (IPAQ)-Short Form. This questionnaire obtains information about how much time is spent while walking and in moderate and vigorous activities in the last 7 days. There is also a separate section on sitting duration (15).

Exercise Barriers: Exercise barriers were evaluated using the Turkish version of the Exercise Benefits/Barriers Scale (EBBS). It consists of 43 items including benefits of exercise (e.g., I enjoy exercise) and barriers (e.g., Exercising takes too much of my time). Benefits subscale scores range between 29 and 116, whereas barriers subscale scores range between 14 and 56 (16).

To examine the exercise barriers in more detail, the questions in the exercise barriers section of EBBS were divided into five sub-parameters: EBBS Lack of Time, EBBS Fatigue, EBBS Emotional Factors, and EBBS Lack of Support. Results of 4^{th},14^{th},24^{th} and 37^{th} questions were summed and divided to four to calculate EBBS Lack of Time, 6^{th},$19^{th,}$ and 40^{th} questions were summed and divided to three to calculate EBBS Fatigue, 9^{th},$16^{th,}$ and 42^{th} questions were summed and divided to three to calculate EBBS Lack of Facilities, 12^{th} and 28^{th} questions were summed and divided to two to calculate EBBS Emotional Factors, 21^{th} and 33^{th} questions were summed and divided to two to calculate EBBS Lack of Support. The minimum and maximum scores ranged

between 1 and 4 for EBBS Lack of Time, EBBS Fatigue, EBBS Emotional Factors, and EBBS Lack of Support. Higher scores indicate greater perception of barriers to exercise.

Fatigue: The Turkish version of the Fatigue Severity scale (FSS) was used to evaluate fatigue in patients. This scale consists of nine questions; each question is scored from 1 to 7, in which a high FSS score indicates severe fatigue (17).

Depression: Depression was assessed using the Turkish version of the Beck Depression inventory (BDI), which consists of 21 items related to depressive symptoms, such as pessimism, sense of failure, guilt, dissatisfaction, sleep, appetite, and fatigue. Each item is scored between 0 and 3. Higher scores indicate increased severity of depression. According to this scale, 1-10 points are defined as normal, scores between 11 and 16 indicate mild mental distress, 17-20 indicate the patient is at the border points for clinical depression, 21-30 indicate moderate depression, and severe depression scores between 31-40 and 40 points above are interpreted as very serious depression (18).

Pain: The Turkish version of the Short Form McGill Pain Questionnaire was used to evaluate the type and severity of pain. This questionnaire consists of 11 sensory and 4 affective descriptive words. These 15 words are scored between 0 and 4. Therefore, three types of pain scores (sensory, affective, total = sensory + affective) are obtained. In the McGill Pain Questionnaire, the current level of pain is measured by Visual Analog Scale (VAS) and Likert scale consisting of 6 points (0= no pain, 1= mild, 2= irritating, 3= bothersome, 4= terrible, 5= unbearable) (19).

Quality of life: Quality of life was assessed using the Behçet Disease Quality of Life Questionnaire. It consists of 15 items about difficulties in social, psychological, and daily living effects for patients with BD. A higher score indicated a high quality of life level (4).

Sleep disorders: Sleep disorders were evaluated using the Turkish version of the Pittsburgh Sleep Quality Index. It is a self-assessment questionnaire that evaluates sleep quality and disturbances over a 1-month time interval. It consists of 19 self-rated items and five questions rated by bedpartner or roommate, which is not included in the total score. A higher score indicates worse sleep quality (20).

Disease activity: Behçet Disease Current Activity Form (BDCAF) was used to evaluate disease activity (21). BDCAF scores clinical features of patients in the last 4 weeks. It has 12 components: headache, oral ulcer, genital ulcer, arthralgia, erythema, skin pustule, arthritis, nausea/vomiting/abdominal pain, diarrhea or frank blood per rectum, eye symptoms, and nervous and vascular system symptoms. Each component is scored as absent (0 point) or present (1 point), and the final BDCAF score is the sum of all components with a maximum of 12. A Turkish version of BDCAF has been validated (22).

Aerobic capacity: Aerobic capacity was assessed with a 6-min walk test (6 MWT). 6 MWT is the distance required to a fast-paced walk on a flat floor of length 30 m. The aim of the 6 MWT is to walk for as long as the patient can walk in 6 min. Dyspnoea and fatigue levels are recorded at the end of the test (23).

Statistical Analysis

Data analyses were performed using IBM® SPSS® Statistics software (Version 25.0. Armonk, NY: IBM Corp.). The normal distribution of the data was investigated using the Shapiro-Wilk test and histograms. Non-parametric analyses were used for further analyses because the data showed a nonnormal distribution. Continuous variables obtained in the study were expressed as median and Interquartile Range IQR. Categorical variables are summarized as numbers and percentages. Spearman correlation coefficients between subjects' EBBS sub-scores and IPAQ, FSS, BDI, VAS, BDQoL, 6 MWT, BDCAF, and PSQI results. Correlation coefficients were interpreted as excellent (rho> 0.90), good (0.90> rho> 0.71), moderate (0.70> rho> 0.51), fair (0.50> rho> 0.31), and poor (rho≤ 0.30) (24). A p-value of <0.05 was assumed to indicate a statistically significant correlation.

RESULTS

The study was completed with forty-five (18 females, 27 males) participants with a median age of 34.0 (IQR P25/P75: 24.0/44.5). Descriptive analysis showed that 9 of 45 patients had a habit of exercising regularly. Furthermore, three of the forty-five participants' levels of physical activity were high, 20 of the participants had moderate levels of physical activity, and 22 had low levels of physical activity. Details of the descriptive and clinical characteristics of the participants are presented in Table 1.

Correlations between EBBS scores and IPAQ, FSS, BDI, VAS, BDQoL, 6 MWT, BDCAF, and PSQI were analyzed to determine the factors associated with exercise barriers. The results of all correlation analyses are presented in Table 2. There was a significant negative fair correlation between IPAQ and EBBS General Barriers (rho: -0.345, $p<0.05$) and EBBS Lack of Facilities (rho: -0.317, $p<0.05$) scores. IPAQ also positively correlated with EBBS General Benefits score at a fair level (rho: 0.320, $p<0.05$). Significant fair correlations were observed between BDQoL and EBBS General Barriers scores (rho: 0.338, $p<0.05$), BDQoL and EBBS Lack of Time scores (rho: 0.341, $p<0.05$), BDQoL and EBBS

Table 1. Demographics and clinical characteristics of the participants

	Median (IQR P25/P75) or number (%)
Age (years)	34.0 (24.0/44.5)
Height (cm)	170.0 (162.5/178.5)
Weight (kg)	75.0 (68.8/86.8)
BMI (kg/m²)	25.1 (21.5/29.7)
Gender (female/male)	(18/27)
Disease duration (years)	7.0 (4.0/11.7)
Regular exercise (yes/no)	9/36
Pain (VAS)	0 (0/4.0)
EBBS general benefits (sum score) **EBBS general barriers (sum score)** EBBS fatigue EBBS lack of time EBBS lack of support EBBS lack of facilities EBBS emotional factors	99.0 (86.8/1098) 32.0 (23.0/41.0) 3.0 (2.0/5.5) 1.75 (1.0/10.0) 2.5 (1.0/4.0) 3.0 (1.0/4.0) 1.0 (1.0-7.3)
IPAQ (MET-min/week)	495.0 (181.5/1388.0)
IPAQ Level Low (IPAQ score <600) Moderate (600< IPAQ score <3.000) High (3.000< IPAQ score)	 22 (48.8%) 20 (44.4%) 3 (6.7%)
FSS (score)	2.7 (1.9/4.7)
6 MWT (meters)	595.5 (514.5/675.3)
BDI (score)	2.0 (7.0/12.5)
BDQoL (score)	16.0 (10.0/22.5)
BDCAF (score)	2.0 (2.0/3.0)
PSQI (score)	5.0 (3.25/7.0)

IQR: Interquartile range, BMI: Body mass index, VAS: Visual analog scale, IPAQ: International physical activity questionnaire, MET: Metabolic energy equivalent, FSS: Fatigue severity scale, 6 MWT: Six-minute walk test, BDI: Beck depression inventory, BDQoL: Behçet Disease Quality of Life Questionnaire, BDCAF: Behçet Disease Current Activity Form 2006, EBBS: Exercise barriers and benefits scale, P25: percentile 25, P75: percentile 75, PSQI: Pittsburgh sleep quality index, cm: centimeters, kg: kilograms, m: meters

Emotional Factors scores (rho: 0.344, $p<0.05$), and a moderate correlation was observed between BDQoL and EBBS Fatigue scores (rho: 0.535, $p<0.01$). No other significant relationships were determined between EBBS scores and other outcome measurements ($p>0.05$), (Table 2).

DISCUSSION

48.8% of BD patients who participated in our study had low levels of physical activity. In addition, self-reported exercise barriers and benefits were correlated with physical activity level. While no statistically significant correlation was found between EBBS and fatigue, exercise capacity, quality of life, disease activity, and pain, a significant correlation was found between depression and some EBBS subscales (lack of time, fatigue, emotional status, and general barriers). Reasons for willingness to exercise can be psychological status rather than other disease-related barriers in BD patients, according to the present study. Also, beliefs in the benefits of exercise can increase the physical activity level in these patients.

Almost half of the participants were found to have low levels of physical activity in our study, which was not surprising as BD is a rheumatic disease with symptoms affecting daily living. Physical inactivity is a general health problem and is commonly observed in rheumatic diseases. To the best of our knowledge, no study has investigated physical activity levels in patients with BD. Similar to our study, physical activity level was found to be lower in RA, AS, and SLE patients. Some barriers were stated as a reason for physical inactivity in these patients (7,8,12).

Researchers stated that there are many disease-related factors preventing physical activity, such as fatigue, pain, morning stiffness, psychological factors, and general barriers that can be observed in patients or healthy populations, such as demographic features, mentality, environmental factors, and socio-cultural factors (7,8,12). We used EBBS to evaluate the general benefits and barriers of exercise. General exercise barriers were found to be negatively correlated and exercise benefits were positively correlated with physical activity level. In other words, patients who believed in the benefits of exercise were found to be more active and imported less general barriers such as age, socioeconomic status, lack of motivation, and time. This is in accordance with the study of Henchoz et al. (25), where perceived physical and psychological benefits were significantly different between physically active and inactive RA patients. In addition, arthritis-specific situational barriers were found to be higher than the general situational barriers in this study (25). Wilcox et al. (26) investigated perceived exercise barriers, enablers, and benefits among exercising and non-exercising adults with arthritis and determined many benefits and barriers associated with both general and arthritis-specific symptoms. The authors included 68 participants (n=36 for exercisers, n=32 for non-exercisers) and stated physical barriers (pain, fatigue, mobility, and comorbid conditions), psychological barriers (lack of time, motivation, fear, and perceived negative outcomes), social barriers (lack of support, no one to exercise with and competing role responsibilities) and environmental barriers (environmental conditions, cost, and transportation). They also stated some benefits, including physical benefits (symptom

Table 2. Correlation analysis

	EBBS general barrier	EBBS lack of time	EBBS fatigue	EBBS lack of facilities	EBBS emotional factors	EBBS lack of support	EBBS general benefit
Pain (VAS)	.193	.095	.207	.208	.106	.226	-.063
IPAQ	**-.345***	-.214	-.193	**-.317***	-.050	-.089	**.320***
FSS	.253	.128	.227	.154	.106	.222	-.215
6 MWT	-.074	-.160	-.131	-.191	-.041	-.004	.042
BDI	.081	.146	.147	.052	.030	.139	-.214
BDQoL	**.338***	**.341***	**.535****	.163	**.344***	.279	-.050
BDCAF	.067	-.105	-.003	.000	-.035	.179	-.019
PSQI	.097	.107	.128	.033	.146	.106	.022

Spearman's Correlation Coefficient (rho), *p <0.05, **p <0.01, EBBS: Exercise barriers and benefits scale, VAS: Visual analog scale, IPAQ: International physical activity questionnaire, FSS: Fatigue severity scale, BDI: Beck depression inventory, BDQoL: Behçet Disease Quality of Life Questionnaire, BDCAF: Behçet Disease Current Activity Form 2006, PSQI: Pittsburgh sleep quality index

management, mobility, function, strength, flexibility, and weight loss), psychological benefits (independence, emotional beliefs, and enjoyment), and social benefits (26).

Although the positive effects of exercise are known, patients with rheumatic diseases were found to be willing to exercise because of disease-related symptoms. Fatigue (2), sleep disturbance (13), decreased aerobic capacity and pulmonary functions (14), impaired quality of life (4), and depression (27) are commonly seen in patients with BD and are found to be poorer than the healthy population. We investigated and concluded no relationship between EBBS and fatigue, aerobic capacity, sleep quality, pain, disease activity, or quality of life. In addition, some subscales of EBBS (general barriers, lack of time, emotional status and fatigue) were found to be correlated with depression. This result suggests that the reason for willingness to exercise may be psychological status rather than other disease-related symptoms in BD patients. Patients with high levels of depression were found to be more reluctant to exercise. This is an expected result that depression is defined as a mental problem causing energy, concentration, self-reliance, and satisfaction loss. To our knowledge, there is no study in the literature investigating physical activity level and exercise barriers in BD; therefore, we could not compare our results with the literature. However, fatigue, depression, and pain were found to be the reasons for physical inactivity in AS patients (28). Rupp et al. (29) concluded a negative correlation between physical activity level and depression (29), whereas Munsterman et al. (30), found no relationship between these parameters in patients with RA (30). It was stated in a recent study that fatigue may be an exercise barrier in RA patients; however, being physically active , even if feeling tired, can decrease the negative effects of fatigue (10).

The strengths of our study include being the first study investigating physical activity level and exercise barriers in patients with BD using quantitative assessments. In addition, we used IPAQ to evaluate physical activity levels, which allows us to classify patients. However, it can be a limitation not to evaluate other rheumatic diseases such as AS, RA, or SLE as a control group. Further studies may include comparison of physical activity levels between patients with BD and other rheumatic diseases.

In conclusion, 48.8% of BD patients who participated in this study had low levels of physical activity. General exercise barriers and benefits were found to be the reason for physical inactivity. Because physical inactivity is a health problem with many negative effects on health, clinicians should be aware of it. Also, they should investigate and treat the factors preventing physical activity in patients with BD. Patients with BD should be encouraged to exercise. Further studies may investigate the effects of exercise in BD patients.

Ethics

Ethics Committee Approval:

Informed Consent: An informed consent form was completed by the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A., M.A.Ö., Concept: S.B.Y., Design: S.B.Y., D.O., Data Collection or Processing: S.B.Y., D.C.S., F.S., G.T., Analysis or Interpretation: S.B.Y., D.C.S, Writing: S.B.Y.

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LOOKING FROM THE STARS: THE ZODIAC SIGN IN COVID-19 PATIENTS

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Abstract

Aim: The time of birth is a factor that affects the health of the individual. In this study, we aimed to determine whether the birth time and zodiac sign distribution of coronavirus disease-2019 (COVID-19) patients, an immune response-related viral disease that negatively affects life in the world, was different from the general population.

Material and Methods: Three thousand one hundred six patients aged 18 years and older who were treated for COVID-19 infection were retrospectively included in the study. Birth dates and demographic and clinical data of patients were recorded.

Results: Nine hundred sixteen (29.5%) patients were born in spring, 635 (19.2%) in summer, 501 (14.8%) in autumn, and 1,135 (36.5%) in winter. Although births in Turkey were statistically more frequent in the summer and autumn seasons, the proportion of people born in spring and winter was higher in COVID-19 patients. The least common zodiac sign in COVID-19 patients was Scorpio (4.4%), whereas the least common zodiac sign in the general population was Sagittarius (5.4%). Compared with the zodiac map of Turkey, the frequency of Capricorn, Aries, Aquarius, and Pisces was higher in COVID-19 patients. It was noteworthy that the mortality rate in COVID-19 patients was highest in the sagittarius (7.1%) and at least in the libitum (1.8%).

Conclusion: The most common zodiac sign in COVID-19 patients was Capricorn, and the least common horoscope was Scorpio. The mortality rate of COVID-19 patients with Scorpio, Virgo, Sagittarius, Aquarius, and Capricorn signs was found to be higher than the others.

Keywords: COVID-19, immunity, zodiac sign

INTRODUCTION

In a healthy person, the immune system is in balance. The disruption of this balance in the immune system facilitates the occurrence of diseases in different spectrum (1-3). Although the factors that cause immune system disruption are still not fully known, many factors can be effective in etiopathogenesis. Many environmental factors, such as low vitamin D levels, ultraviolet radiation, infections, and melatonin levels, can cause the imbalance of the immune system (4-8). All of these factors can be effective at different seasonal levels. For example, the frequency of infection may increase because of a decrease in vitamin D levels in winter (9).

In the science of astrology, which has kept its mystery for centuries, especially the time of birth (detailed date, day, time, etc.) has become a particular focus of attention. In recent years, medical astrology has increased in popularity by attracting more and more people's attention. Within the Zodiac is the area of the sky where the sun, moon, planets, and stars are located. the

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various characteristics of the signs have emerged as a result of the celestial bodies in the zodiac at the time of birth and the position of these bodies. However, there are limited data on the health effects of zodiac signs. Although our lifestyle, healthy living, and eating habits affect our health, zodiac signs are also claimed to be associated with some diseases (10,11). For example, it is claimed that the most anxious signs of the disease are crab and pisces, the fastest healing sign is scorpio, and the most durable sign is capricorn.

Coronavirus disease-2019 (COVID-19) is still a serious viral disease that results in ongoing mortality and morbidity. In COVID-19 infection, sometimes an asymptomatic or very severe clinical course can be observed in the person's immune system (12,13). Numerous studies have been conducted on risk factors such as gender, age, and chronic diseases that can affect the clinical course of COVID-19, which currently has no effective treatment (14). In addition, the association of COVID-19 infection with autoimmune response is known (13). Considering the possible relationship between seasonal factors and immune response, the effect of seasonality and medical astrology in COVID-19 patients was investigated. For this purpose, in our study, birth seasons and horoscope distribution were investigated in COVID-19 patients who had recovered and died.

MATERIAL AND METHODS

Three thousand one hundred six patients aged 18 years and older diagnosed with COVID-19 at University of Health Sciences Turkey, Elazığ Fethi Sekin City Hospital between April 2020 and April 2021 were included in the study. The age, gender, date of birth, and discharge status were retrospectively scanned from the files of patients hospitalized and treated according to the COVID-19 Diagnosis and Treatment Protocol published by the Turkish Ministry of Health. Patients with a history of Alzheimer's disease, malignancy, and immunological and inflammatory rheumatic diseases were not included in the study. The diagnosis of COVID-19 pneumonia was confirmed by reverse-transcription polymerase chain reaction and computed tomography scans that detected severe acute respiratory syndrome-coronavirus 2 nucleic acid in the nasopharyngeal swab. The dates of birth of the patients were categorized as Capricorn, Aquarius, Pisces, Aries, Taurus, Gemini, Crab, Leo, Virgo, Libra, Scorpio, and Sagittarius, which are known as 12 zodiac signs (15). This study was approved by Fırat University Non-invasive Research Ethics Committee (date: 12.04.2021, approval no: 2021/1757).

Statistical Analysis

The continuous data obtained in the study are presented as mean ± standard deviation. Statistical analyses were conducted using the International Business Machines-Statistical Product and Service Solutions (IBM-SPSS, version 22.0) software (IBM Corp., Armonk, NY, USA). The demographic and clinical characteristics of the groups were determined. The compliance of the data with normal distribution was analyzed using the Kolmogorov-Smirnov test. Analysis of continuous variables with normal distribution was performed using Student's t-test, and analysis of continuous variables not showing normal distribution was performed using Mann-Whitney U test. The continuous data obtained in the study are presented as mean ± standard deviation. The chi-square test was used for categorical data. For dual comparison, the Student's t-test was performed p values <0.05 were considered significant.

RESULTS

Of the 3,106 patients who participated in the study, 1,756 (56.5%) were women and 1,350 (43.5%) were men. The average age of the patients who recovered was 63.2±17.1 [(minimum (min): 18, maximum (max): 100], and the average age of the patients who died was 73.7±11.8 (min: 19, max: 101). The number of patients who recovered was 2,939 (94.6%) and the number of patients who died was 167 (5.4%). Of the patients who died, 104 (62%) were male and 63 (38%) were female. Patients were divided into four groups: spring, summer, autumn, and winter, according to the season in which they were born. Accordingly, 916 (29.5%) patients were born in spring, 635 (19.2%) in summer, 501 (14.8%) in autumn, and 1135 (36.5%) in winter. According to 2010-2019 Turkey birth statistics, 23.8% of births in Turkey occurred in spring, 25% in summer, 27.4% in autumn, and 23.8% in winter, and the seasons where births were most frequent were summer and autumn with a rate of 52.4%. In contrast to these data, 66% of COVID-19 patients were born in spring and winter.

The demographic characteristics of COVID-19 patients in our study according to zodiac sign distribution are presented in Table 1. In our study, Scorpio (4.4%) was the least common zodiac sign in COVID-19 patients, whereas Capricorn was the most common sign (19.3%). The zodiac sign map of Turkey according to population data is given in Table 2 (16). According to this table, the most common zodiac sign in Turkey was Capricorn (13.1%), and the least common sign was Sagittarius (5.4%). Compared with the horoscope map of Turkey, the frequency of Scorpio, Leo, and Virgo horoscopes was lower in COVID-19 patients, whereas the frequency of Capricorn, Aries, Aquarius, and Pisces horoscopes was greater (Figure 1). The mortality rate in COVID-19 patients was 7.1% in Sagittarius, 7% in Capricorn, 2.4% in Taurus, and 1.8% in Libra (Table 1, Figure 2). There were no statistical differences between Libra and Sagittarius in terms of average age and gender (p=0.997 for average age, p=0.132 for gender).

Table 1. The Demographic characteristics of COVID-19 patients by zodiac sign

Zodiac sign	Incidence (%)	Age (years*)	Gender (F/M), n (%)	Mortality, n (%)
Scorpio	136 (4.4)	66.6±14.2	48/88 (35.2/64.8)	9 (6.2)
Leo	148 (4.8)	65.4±14.4	48/100 (32.4/67.6)	5 (3.3)
Virgo	160 (5.2)	67.2±14.2	57/103 (35.6/64.6)	11 (6.5)
Libra	164 (5.3)	66.2±16.1	70/94 (42.6/57.4)	3 (1.8)
Sagittarius	183 (5.8)	65.8±14.9	80/103 (43.7/56.3)	13 (7.1)
Gemini	184 (5.9)	65.4±16.8	68/116 (36.9/63.1)	6 (3.2)
Taurus	228 (7.3)	64.9±16.2	109/119 (47.8/52.2)	6 (2.6)
Crab	266 (8.6)	66.3±15.2	111/155 (43.6/56.4)	14 (5.2)
Aries	325 (10.4)	65.7±15.3	133/192 (40.9/59.1)	19 (4.6)
Aquarius	327 (10.5)	65.7±15.1	143/184 (43.7/56.3)	19 (5.7)
Pisces	388 (12.5)	66.9±14.3	135/253 (34.8/65.2)	20 (5.1)
Capricorn	598 (19.3)	65.6±15.4	245/353 (40.9/59.1)	42 (7)

*The data have been given as mean ± standard deviation

Table 2. The zodiac sign distribution of Turkey according to population

Capricorn n (%)	10,641,392 (13.1)
Crab n (%)	8,564,783 (10.5)
Pisces n (%)	7,770,373 (9.6)
Aquarius n (%)	6,999,345 (8.6)
Taurus n (%)	6,836,049 (8.45)
Aries n (%)	6,804,041 (8.41)
Gemini n (%)	6,146,499 (7.6)
Virgo n (%)	6,128,562 (7.5)
Libra n (%)	5,802,047 (7.1)
Leo n (%)	5,704,819 (7)
Scorpio n (%)	5,014,785 (6.2)
Sagittarius n (%)	4,406,373 (5.4)

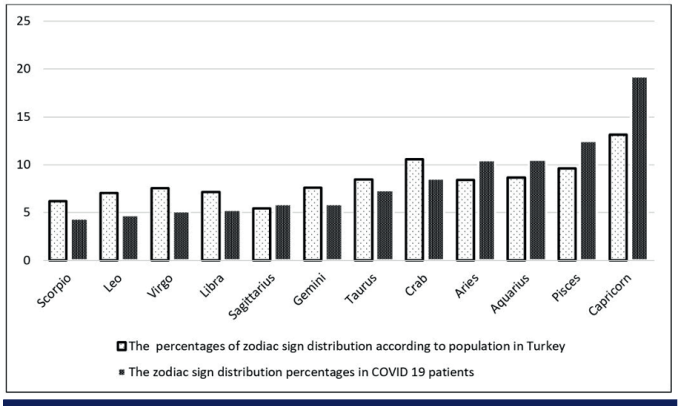

Figure 1. Zodiac sign distribution (%) in the general population and COVID-19 patients
COVID-19: Coronavirus disease-2019

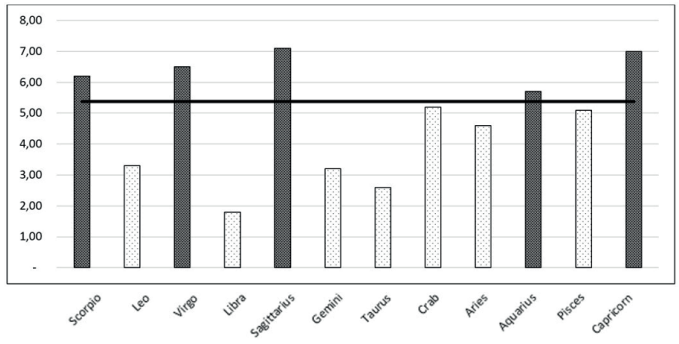

Figure 2. Mortality rates (%) by zodiac sign in COVID-19 patients. In our study, the mortality rate in COVID-19 patients was 5.38%. The mortality rate was above the average in COVID-19 patients with Scorpio, Virgo, Sagittarius, Aquarius, and Capricorn signs
COVID-19: Coronavirus disease-2019

DISCUSSION

The global healthcare system is still severely affected by the COVID-19 epidemic. By April 18, 2021, close to 140 million people worldwide had been infected with COVID-19 and approximately 3 million people had died. Immune-mediated damage seen in the disease adversely affects morbidity and motality (17). The increasing number of cases and deaths due to the epidemic triggers anxiety and stress in humans. In this respect, studies on COVID-19 have attracted considerable attention. Scientists have focused on studies on the diagnosis, prognosis, and treatment of COVID-19. Factors such as male gender, advanced age, comorbid diseases such as diabetes and hypertension, high C-reactive protein, D-dimer, and lymphopenia are known to negatively affect the prognosis of COVID-19 (18). However, most of these

factors are the result of the disease. It is much more important to determine why these factors occur in some patients. Only in this way can effective treatments be developed by determining pathogenetic pathways.

The immune system can be affected in different ways depending on the season. For example, because melatonin levels may decrease in spring, those born during this season may have a higher risk of multiple sclerosis (MS). In those born in summer, the risk of MS disease due to vitamin D height may decrease. However, infectious agents may vary by season. For example, in summer, the risk of *E. coli* infection can increase, which can trigger the risk of primary biliary cirrhosis. In winter, the risk of rotavirus infection may increase, which can trigger type 1 diabetes. As a result, seasonal hormones and infectious factors can facilitate or prevent the formation of certain diseases by affecting immunity even in the womb (19,20). The severity of the immune response in COVID-19 infection may vary.

If the immune system responds excessively, various immune-related diseases, such as vasculitis and macrophage activation syndrome, can be triggered (13). Considering all this information, we conclude that hormonal and immunological factors from the embryological period can be affected by the season cycle. Therefore, whether the prognosis of COVID-19 is related to the time of birth of the individual is a question that needs to be answered. In our study, patients diagnosed with COVID-19 were mostly born in spring and winter. This can be associated with lower vitamin D levels in winter and lower melatonin levels in spring. Studies have shown that more positive results are obtained with supplementation of vitamin D and melatonin for treating COVID-19 (21,22).

Another classification method related to the time of birth of an individual is the zodiac sign. Although it is said that the history of astrology is based on the Assyrian and Babylonian civilizations, it is not known exactly when it emerged. the various characteristics of the signs are related to the position of the celestial bodies in the zodiac at the time of birth. According to medical astrology, signs can be associated with certain diseases (10,11). The number of scientific studies on the relationship between zodiac signs and diseases is limited. In a study, it was shown that there was a relationship between signs and the degree of malocclusion (23). Another study investigated whether the leo sign was a risk factor for heart disease, but no such relationship was found (24). In a different study, it was concluded that the result that survival after stem cell transplantation in patients with chronic myeloid leukemia is related to signs is erroneous (25).

CONCLUSION

In our study, the most common zodiac sign in COVID-19 patients was Capricorn, and the least common horoscope was Scorpio. It was a remarkable finding that the lowest mortality rate in COVID-19 patients compared with the overall mortality rate was found in Libra and the highest mortality rate in Sagittarius. The number of babies born in autumn and summer was less than that born in spring and winter. While the least common sign in patients was scorpio, the least common sign in those who died was libra. These results suggest that the immune system response in COVID-19 disease may change with the season. A broader, multicenter, and randomized study can be conducted to explain this relationship in more detail, and a broader perspective can be provided for COVID-19. The fact that the study was conducted retrospectively and single-center is seen as a limitation in terms of the results.

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Ethics

Ethics Committee Approval: This study was approved by Fırat University Non-invasive Research Ethics Committee (date: 12.04.2021, approval no: 2021/1757).

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Authorship Contributions

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

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ASSOCIATION OF THE PLATALET-TO-ALBUMIN RATIO WITH DISEASE ACTIVITY SCORES IN PSORIATIC ARTHRITIS PATIENTS

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Abstract

Aim: Psoriatic arthritis (PsA) is a chronic inflammatory disease that can cause musculoskeletal involvement in the form of sacroiliitis, spondylitis, enthesitis, dactylitis, and arthritis and can cause disability in patients. PsA does not have a single blood test that can show disease activity; therefore, complex and difficult-to-apply composite indexes are often used in activity tracking. The serum platelet-to-albumin ratio (PAR), calculated as the ratio of one positive and one negative phase response parameter, is a newly defined index and has been shown to be related to activation and disease survival in inflammatory diseases and malignancies. In this study, we investigated the relationship of this index with disease activity and disease processes in patients with PsA.

Material and Methods: The study was conducted on 66 patients diagnosed with PsA according to the CASPAR criteria. Physician global assessment, patient global assessment, Disease Activity in Psoriatic Arthritis (DAPSA), Psoriasis Area Severity Index (PASI), Psoriasis Nail Severity Index (NAPSI), and Leeds Enthesitis Index (LEI) were evaluated. The erythrocyte sedimentation rate, which is a routine test, was measured by the Westergren method (mm/hour), and C-reactive protein (CRP) was measured as nephelometric (mg/dL).

Results: A positive correlation was detected between PAR and DAPSA and CRP levels in patients with PsA ($p<0.05$). In addition, a correlation was detected between the onset of nail disorder and joint pain, but no relationship was detected between the duration of rash. On the other hand, there was no significant relationship between PAR and other measures of disease activity, including patient global assessment, physician global assessment, PASI, NAPSI, LEI, and sedimentation ($p>0.05$).

Conclusion: In this study, we found a significant positive correlation between serum PAR and DAPSA, which is the disease activity score for PsA, and CRP, which is an acute phase marker. These results suggest that PAR may be a biomarker for monitoring PsA activity.

Keywords: Psoriatic arthritis, serum platelet-to-albumin ratio, disease activity index

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis that can cause disability by involving the musculoskeletal system. PsA can cause very different heterogeneous clinical presentations, such as sacroiliitis, spondylitis, peripheral arthritis, dactylitis, and enthesitis, as well as cause many comorbid diseases, especially cardiovascular disease (1). There is no single blood test that can show disease activity in PsA. In addition, because of the heterogeneous nature

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of the disease, different composite indices should be used according to the affected regions. Therefore, intensive studies are required to predict the activity and future course of the disease.

In inflammatory pathologies, platelets increase, indicating an acute phase response. In addition, the relationship between platelet number and function and thromboembolic events is well known. It is known that the risk of cardiovascular events increases with PsA (2).

Albumin is a negative acute phase reactant, and its value can vary in many inflammatory and non-inflammatory conditions throughout the course of the disease. Low albumin levels have been shown to be closely associated with mortality in some diseases and intensive care processes (3).

In addition to the relationship between albumin and platelet levels, each with different disease activations and clinical courses, serum platelet-to-albumin ratio (PAR) has been shown to be associated with survival in many diseases. It has been demonstrated that the pre-operative PAR value, especially in cancer patients, may be a potential prognostic biomarker in cancer patients undergoing primary resection (4-8).

There are limited studies on the PAR index in rheumatic inflammatory diseases. In a retrospective study, a significant correlation was found between PAR and disease activation markers (5). In another study, 198 axial SpA and 48 healthy volunteers were retrospectively examined. PAR, C-reactive protein (CRP), and sedimentation were higher in the axial SpA group than in the control group (6).

Because of the close relationship of PAR with inflammation and the surveillance of other diseases, it can be thought that this index may be associated with disease activity and disease process in patients with PsA. When we searched the common literature, we could not find any study evaluating the PAR value in PsA. This parameter appears to be an inexpensive and easily applicable index that can be obtained from routine blood tests. In this study, we attempted to show the relationship between the platelet albumin ratio in PsA and disease activity scores and disease process.

MATERIAL AND METHODS

This research was conducted by selecting patients who applied to İnönü University Turgut Özal Medical Center Rheumatology Clinic. Patients were selected from among the first 66 patients diagnosed with PsA according to the CASPAR criteria between the specified dates.

Ethics committee approval was obtained from İnönü University Clinical Research Ethics Committee (no: 2019/212, date: 08.01.2020). All patients provided consent for the use of their clinical and demographic data.

The patient's demographic, clinical, laboratory, and medication data were obtained from the patient file and the hospital's electronic information system. The erythrocyte sedimentation rate (ESR) was measured by the Westergren method (mm/h), and serum CRP was measured as nephelometric (mg/dL). The PAR value, calculated from routine tests performed in hospitals, was calculated by dividing the platelet count (10^9/L) by the serum albumin level (g/L).

Previously recorded Disease Activity in Psoriatic Arthritis (DAPSA), Psoriatic Arthritis Response Criteria (PsARC), Psoriasis Area Severity Index (PASI), Psoriasis Nail Severity Index (NAPSI), and Psoriasis Enthesitis Assessment Scale (LEI) were evaluated.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software package version 25 (released 2017, IBM SPSS Statistics for Windows, Version 25.0., Armonk, IBM Corp., NY, USA). Demographic variables were analyzed using descriptive analysis. Conformity to normal distribution was determined by Shapiro-Wilk and Kolmogorov-Smirnov tests. Continuous parameters were compared using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test. A p value <0.05 is accepted as statistically significant.

RESULTS

A total of 66 people, 12 (18.2%) women and 54 (81.8%) men, were included in our study. Fourty-six (69.7%) of the patients were housewives, the rest were workers, farmers, students, tradesmen, and retired. Fourty-nine (74.2%) of the patients had psoriasis, and 17 (25.8%) did not. There was additional disease in 54 (81.8%) patients. The comorbidities were mostly diabetes, hypertension, and hyperlipidemia. Thirteen patients were smokers. Rash was detected in 49 (74.2%) patients. Nail disorder was detected in 32 (48.5%) patients. Enthesitis was observed in 41 (62.5) patients, whereas dactylitis was detected in 31 (47%) patients. Uveitis was detected in 3 (4.5%) patients (Table 1).

There was no significant relationship between PAR value and smoking, body mass index, presence of psoriasis, diabetes, hypertension, presence of hyperlipidemia, presence of nail disorders, presence of enthesitis, presence of dactylitis, presence of uveitis, non-steroidal anti-inflammatory drugs use, disease-modifying antirheumatic drugs use, steroid use, and biological agent use in PsA patients ($p>0.05$).

A positive correlation was detected between PAR, DAPSA, and CRP levels in patients with PsA ($p<0.05$). In addition, a correlation

was detected between the onset of nail disorder and joint pain, but no relationship was detected between the duration of rash. On the other hand, there was no significant relationship between PAR and other measures of disease activity, including patient global assessment, physician global assessment, PASI, NAPSI, LEI, NAPSI, and sedimentation (p>0.05) (Table 2).

DISCUSSION

In this study, a significant positive correlation was found between PAR value and DAPSA, CRP, nail disorder time, and time to start joint pain. However, no correlation was found between PAR and other disease parameters such as ESR.

To date, no single test or biomarker has been identified that is specific enough to diagnose PsA, provide a definitive differential diagnosis from other rheumatic diseases, or indicate disease activity. Acute phase reactants can be seen in 30-40% of patients with PsA. Additionally, leukocytosis, thrombocytosis, and chronic disease anemia may be observed because of this disease activity and inflammation (7). Studies have shown that chronic disease anemia, low albumin, increase in ESR, and CRP fibrinogen levels are associated with disease activity (8). In addition, thrombocytosis can be seen in patients because of the increase in tumor necrosis factor-alpha and Il-6 by triggering inflammation. Some parameters such as rheumatoid factor, antinuclear antibody, and anti-citrullinated peptide antibodies, which may be relatively more specifically positive in other diseases, may be positive in lower rates in patients with PsA.

The PAR, which has been used in recent years, has been reported as a survival indicator in some malignancies. When looking at rheumatic diseases, a limited number of studies have been conducted on ankylosing spondylitis and rheumatoid arthritis (RA). There is no study yet on PsA. In a retrospective study 136 patients with RA and 87 control groups were evaluated (5). While PAR was found to be higher in RA patients than in the control group, albumin was found to be lower. In addition, there was a positive correlation between the PAR value and DAS28, CRP, and sedimentation. In another study, 198 axial SpA and 48 healthy volunteers were retrospectively examined. PAR, CRP, and sedimentation were higher in the axial SpA group than in the control group. Albumin and hemoglobin were found to be lower (6).

In our study, we found that there was no correlation between PAR and physician and patient global assessment, PASI, NAPSI, and LEI scores, whereas there was a correlation with DAPSA scores. This finding may indicate that PAR may be an activity indicator for peripheral joint involvement of PsA but not a biomarker for extra-articular involvement. The correlation between PAR and DAS28 score, which is an indicator of peripheral joint involvement, in RA studies also supports this thesis (5).

Table 1. Demographic, clinical and laboratory information of the patient

	Mean ± SD
Age	48.39±11.36
BMI	30.50±6.51
ESR mm/hour	16.33±13.40
CRP mg/dL	1.01±1.97
Plt/alb ratio	74.19±22.48
Skin rash time (year)	13.79±13.23
Nail disorder time (year)	5.76±8.82
Enthesitis time (year)	3.24±4.83
Dactilitis time (year)	5.03±7.20
Uveit time (year)	2.66±1.15
Patient global assessment	3.09±3.02
Doctor global assessment	2.69±2.21
Dapsa score	13.64±13.50
PASI score	1.55±5.33
LEI score	2.12±2.05
NAPSI total score	14.06±30.66

SD: Standard deviation, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Plt/alb: Platalet/albumin, DAPSA: Disease Activity in Psoriatic Arthritis, PASI: Psoriasis Area Severity Index, LEI: Psoriasis Enthesitis Index, NAPSI: Nail Psoriasis Severity Index

Table 2. Correlation of platelet-to-albumin ratio with clinical variables

	PAR	
	r	p
Patient global assessment	0.110	0.380
Doctoral global assessment	0.112	0.371
PASI score	-0.027	0.832
LEI score	0.200	0.108
NAPSI score	0.040	0.752
DAPSA score	0.254	0.044
ESR	0.224	0.07
CRP	0.327	0.007
Nail disorder time	0.501	0.003
Time to start rash	0.061	0.676
Time to start joint pains	0.319	0.009

PAR: Platelet/albumin ratio, PASI: Psoriasis Severity Index, LEI: Psoriasis Enthesitis Index, NAPSI: Nail Psoriasis Severity Index, DAPSA: Disease Activity in Psoriatic Arthritis, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

CRP is an acute-phase protein released from hepatocytes. Studies have previously shown that there is a correlation between CRP levels, sedimentation levels, and disease activity in patients with PsA (8). In our study, although there was no correlation between PAR and ESR, a positive correlation was detected with CRP. This may be related to the late onset and late regression of the ESR response. In addition, the CRP response occurs quickly. However, the PAR value may indicate PsA activity in its early stages.

In addition, when the skin, joint, and nail involvement time of the disease and PAR ratio were examined, a correlation was found with the onset of nail disorder and joint pain, but not with the time of rash. This situation may be related to the fact that the patients participating in our study work in jobs that require more labor.

Study Limitations

The limitation of our study was the small number of patients. There were not enough patients to analyze the PsA subgroups. The limitations of the study were that most of the patients were follow-up patients and were taking antirheumatic drugs, and there were very few new patients.

CONCLUSION

In this study, we found a significant positive correlation between PAR and DAPSA, which is the disease activity score for PsA, and CRP, which is an acute phase marker. These results suggest that PAR may be a biomarker for monitoring PsA activity. Clinical studies involving more patients are needed for the use of this parameter in clinical practice.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from İnönü University Clinical Research Ethics Committee (no: 2019/212, date: 08.01.2020).

Informed Consent: All patients provided consent for the use of their clinical and demographic data.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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CASE REPORT AND LITERATURE REVIEW

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ANAKINRA-INDUCED PARADOXICAL PSORIASIS AND A CASE REPORT AND REVIEW OF LITERATURE

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Abstract

Familial mediterranean fever (FMF) is the most common inherited autoinflammatory disease and is characterized by recurrent episodes of fever and serositis. Anakinra, an interleukin (IL)-1 antagonist, is commonly used in patients with FMF who are resistant or intolerant to colchicine. In this case, the FMF patient who developed paradoxical psoriasis after the use of anakinra will be discussed. Paradoxical psoriasis is a side effect of drug treatment that results in the formation of psoriasis-like plaques. Paradoxical reactions have been reported with many biological drugs (anti-tumor necriosis factor, IL17, IL-23 inhibitors, etc.) or other classes (e.g. tocilizumab). The etiology of paradoxical psoriasis is not fully understood. Paradoxical psoriasis may be caused by an exaggerated interferon response without T-cell induction. Herein, we describe a rare case that used anakinra and developed palmoplantar psoriasis after a while and evaluate the literature.

Keywords: Anakinra, paradoxial psoriasis, familial mediterranean fever, classical psoriasis

INTRODUCTION

Familial mediterranean fever (FMF) is the most common inherited autoinflammatory disease and is characterized by recurrent episodes of fever and serositis. Anakinra, an interleukin (IL)-1 antagonist, is commonly used in FMF patients who are resistant or intolerant to colchicine. An injection site reaction is the most common side effect of anakinra. It can cause headaches (1), decreased blood cell (2) or platelet counts, headaches, and increased cholesterol levels. There is limited data in the literature about anakinra causing paradoxical psoriasis. Paradoxical psoriasis is a side effect of drug treatment that results in the formation of psoriasis-like plaques on the skin. Although it was initially reported that paradoxical reactions developed only against anti-tumor necriosis factor (TNF) drugs, paradoxical psoriasis has also been shown to develop with all other biological classes. For example: anti-TNF, secucinumab, baricitinib (3), risankizumab (4), ustekinumab, rituksimab, abatacept, tocilisumab, anakinra (5-8). Herein, we describe a rare case that used anakinra and developed palmoplantar psoriasis after a while and evaluate the review of the literature.

CASE REPORT

We present a 33-year-old female patient who was diagnosed with FMF in 2010. In the patient's medical history, it was learned that she had many recurrent peritonitis and arthritis attacks that started 13 years ago, and she was diagnosed with FMF and colochicine treatment was started. There was a good response to colchicine at first. She had no illnesses in her

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medical history. She stated that there was no rheumatological or other disease in his family history, his mother, father, and siblings. Because of the severe abdominal attacks that occurred some time after starting colchicine treatment, a diagnosis of resistant FMF was made and anakinra treatment was initiated. She stated that she benefited from the treatment and that her abdominal pain attacks were gone. There were no problems with the laboratory tests performed after starting anakinra. At the patient's 2-month follow-up visit, there was a pustular psoriasis rash only in the palmar region of the hand. No past personal or familial history of psoriasis was recalled. With dermatological consultation, a biopsy was not needed, and it was decided to discontinue the treatment, considering paradoxical psoriasis developing secondary to anakinra treatment. Blood tests revealed fibrinogen: negative, C-reactive protein: 5 mg/L, and erythrocyte sedimentation rate (ESR): 18 mm/h. Proteinuria was not found. No pathology was detected in the complete blood count and biochemistry tests. Hepatitis markers were negative. The respiratory system, cardiovascular system, and abdominal examination were normal. There were no abnormalities in other rheumatological examinations. With dermatological consultation, a biopsy was not needed, and it was decided to discontinue the treatment, considering paradoxical psoriasis developing secondary to anakinra treatment. The patient was followed closely and canakinumab treatment was initiated. At the outpatient clinic visit 1 month later, rashes in the palmar region of the hands regressed. Paradoxical psoriasis did not develop again. The patient has been receiving canakinumab treatment for several years and has never experienced episodes of abdominal pain.

DISCUSSION

Here we describe a rare case of cutaneous side effects of anakinra, which induced paradoxical psoriasis. This side effect is a well-established phenomenon. Paradoxical psoriasis is a condition that results in the formation of scaly, red, psoriasis-like plaques on the skin after a period of treatment with certain medications. In paradoxical psoriasis, the palmoplantar area is often affected and it also has many forms. For example, it can be found in plaque type, guttate, pustular forms, and eczematiform forms. Paradoxical psoriasis is caused by the absence of TNF and represents an ongoing IFNα-driven acute immune inflammation independent of T-cells (6). Anakinra exhibited a higher rate of skin reactions than placebo in the clinical trial. The pathomechanism underlying paradoxical psoriasis due to anakinra treatment is difficult to explain. It showed overexpression of IL-1ra, whose action was mimicked by anakinra, in the psoriatic epidermis compared with the normal epidermis (7).

Furthermore, this resulted in a 10-fold increase in the amount of IL-Ira relative to IL-Ia in psoriatic lesions compared with normal skin (9). The increased expression of IL-1ra protein in the lower level of the lesional psoriatic epidermis may represent activation of IL-1ra in concert with other terminal differentiation-associated proteins. Alternatively, a possible explanation would be that, considering that IL-1 is a control point in the regulation of the immune response, reduction in the level of IL-1 signaling may have effects on other cytokines or regulatory cells involved in the pathogenesis of psoriasis (5).

It is unusual for it to cause paradoxical psoriasis. The estimated prevalence of paradoxical psoriasis in patients taking anakinra is unknown. Studies are needed to understand it better. There are few epidemiological data on paradoxical psoriasis in the literature. Table 1 shows a summary of the published cases of IL-1 inhibitor-associated paradoxical psoriasis in the literature (5,8).

As mentioned above, this is a very common side effect, but it has been observed to regress with discontinuation of the drug. Studies in the literature have reported that approximately 50% of cases improve or disappear after discontinuation of the biological drug. In the other 50%, these lesions persisted or appeared again. Discontinuing the medication causing paradoxical psoriasis, taking a break, or switching to another

Table 1. Literature review of IL-1 inhibitor-associated paradoxical psoriasis

Year, author	Age (years), gender	Disease	Location	Onset	Treatment	Outcome
Our study	33, female	FMF	Hands	2 months	Discontinuation of anakinra	Psoriatic lesions improved significantly
2022, Bauer-Alonso et al. (8)	74 , female	Schnitzler's syndrome	Lower limbs	1 month	Acitretin 35 mg/day) was added to anakinra	Psoriatic lesions improved significantly
2008, González-López et al. (5)	75, female	Rheumatoid arthritis	Elbows	9 months	Discontinuation of anakinra, topical steroids, and vitamin D	Psoriatic lesions improved significantly

FMF: Familial mediterranean fever

agent is an option that should be considered on a case-by-case basis. Although there is not strong evidence, there is a risk of paradoxical psoriasis development with the administration of the same biological. For cutaneous paradoxical reactions, symptom-based scores such as severity of involvement, itching, pain, and patient-reported quality of life indexes should also be evaluated. Topical or systemic treatments that are effective on the skin should be planned. Topical corticosteroids, keratolytic agents, and immunomodulators may be preferred among topical treatment options. In cases of severe paradoxical reactions (body psoriasis area >10%), traditional agents such as phototherapy and methotrexate, cyclosporine, retinoids, and oral corticosteroids may be considered.

CONCLUSION

Paradoxical psoriasis should definitely come to mind in inflammatory skin lesions that develop while using biological or other drugs. Skin biopsy should be considered in terms of differential diagnoses and should be evaluated together with dermatology. As mentioned in this case, it should not be forgotten that paradoxical psoriasis develops as a side effect of anakinra.

Ethics

Informed Consent: Written consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.A., Concept: F.A., Design: F.A., Data Collection or Processing: I.I., Analysis or Interpretation: I.I., Literature Search: I.I., Writing: I.I.

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CASE REPORT AND LITERATURE REVIEW

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INFLIXIMAB TREATMENT OF CROHN'S DISEASE AND SECONDARY AMYLOIDOSIS: CASE REPORT AND LITERATURE REVIEW

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Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that affects the digestive system from the mouth to the ans. Joint involvement is common among extraintestinal findings. Renal involvement is seen in IBD and often in the form of nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, and amyloidosis. Secondary amyloidosis is a rare but serious complication of CD. In this case report, we present a 58-year-old male patient with CD who developed nephrotic syndrome due to renal amyloidosis. Renal functions and general condition of this patient, who was being treated with infliximab (IFX), were good in the follow-up. Here we review similar cases with successful treatment with IFX. In this case, we wanted to emphasize the early recognition of amyloidosis and rapid initiation of IFX treatment.

Keywords: Crohn's disease, renal failure, amyloidosis, infliximab

INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) in which transmural inflammation can affect the digestive tract, from the oral cavity to the anus, and is characterized by skip lesions. IBD is a multisystemic disease, with extraintestinal manifestations ranging from 21% to 36%. The most frequently involved organs are the joints (peripheral arthritis, sacroiliitis, ankylosing spondylitis), skin, eyes, liver, and biliary tract (1).

The intestinal joint relationship was first described in 1922, and the presence of sacroiliitis in patients was also described in the late 1950s (2). Intestinal dysbiosis and increased intestinal permeability due to local inflammation are believed to play a role in this pathogenesis. Luminal epithelial inflammation initiates an inflammatory cascade, followed by the translocation of immune complexes to the joints. Most extraintestinal manifestations are directly related to ongoing intestinal activity (3).

Chronic diarrhea, bloody stools, abdominal pain, fever, weight loss, weakness, and perianal disease (pain, abscess, or fistula) can be seen in the IBD clinic. In the laboratory, elevated acute phase reactants, anemia, low albumin, and electrolytes are also clinical findings (1,4). Renal involvement is seen in patients with IBD and is often in the form of nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, and amyloidosis (5). Amyloidosis occurs when insoluble fibrillar proteins aggregate in the extracellular tissue of various organs and eventually cause dysfunction. Secondary amyloid A (AA) amyloidosis can occur as a result of many chronic inflammatory diseases, including IBD. The incidence of secondary AA amyloidosis varies from 0.3% to

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10.9% in patients with CD. Amyloidosis is a rare but important complication, and the presence of renal amyloidosis may be more prognostic than the underlying disease (6).

Here, we present a male patient with CD who first presented with arthritis and then developed nephrotic syndrome due to renal amyloidosis. He was successfully treated with infliximab (IFX) with a good response and absence of complications.

CASE REPORT

A 58-year-old male had right knee pain and swelling as the first complaint, which started 10 days ago and gradually increased. In his history, knee pain was severe in the mornings and was accompanied by stiffness for approximately an hour. He stated that he took painkillers when his pain was severe and benefited from them. The patient had no history of trauma, infection, or family history of autoimmune or autoinflammatory disease.

On musculoskeletal examination, the bilateral knee was painful and swollen with movement, consistent with active arthritis. The patient's left knee effusion was aspirated by ultrasonography, and fluid analysis (culture-staining-crystal) was performed. Septic arthritis was ruled out, and no crystals were found.

Laboratory examinations showed moderate leukocytosis and rising levels of erythrocyte sedimentation rate: 67 mm/hour (n=0-20) and C-reactive protein (CRP): 19.8 mg/dL (n=0-5). Blood urea nitrogen, creatinine, and liver function tests were all normal, and rheumatoid factor and anti-cyclic citrullinated peptide tests were negative.

A non-steroidal anti-inflammatory drug was started with a preliminary diagnosis of undifferentiated peripheral arthritis. Due to bilateral ankle swelling in the follow-ups, sulphasalazine (500 mg 2x2/day) was added to the treatment. Two months later, when the patient's arthritis persisted and he could not tolerate sulphasalazine well, he was treated with methotrexate (15 mg/week).

The patient was referred to gastroenterology after 2 months because of weight loss (6 kg/month) and diarrhea. The patient who did not undergo colonoscopy had severe abdominal pain, watery diarrhea 7-8 times a day, and a weight loss of approximately 15 kg after three months. In the laboratory values of the patient, was 716 U/L and lactate dehydrogenase was 405 U/L. Human leukocyte antigen was negative. Abdominal computed tomography showed that the liver size increased by 20 cm, and intra- and extrahepatic bile ducts were evaluated as normal. He underwent endoscopy and colonoscopy. Endoscopy was within the normal range. Colonoscopy revealed edematous and hyperemic descending colon mucosa and rectosigmoid colon. Histopathological examination showed ulcerous inflammation in a microscopic focus and reactive and hyperplastic changes in a few crypts around the ulcer. A diagnosis of CD was made for the patient, who was managed with corticosteroids followed by azathioprine (2.5 mg/kg).

The patient was followed up for 6 months until he was admitted again because of weight loss (10 kg/month) and peripheral edema in both lower extremities. Laboratory examinations revealed creatinine levels of 2.21 mg/dL and urinary protein excretion of 6.98 g/day. The serum albumin level was 2.4 g/dL. A kidney biopsy was performed because it was suspicious of secondary amyloidosis. Congo red-stained cells were examined by light microscopy and polarized light, which showed amyloid deposits. He was treated with intravenous IFX (5 mg/kg at 0, 2, and 6 weeks). The patient has been receiving IFX treatment regularly for three years. While serum creatinine (2.35 mg/dL) was at the same level, urinary protein excretion (3.7 g/day) also decreased; before treatment, it had been 6.98 g/day. The patient's clinical and general condition has been good since treatment.

DISCUSSION

Crohn's disease is characterized by chronic recurrent intestinal inflammation and is among the spondyloarthritis (SpA) group of diseases known as enteropathic arthritis. In SpA patients, 25-49% of subclinical inflammation is seen with ileocolonoscopy, and this rate increases to 50-60% with microscopic examination (7).

Findings of chronic inflammation in SpA, high CRP levels, radiological sacroiliitis, and peripheral arthritis are considered risk factors for IBD (8).

Musculoskeletal manifestations occur in approximately 40% of patients with IBD and are the most common extraintestinal manifestations. Peripheral arthritis is seen in 20% of Crohn's patients and is classified as type 1 or type 2 peripheral arthritis. In type 1 peripheral involvement, oligoarticular involvement is mostly seen in the lower extremities (most commonly the knee and ankle), and it is a self-limited, non-erosive type of involvement that is closely related to intestinal activity (3,9). Our patient was diagnosed with IBD, which started with monoarthritis and then continued with oligoarthritis in the lower extremity. In this state, there was a clinical similarity to type 1 arthritis. The patient did not describe inflammatory lower back pain, and there was no axial involvement in his imaging.

His general condition deteriorated while he had been followed up for CD, and his treatment was changed when renal AA amyloidosis was detected on suspicion of amyloid secondary to inflammation. Secondary amyloidosis, especially secondary to familial Mediterranean fever, is a rare but serious complication

that can worsen the prognosis of patients with cancer, infection, or chronic inflammatory disease, including IBD and CD. The relationship between IBD and amyloidosis was first described in 1936 (10).

The time interval between the onset of IBD and AA diagnosis is different. In IBD, secondary amyloidosis occurs because of long-term uncontrolled inflammation. AA is usually diagnosed 10-15 years after the diagnosis of IBD, sometimes discovered at the same time as IBD, and rarely identified before the onset of IBD (11).

Anti-tumor necrosis factor (TNF) agents can improve amyloid nephropathy in inflammatory diseases through two mechanisms: 1) by reducing glomerular inflammation and the increase in glomerular permeability to albumin induced by TNF cytokines and interleukin-6; and 2) by reducing the synthesis of acute-phase proteins mediated by the same cytokines.

Basturk et al. (12) predicted secondary amyloidosis to occur as an early complication of CD based on the fact that hypoalbuminemia and proteinuria were detected in a 31-year-old male patient approximately one year after initiation of gastrointestinal therapy.

Amyloidosis is frequently described as a major cause of death in patients with CD, with long-term mortality between 40% and 60% (13). Although there is no definite cure for amyloidosis, the main treatment is to control the disease that causes chronic inflammation, which is a constant source of serum AA. Various therapeutic interventions have been tried, such as azathioprine, colchicine, dimethyl sulfoxide, IFX, and elemental diets, but there is no definitive cure for secondary amyloidosis in CD. Renal transplantation may offer the best prospect for patients who have developed amyloidosis (12,14). Anti-TNF therapy has been an important agent used in CD for a long time. The characteristics of three cases treated with IFX after amyloidosis secondary to IBD (CD) are summarized in Table 1.

In the first case, in which successful results were obtained with the IFX treatment presented by Park et al. (15), amyloidosis was observed differently in the thyroid. Our case was older than the other cases, and the difference between the time of renal amyloid occurrence and the age at diagnosis of the disease was much shorter than that of the other cases.

In the second case, Cabezuelo et al. (16) found that amyloidosis and CD were diagnosed simultaneously, although minor and non-specific digestive manifestations had been present for

Table 1. Comparison of clinical and laboratory features of the patients

	1	2	3	Our case
Age/gender	34-year-old male	33-year-old male	24-year-old male	61-year-old male
Age at diagnosis of IBD	23	18	18	58
Clinical findings	Diffuse abdominal pain, watery diarrhea, and peripheral edema in both lower extremities	Iron-deficiency anemia, gastroesophageal reflux, and postprandial heaviness, without any other gastrointestinal manifestations	Terminal ileitis and right-sided colitis complicated with pararectal fistula, persistent abdominal pain, anemia, and marked peripheral edema in the lower extremities developed due to hypoalbuminemia, small ascites, diarrhea, and severe malnutrition	Lower extremity oligoarticular involvement, followed by diarrhea and weight loss, and peripheral edema in both lower extremities
Laboratory findings	The size of the right lobe of the thyroid was 8.5 cm, and the left was 7.5 cm Proteinuria was 7.3 g/day with a decreased creatinine clearance of 40.4 mL/min	Cr: 1.47 mg/dL; eFGR: 59 mL/min/1.73 m proteinuria: 200 mg/24 hours	Serum amyloid A protein level was increased to 1.082 mg/L, CRP level was increased to 13.0 mg/L, and serum creatinine level was 0.88 mg/dL	Cr: 2.21 mg/dL; urinary protein excretion was 6.98 g/day.
Prior treatments	5-ASA, azathioprine, and metronidazole	Azathioprine at 1-1.5 mg/kg/day	5-ASA and azathioprine	Sulphosalazine, methotrexate, and corticosteroids were followed by azathioprine (2.5 mg/kg)

Table 1. Continued

Amyloid involvement sites	The kidney, colon, and thyroid revealed AA-type amyloid deposits	Renal AA amyloidosis	Renal AA amyloidosis	Renal AA amyloidosis
Time between IBD symptom onset and amyloid development	11 year	15 year	6 year	3 year
Patient's condition after treatment	Improvement of renal function and proteinuria, reduction of thyroid mass, and decrease of SAA protein level	The renal parameters improved, with no major complications of CD or side effects. from the medication	Significant improvement after IFX induction therapy: SAA protein level decreased to 22.5 mg/L (by 97.9%) and CRP to 3.9 mg/L (by 70%); there had been no notable changes in proteinuria (13.2 g/day), but significant reductions in renal function had been noticed during the treatment; a progressive increase in Cr level to 3.69 mg/dL	While Cr. (2.35 mg/dL) was at the same level, urinary protein excretion (3.7 g/day) also decreased The patient's clinical and general conditions were good

IBD: Inflammatory bowel disease, eFGR: Glomerular filtration rate, CRP: C-reactive protein, Cr: Serum creatinine, 5-ASA: 5-aminosalicylate, SAA: Serum amyloid A, IFX: Infliximab, CD: Crohn's disease, AA: Amyloid A

several years. Here, it was emphasized that CD extraintestinal involvement played an important role in the development of amyloidosis, similar to the previous oligoarticular involvement in our patient.

In the third case, a younger patient first developed a pararectal fistula at the age of 18 years. Amyloid-related nephrotic syndrome has emerged. After IFX induction therapy, serum amyloid levels decreased, but proteinuria (13.2 g/day) continued. As can be seen, the other cases were younger than our patient. In our patient, the time between CD and secondary amyloidosis was shorter than that in other cases. All patients tolerated IFX treatment well.

CONCLUSION

Secondary AA amyloidosis may occur because of many inflammatory diseases, and there are opinions that the relationship may be more common in chronic diseases than previously thought. Renal amyloidosis is a serious cause of mortality. Therefore, close monitoring of the clinical situation and regular urine testing for proteinuria will be helpful for the early diagnosis of amyloidosis in CD. Early recognition of amyloidosis and appropriate treatment of the underlying disease are essential.

Ethics

Informed Consent: Informed consent was obtained verbally and in writing from the patient and his relatives.

Authorship Contributions

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

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