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TURKISH JOURNAL OF INTERNAL MEDICINE
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Systematic Review

Nursing Education and Stress

Yasemin KARACAN[1], Hicran YILDIZ[1]

[1]Bursa Uludag University, Health Science Faculty, Bursa, Turkey

ABSTRACT

It is necessary to provide a nursing education that includes sufficient theoretical and practical teaching to respond to society's health problems and needs and train nurses who are open to learning and aware of their social responsibility. Students may face various interpersonal and environmental stressors during their nursing education that affect their learning and performance. Students experience different levels of anxiety and stress during their nursing education. Nursing students' fear of failing exams and problems caused by the professor, team conflicts in the clinical environment, difficulties experienced during patient care, pain and suffering of patients, lack of knowledge, inability to cope in emergencies, the attitude of clinical staff to the student, theoretical training in the clinic problems such as incompatibility are cited as a source of stress. Students can give physiological, emotional, and behavioral reactions due to the stress they experience. Stress in the nursing education process can negatively affect students' learning and performance.

Individuals use different methods of coping with stress, depending on their characteristics. Effective use of coping strategies with stress contributes to the successful coping of stressful situations that individuals encounter in their lives. This review was conducted in order to draw attention to the stress experienced by students during their nursing education and the approaches to control this stress.

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Keywords: *Nursing eductaion, stress, coping with stress.*

Introduction

Nursing education is a training program that includes sufficient theoretical and practical training to respond to society's health problems and needs and to train nurses who are open to learning and are aware of their social responsibility.[1] Student experiences different levels of anxiety and stress during their nursing education.[2] For nursing students, fear of failing exams and problems caused by the professor, team conflicts in the clinical environment, difficulties experienced inpatient care, pain, and suffering in patients, lack of knowledge, inability to cope

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Address for Correspondence:
Hicran Yildiz

Bursa Uludag University, Health Science Faculty, Bursa, Turkey
E-mail: hicran_yildiz@yahoo.com

in emergencies, the attitude of clinical staff to the student, theoretical training in the clinic problems such as incompatibility are cited as a source of stress. Stress in the nursing education process can negatively affect students' learning and performance.[3] In the event of intense stress, students' correct thinking and decision-making process deteriorate, their motivation is negatively affected, and their academic success may decrease. Therefore, it should be ensured that the stress in nursing students is kept at the desired level. The desired stress level is the low-stress level that has a motivating effect on students, can be controlled, and appropriate coping methods are used.[4]

When nursing students begin to take responsibility for patient care, they experience high-stress levels due to the intense academic and emotional demands. This stress experienced while the student is studying at school can continue when working as a professional nurse.[5] This review was conducted to draw attention to students' stress during their nursing education and the approaches to control it.

Factors Causing Stress

During nursing education, students may be faced with various individual, interpersonal and environmental stressors, including physical, psychological, social, spiritual, clinical environment, and situational, affecting their learning and performance.[6]

Individual Factors

It is seen that individuals with high levels of psychological resilience experience less anxiety and have a higher sense of self-confidence.[7] Psychological resilience is a concept that expresses individual characteristics such as premature birth, negative life experiences, and chronic diseases; It can also be affected by external factors at any stage of the developmental period. Many environmental factors such as family environment, social support, school success, peer relationships, and socioeconomic status affect resilience.[8] Nursing students with limited resilience capacity may be more vulnerable to negative psychological consequences such as anxiety and depression.[5] However, to be successful in the nursing profession, resilience capacity must be high.[9] In their study of Chinese nursing students, Smith and Yang found that psychological well-being was impaired in senior students.[10] Many researchers recommend training students on resilience before nursing education and developing strategies to learn how to cope with stress.[11] It is stated that there is a significant, positive, and weak relationship between the students' psychological resilience and academic self-efficacy who can identify the risk factors for students related to the concepts of psychological resilience and academic self-efficacy, or support the increase of their awareness of protective factors. It has been suggested that this situation may play an essential role in increasing psychological resilience in the face of difficulties experienced by student nurses.[12,13]

Interpersonal Factors

In addition to the above-mentioned risk factors for psychological resilience, protective factors are also important. Protective factors are factors that prevent the occurrence of risky situations, reduce the effects of negative consequences, increase the individual's emotional and physical well-being, and ensure success in the individual's life. Individual/internal protective factors; includes characteristics such as being physically, mentally, and socially healthy, intelligence, high self-esteem, self-efficacy, self-confidence, effective communication, and problem-solving skills.[13] Academic stress is thought to occur among nursing students due to the clinical learning environment and interpersonal relationships. Teacher-student relationships are another source of stress for many students, and adequate support should be provided for students in clinical practice.[14] While providing this support to nursing students, it is necessary to establish positive interpersonal relationships, flexible, critical, and creative thinking, self-efficacy, using humor, emotional intelligence, and developing skills. This positively affects students' coping.[15]

Environmental Factors

Environmental protective factors can be listed as a supportive society, developed socioeconomic level, positive school relations, peer support, being in the social environment, and getting a good education. Therefore, resilience is a process

that is directly affected by the interaction of risk and protective factors.[16,17] Clinical practice is an education in which students develop their problem-solving skills, learn about the multidisciplinary team approach, the principles associated with being in the clinic, the holistic approach, and the roles of their colleagues.[6] However, although clinical practice areas are an indispensable part of students' professional knowledge and skills development, they are also an important source of anxiety and stress.[3]

Stress-Related Reactions

Students can give physiological, emotional, and behavioral reactions due to their stress.[18]

Physiological Reactions

Physiological reactions such as headache and back pain, sleep disturbance, gastrointestinal changes, fatigue, decrease in energy, tachycardia, increase in blood pressure, sweating in the palm, itching occurs.

Emotional Reactions

Emotional reactions such as lack of attention, decreased self-esteem, loss of meaning in life, lack of control or need for too much power, negative thoughts, difficulty in making decisions, anxiety, change in mental state, nervousness, decreased self esteem, burnout, crying and anger bursts.

Behavioral Responses

With withdrawal and socialization problems; They show behavioral responses such as alcohol, nicotine, or drug use, eating too little or too much, accident-prone and careless, impatient, aggressive (such as swearing, hitting, breaking), and impaired time management.

Approaches to Coping with Stress

Individuals use different methods of coping with stress, depending on their characteristics. Effective use of coping strategies with stress contributes to the successful coping of stressful situations that individuals encounter in their life.[3] In Reeve *et al*.'s statement on undergraduate students' approach to cope with stress in the clinic, students stated that they feel better when they talk to someone who is faced with the same situation.[5] In the same study, it was found that students applied positive stress coping strategies such as meditation, running, taking a shower, and listening to music. Besides, psychological well-being can be increased by encouraging students to have a quality sleep, regular exercise, leisure time activities, and a balanced diet.[19] Silva *et al*.[20], in their study, stated that nursing students should be informed that they can provide their sleep arrangements with cognitive and behavioral interventions and that programs that can help improve their sleep quality should be implemented. They stated that this situation is a determining factor in minimizing stress and anxiety related to academic performance.

Curriculum and theoretical knowledge play an essential role in reducing the stress experienced during clinical practice.[2] Educating students in the nursing curriculum to develop reasoning skills and to be proactive, resourceful, and collaborative is a factor that increases psychological resilience. It is believed that when strategies such as critical case analysis and clinical skills teaching sessions are applied with online education and information, nursing students will be able to overcome difficulties and maintain positive psychological well-being during their education.[19] Stressful life events and coping styles experienced by the individual may differ according to culture and ethnicity. Hypersensitive individuals have emotional reactions, evaluate events as good or bad, and have passive and immature personality traits that fail to cope with stress. Individuals with assertive personality traits mostly use active planning, which includes rational steps and methods for problem-solving in coping with stress.[21,22]

In cases such as the students' physical field problems in their educational institutions, the absence of skill laboratories, and the inability to perform the application in laboratory conditions, readiness cannot be provided, and a lack of self-confidence arises. In this case, clinical practice becomes a stressful factor for the student.[22] Nursing education includes practical experiences such as clinical practice and simulation to develop students' professional competencies. Simulation and clinical practice are essential components of the nurse to nursing students to better prepare

for the transition from student to post-graduate work.[23] According to the pre-clinical learning needs, the simulation of practices such as patient care, intervention, and communication performed by the instructor in a planned, predictable and controllable environment enables students to develop an interprofessional team approach, allow students to make mistakes, and learn from them, and increase the skill through repeated practice.[23] Thus, the student's stress level regarding clinical practice decreases.[24] To increase nursing students' success during clinical practice, it is recommended to increase simulation training before and during clinical practices and implement resilience-building strategies (such as reflection, training, and support) in the nursing curriculum.[11]

Problems may also occur due to the high number of students in clinical practice, other faculty students in the same clinical practice environment, the lack of sufficient application areas, and the team's acceptance by the team reduced. This situation causes an increase in the stress level in nursing students.[22] Ensuring the effective use of clinical application areas causes a decrease in students' stress levels.[18] The use of different nursing education models such as the Collaborative Clusters Training Model (CCTM) is recommended for effective use of clinical practice areas. The Collaborative Clusters Education Model (CCEM) is an educational model that allows students to easily follow their clinical practice experience, position students close to the clinical nurse, and present their experiences to learners individually and in small groups by an experienced nurse or instructor.[25]

Instructors working in nursing programs should help students successfully cope with stress during their undergraduate education. Instructors should know their roles in support systems developed for coping with stress for students. Reeve *et al*.'s study, the student statement, "This was the death of my first patient, and I felt that my clinical instructor did not understand how the incident affected me", expresses the clinical instructor's ignoring the undergraduate student's affections towards death, is a good example showing the importance of the role of the instructor in support systems.[5]

Conclusion

During nursing education, students may be faced with various individual, interpersonal and environmental stressors, including physical, psychological, social, spiritual, clinical environment, and situational, affecting their learning and performance. This stress may occur due to lack of professional knowledge and skills, fear of making medical mistakes, heavy workload, social problems, exposure to the death of patients. Students can give physiological, emotional, and behavioral reactions due to the stress they experience. Stress can cause disruption in the correct thinking and decision-making process, decrease motivation, and decrease academic success. It can be suggested that nursing students should be trained in the curriculum to develop reasoning skills and be proactive, resourceful, and collaborative from the first years of nursing education, including psychological resilience, and continue at regular intervals. Thus, it is recommended to teach the students coping methods with stress and implement stress reduction interventions.

Conflict of Interest

Authors have no conflict of interest to declare.

Authors' Contribution

Study Conception: HY, YK; Study Design: HY, YK; Literature Review: HY, YK; Manuscript Preparation: HY, YK; Critical Review: HY.

References

1. Kaya H, Ulupınar S, Şenyuva E, Bodur G, Küçük N. Hemşirelikte Eğitim Süreci. İstanbul Üniversitesi Açık ve Uzaktan Eğitim Fakültesi Ders Notu. Available at: http://auzefkitap.istanbul.edu.tr/kitap/hemsirelik_ao/hemsirelikteegitimsureci.pdf. Accessed February 10, 2021.
2. Karaca A, Yıldırım N, Ankaralı H, Açıkgöz F, Akkuş D. Perceived level of clinical stress, stress responses and coping behaviors among nursing students. J Psy Nurs. 2017;8(1):32-9. doi: 10.14744/phd.2017.22590.
3. Van Hoek G, Portzky M, Franck E. The influence of socio-demographic factors, resilience and stress reducing activities on academic outcomes of undergraduate nursing students: A cross-sectional research study. Nurse Educ Today. 2019 Jan;72:90-6. doi: 10.1016/j.nedt.2018.10.013.
4. Çapık C, Durmaz H, Öztürk M. Nursing students' styles of coping with stress and factors that affect them: The case of Nicosia. Journal of Anatolia Nursing and Health Sciences. 2017;20(3):208-16 (in Turkish).

5. Reeve KL, Shumaker CJ, Yearwood EL, Crowell NA, Riley JB. Perceived stress and social support in undergraduate nursing students' educational experiences. Nurse Educ Today. 2013 Apr;33(4):419-24. doi: 10.1016/j.nedt.2012.11.009.
6. Alkan SA, Özdelikara A, Boğa NM. Determination of nursing students' health perception. GümüÇhane University Journal of Health Sciences. 2017;6(2):11-21 (in Turkish).
7. Abdollahi A, Abu Talib M, Yaacob SN, Ismail Z. Hardiness as a mediator between perceived stress and happiness in nurses. J Psychiatr Ment Health Nurs. 2014;21(9):789-96. doi: 10.1111/jpm.12142.
8. Akdogan B, Yalcın B. The prediction of subjective well-being by psychological resilience and conflict resolution behavior in high school students. Mehmet Akif Ersoy Üniversitesi Eğitim Fakültesi Dergisi. 2018;46:174-97 (in Turkish).
9. Jackson D, Hutchinson M, Everett B, Mannix J, Peters K, Weaver R, Salamonson Y. Struggling for legitimacy: nursing students' stories of organisational aggression, resilience and resistance. Nurs Inq. 2011 Jun;18(2):102-10. doi: 10.1111/j.1440-1800.2011.00536.x.
10. Smith GD, Yang F. Stress, resilience and psychological well-being in Chinese undergraduate nursing students. Nurse Educ Today. 2017 Feb;49:90-5. doi: 10.1016/j.nedt.2016.10.004.
11. McMullin NN. Exploring resiliency during the nursing student clinical experience. The Organizational Improvement Plan at Western University, 150. 27 May 2020. Available at: https://ir.lib.uwo.ca/oip/150/. Published 2020. Accessed February 12, 2021.
12. Taylor H, Reyes H. Self-efficacy and resilience in baccalaureate nursing students. Int J Nurs Educ Scholarsh. 2012 Feb 17;9:Article 2. doi: 10.1515/1548-923X.2218.
13. Turgut N. Pyschological resilience academic achievement, and self-efficacy levels in nursing student. 2018. http://docs.neu.edu.tr/library/6689569321.pdf.
14. Timmins F, Kaliszer M. Aspects of nurse education programmes that frequently cause stress to nursing students - fact-finding sample survey. Nurse Educ Today. 2002 Apr;22(3):203-11. doi: 10.1054/nedt.2001.0698.
15. Çam O, Büyükbayram A. Nurses' resilience and effective factors. Journal of Psychiatric Nursing. 2017;8(2):118-26. doi:10.14744/phd.2017.75436.
16. Kaygısız F, Traş Z. A review on adolescents' resilience in terms of submissive behaviors and self-compassion. Research on Education and Psychology (REP). 2019;3(2):127-41.
17. Gizir CA. Psikolojik sağlamlık, risk faktörleri ve koruyucu faktörler üzerine bir derleme çalışması. Türk Psikolojik Danışma ve Rehberlik Dergisi. 2006;3(28):113-28 (in Turkish).
18. Gomathi S, Jasmindebora S, Baba V. Impact of stress on nursing students. IJIRAS. 2017;4(4):107-10.
19. He FX, Turnbull B, Kirshbaum MN, Phillips B, Klainin-Yobas P. Assessing stress, protective factors and psychological well-being among undergraduate nursing students. Nurse Educ Today. 2018 Sep;68:4-12. doi: 10.1016/j.nedt.2018.05.013.
20. Silva S, Frag S. Qualitative research in epidemiology. Epidemiology - Current Perspectives on Research and Practice. 2012;4:63-84. doi: 10.5772/32986.
21. Ekinci M, Sahin Altun O, Can G. Examination of the coping style with stress and the assertiveness of the nursing students in terms of some variables. Journal of Psychiatric Nursing. 2013;4(2):67-74. doi: 10.5505/phd.2013.85856.
22. Akkaya G, Babacan Gümüş A, Akkuş Y. Determining the factors affecting the education stress of nursing students. Journal of Education and Research in Nursing. 2018;15(4):202-8. doi: 10.5222/head.2018.202.
23. Canadian Association of Schools of Nursing. Practice Domain for Baccalaureate Nursing Education: Guidelines for Clinical Placements and Simulation. 2015:1-15. Available at: https://www.casn.ca/wp-content/uploads/2015/11/Draft-clinical-sim-2015.pdf. Accessed February 8, 2021.
24. Durham CF, Alden KR. Enhancing patient safety in nursing education through patient simulation. In: Hughes RG, ed. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Apr. Chapter 51. Available at: https://www.ncbi.nlm.nih.gov/books/NBK2628/. Accessed September 10, 2021.
25. Grealish L, van de Mortel T, Brown C, Frommolt V, Grafton E, Havell M, Needham J, Shaw J, Henderson A, Armit L. Redesigning clinical education for nursing students and newly qualified nurses: A quality improvement study. Nurse Educ Pract. 2018 Nov;33:84-9. doi: 10.1016/j.nepr.2018.09.005.

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Original Article

Role of Neutrophil Lymphocyte Ratio in Predicting Disease Severity in COVID-19

Khadija ASIF[1], Farhat ABBAS[2]

[1]Unit of Medicine (PMDC-97676-P), Department of Medicine, Allied Hospital, Faisalabad Medical University, Faisalabad, Pakistan.
[2]Unit of Medicine (PMDC-97035-P) Department of Medicine, Allied Hospital, Faisalabad Medical University, Faisalabad, Pakistan.

ABSTRACT

Background To evaluate the role of NLR as a prognostic indicator for severe COVID-19, due to its positive correlation with disease severity, easy accessibility and low cost.

Material and Methods A multicenter retrospective observational study was conducted in COVID-19 wards of two tertiary care hospitals of Faisalabad city, Pakistan, treating COVID-19 patients between May 2021 - July 2021. A predesigned proforma was filled to collect the data. SPSS 21 was used for the statistical analysis of this research.

Results A record of 100 COVID-19 patients admitted between May 2021 - July 2021, fulfilling the inclusion criteria was included in the study. All patients were divided into two groups. The non-severe group included 37 patients while the severe group included 63 patients. The mean age of the study population was 56 years with male predominance (63%). Overall, 50% of patients in the non-severe group and 71% in the severe group had some co-existent comorbidity. Fever and cough were the most commonly reported symptoms in both groups while shortness of breath was more widely reported in the severe group (74.2%). The mean NLR in the non-severe group was 4 as compared to 12 in the severe group.

Conclusions Higher neutrophil lymphocyte ratio (NLR) is associated with severe COVID -19 and can be used as an effective tool to predict the progression of the non-severe disease to severe disease.

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Address for Correspondence:
Khadija Asif, MD

Department of Medicine, Allied Hospital, Faisalabad Medical University, Faisalabad, Pakistan.
E-mail: dr.khadija.asif@outlook.com

Introduction

COVID-19, an extremely contagious and rapidly spreading viral infection caused by a novel corona virus SARS-COV-2 was first reported in China on December 5, 2019. It was declared a pandemic by WHO on March 11, 2020.[1] The pandemic has affected millions of people since the emergence of the first case. Till October 01, 2021, 219 million people worldwide got infected and almost 4.55 million deaths.[2] The statistical data of Pakistan till October 01, 2021, report 2.16 million diagnosed cases of COVID-19 with almost 28k fatalities.[2] The SARS-COV-2 is transmitted primarily through respiratory droplets and direct contact with infected body fluids or people.[3,4] The median incubation period reported is four to five days (range: 2-14 days).[5] The disease manifests most commonly as fever, cough, fatigue, shortness of breath, loss of taste and smell et cetera.[6,7] The novel infection under research exhibits a broad spectrum of severity ranging from no symptom to severe pneumonia leading to death. The majority of affected people have a mild form of the illness (81%) while some deteriorate and progress to moderate (14%) or severe disease (5%). Patients with moderate symptoms develop dyspnea due to pneumonia after the seventh day of illness, whereas severe disease is complicated by ARDS, acute respiratory failure, coagulopathy, septic shock, multi-organ failure and metabolic acidosis ending up in ventilator support and death.[3] This alarming situation highlights the urgent need to evaluate any reliable, widely available and cost-effective prognostic indicator to identify the patients likely to experience deterioration and progression to critical disease status and mortality. Early identification of high-risk cases may facilitate patient prioritization, arranging appropriate health care facilities, and tailoring appropriate treatment plans to enable good supportive care and reduce mortality.[8]

Sustained neutrophilia and lymphopenia have been witnessed in severe COVID at the onset of the disease compared to mild COVID (84.6% vs. 44.4%).[9] Neutrophil to lymphocyte ratio (NLR), one of the leading indicators for prediction of high-risk COVID-19 cases, can be easily calculated from differential leucocyte count (NLR [million per liter]=absolute neutrophil count/ lymphocyte count) on admission. It has been hypothesized to be an effective screening tool for identifying patients likely to have complicated diseases. Available literature shows higher NLR values in patients with severe COVID symptoms as compared to mild or moderate symptoms.[1,10,11] Higher NLR has also been found to be positively correlated with bilateral pulmonary involvement in 80% of cases.7 To predict severe COVID and low survival rate, the so far suggested NLR cut-off value is >3.3.[11,12]

To evaluate the role of NLR as a prognostic indicator for severe COVID-19, due to its positive correlation with disease severity, easy accessibility and low cost. COVID-19, a highly contagious and rapidly spreading viral infection caused by a novel coronavirus SARS-COV-2 was first reported in China on December 5, 2019. The novel infection under research exhibits a broad spectrum of severity ranging from no symptom to severe pneumonia leading to death.

Material and Methods

It was a multicenter retrospective observational study conducted in COVID wards of two tertiary care hospitals (Allied Hospital and DHQ hospital, Faisalabad) treating COVID-19 patients between May 2021-July 2021. Informed consent was waived after permission from the Institutional ethics committee due to this study's retrospective and observational character. Anonymity and confidentiality were ensured. This study was approved by the Institutional ethics committee of Allied hospital (Faisalabad Medical University) with approved no. AHF-402-FMU-04/15.

Hospital record was reviewed and patients with age >18 years and positive COVID-19 RT PCR for nasopharyngeal swab specimens were enrolled in the study. Cases were diagnosed based on the interim guidance of the WHO and divided in two groups named non-severe and severe. The patients meeting the following conditions were enrolled in the non-severe group: (1) Epidemiology history, (2) Fever or other respiratory symptoms, (3) Typical chest X-ray abnormalities of COVID-19, and (4) Positive result of RT-PCR for SARS-CoV-2 RNA. Patients having at least one of the following in addition to the above criteria were enrolled in the severe group: (1) Shortness of breath, respiratory

Table 1. Demographics and clinical features of patients.

Variables	All patients (n=100)	Non-severe group (n=37)	Severe group (n=63)	p value
Age (mean±SD)	56.82 (15.61)	51.71 (18.90)	59.03(13.13)	0.03
Gender, n (%)				
Male	63 (63%)	20 (58.82%)	43 (65.15%)	0.39
Female	37 (37%)	14 (41.18%)	23 (34.85%)	0.39
Comorbidity, n (%)	64 (64%)	17 (50%)	47 (71.21%)	0.04
Symptoms, n (%)				
Fever	77 (77%)	26 (76.47%)	51 (77.27%)	0.93
Cough	55 (55%)	16 (47.06%)	39 (59.09%)	0.25
SOB	57 (57%)	8 (23.53%)	49 (74.24%)	0.000
Myalgia	26 (26%)	9 (26.47%)	17 (25.76%)	0.94
Diarrhea	9 (9%)	1 (2.94%)	8 (12.12%)	0.13
Sore throat	8 (8%)	2 (5.88%)	6 (9.09%)	0.58
Headache	7 (7%)	1 (2.94%)	6 (9.09%)	0.25

rate (RR) ≥30 times/min, (2) Oxygen saturation (resting-state) ≤93% or PaO2/FiO2 ≤300 mmHg. Patients with COVID symptoms but negative PCR were excluded from the study.

Data Collection

A predesigned proforma was filled to collect the data. Demographic details, clinical symptoms and signs, and laboratory findings including CBC, TLC, DLC, NLR, CRP, serum ferritin, D-dimer, LDH, liver function tests, renal function tests on the first day of hospitalization were obtained from medical records. In addition, the number of days of hospital stay, need for mechanical ventilation, ICU admission, mortality, recovery and discharge from hospital were also noted.

Statistical Analysis

SPSS 21 was used for the statistical analysis of this research. Continuous variables were expressed as means±standard deviation or medians and interquartile ranges. Categorical variables were summarized as frequency and percentages in each category. Pearson product-moment correlation and independent-sample t-test was used to find out the relationship of NLR with different parameters of COVID and compare severe and non-severe groups in various parameters of COVID respectively.

Results

Records of 100 COVID-19 patients admitted between May 2021 - July 2021 fulfilling the inclusion criteria was included in the study. The non-severe group included 37 patients while the severe group included 63 patients. The mean age of the study population was 56 years with male predominance (63%). Overall, 50% of patients in the non-severe group and 71% in the severe group had some co-existent comorbidity. Fever and cough were the most commonly reported symptoms in both groups while shortness of breath was more widely reported in the severe group (74.2%). The rest of the symptoms like myalgia, diarrhea, and headache were equally noted in both groups *(Table 1)*.

The severe group showed a higher mean respiratory rate/min (36.24, p<0.001) as compared to the non-severe group. Similarly, oxygen requirement was also found to be higher in the severe group (7.48±5.09). Mean SpO2 was

Table 2. Comparison of investigations and disease outcome.

Parameters	All patients (n=100)	Non-severe group (n=37)	Severe group (n=63)	p value
Clinical parameters (mean±SD)				
RR (/minute)	33.60 (5.86)	19.72 (2.76)	36.24 (5.65)	0.000
SPO_2 (%)	87.52 (11.78)	95.81 (2.04)	83.30 (12.44)	0.000
Oxygen requirement (L)	5.06 (5.21)	1.09 (1.71)	7.48 (5.09)	0.000
Lab investigation (Mean±SD)				
TLC (*10^3/UL)	11.67 (5.55)	9.54 (3.99)	12.90 (6.02)	0.005
NLR	9.53 (9.52)	4 (2.29)	12.81 (10.65)	0.000
D-dimers (mg/L)	1.21 (1.36)	1.14 (1.40)	3.27 (1.65)	0.04
CRP (mg/L)	31.7 (25.99)	23.59 (22.83)	35.76 (26.69)	0.03
Ferritin (ng/mL)	743.74 (543.09)	603.75 (574.93)	807.80 (520.35)	0.03
LDH (U/L)	476.13 (373.14)	327.55 (262.69)	575.55 (406.04)	0.001
S.ALT (U/L)	48.09 (37.37)	37.75 (17.95)	54.69 (44.33)	0.04
Chest X-ray (PA view), n (%)				
<50% involvement	37 (37%)	16 (47.06%)	21 (31.82%)	0.14
>50% involvement	44 (44%)	2 (.61)	42 (63.64)	0.000
Duration of ICU stay (mean±SD)	4.42 (6.34)	0.84 (1.79)	6.59 (7.04)	0.000
Duration of hospital stay (mean±SD)	10.67 (5.38)	9.28 (3.73)	11.81(5.83)	0.01
Outcome, n (%)				
Expired	11 (11%)	0 (0%)	11 (16.67%)	0.01
Discharge	89 (89%)	34 (100%)	55 (83.33%)	0.01

RR: respiratory rate, SPO2: Oxygen saturation, ICU: intensive care unit, CRP: C-reactive protein, LDH: lactate dehydrogenase, ALT: alanine aminotransaminase.

significantly lower in the severe group (83.30, p <0.001). The mean NLR in the non-severe group was 4 as compared to 12 in the severe group. Other Lab investigations like D-dimer, ferritin, LDH, troponin I, serum creatinine and serum ALT were significantly higher in the severe group than the non-severe group *(Table 2)*. On average, patients of the severe group stayed in ICU for almost 6.6 days compared to 0.84 days in the non-severe group. The total duration of hospital stay was 9 days in the non-severe group while 11 days in the severe group. Overall, 89% of patients recovered and were discharged from hospitals. We noted 11 mortalities in the severe group whereas all patients recovered and were discharged in the non-severe group *(Table 2)*.

Pearson product moment correlation was used to determine the relationship of NLR with different COVID symptoms experienced by patients. NLR showed a significant positive relationship with respiratory rate, oxygen usage, LDH, troponin I, serum ALT, serum creatinine, D-dimer, CRP, ferritin, >50% involvement on chest x-ray, duration of ICU stay, duration of hospital stay and mortality. Moreover, NLR showed a significant negative relationship with SpO_2 and chest x-ray <50% involvement. The NLR value did not influence the occurrence of symptoms *(Table 3)*.

Discussion

COVID-19 has spread exponentially worldwide causing devastating loss of human life and economic crisis in developed and developing countries. The disease is under research worldwide; the literature available so far reports higher morbidity and mortality in severe disease than the non-severe disease, emphasizing the importance of early identification of patients at risk of developing severe disease. Prediction of severe disease may facilitate

Table 3. Relationship of NLR with different Severity Parameters of COVID-19 (n=100).

Severity parameters	NLR and parameter relationship (correlation coefficient r)
RR (/min)	.36***
SPO_2 (%)	-.28**
Oxygen requirement (L)	.33**
Shortness of breath	.35***
Chest X-ray <50% involvement	.43***
Chest X-ray>50% involvement	.43***
ICU days	.55***
Hospital days	.46***
D-dimers (mg/L)	.33**
CRP (mg/L)	.32**
Ferritin (ng/mL)	.35**
LDH (U/L)	.40***
Troponin-I (ng/L)	.25*
Serum ALT (U/L)	.27*
Serum creatinine (mg/dL)	.29**
Mortality	-.44***

***p<.001, **p<.01, *p<.05. RR: respiratory rate, SPO2: oxygen saturation, ICU: intensive care unit, CRP: C-reactive protein, LDH: lactate dehydrogenase, ALT: alanine aminotransaminase.

timely hospitalization, anticipation and prevention of complications and initiation of appropriate management.[13,14] For this purpose, simple, easily available, quick and cost-effective investigations are required. NLR is one of the leading tests under research in this context.[1] We recovered and analyzed data of 100 COVID-19 PCR positive patients from two different tertiary care hospitals and divided them into severe and non-severe groups according to the criteria mentioned above and found 63 patients with severe disease and 37 with the non-severe disease. We found higher NLR (12.8) in severe disease as compared to the non-severe group (4.0). In accordance with our results other researchers also found NLR >4.7 to be an independent risk factor for severe disease.[11,15] Lagunas-Rangel[1] also reported higher NLR levels to suggest a poor prognosis reflecting exaggerated inflammatory response. Many other researchers also established the role of NLR and even platelet lymphocyte ratio (PLR) as independent prognostic markers for early recognition of the severe disease facilitating early triage and well-timed commencement of appropriate management.[16]

In our study mean RR was significantly less (19.72/min) in the non-severe group in comparison to the severe group (36.24/min). In the non-severe group, patients presented with a mean SpO2 of 95.81% while 83.30% was the mean SpO2 in the severe group. The non-severe group of patients used 1.09 liters of oxygen in the mean, while the other group used 7.48 liters as mean. Then regarding blood tests, a noticeable difference was noted among both groups out of which NLR we have already discussed above. Mean TLC was 9.54x10 in the non-severe group while 12.9x10 in the severe group.[3] Inflammatory markers were also found to be raised in the severe group. Ferritin, LDH, CRP had a mean value of 807.80, 575.55, 35.76 respectively in the severe group as compared to 603.75, 327.55, 23.59 respectively in the non-severe group. D-dimer was also raised in the severe group with a mean of 3.27, while in non-severe 1.14 value was noted. Chest X-ray involvement >50% was more commonly present in the severe group as compared to the non-severe group. ICU stay and total hospital stay were also more in the severe group than the non-severe group. It was also seen that different severity parameters had direct concordance with the increased NLR, like increased RR, decreased saturation at time of admission, increased oxygen usage, and more frequently having shortness of breath as patients' presenting symptoms. Chest x-ray involvement of more than 50%, which is also a feature of COVID severity had a direct relation with NLR and the same finding was noted in CRP, ferritin and D-dimer levels that they were raised with increased NLR depicting that increased NLR has a direct relationship with all the severity parameters of COVID-19 disease. However, no relationship was noted between NLR and the general symptoms of COVID patients, i.e., cough, fever, headache, myalgias, and diarrhea.

Moreover, in our study patients with increased NLR were observed to have prolonged hospital and ICU stay. In addition, all patients who died had increased NLR correlating with other studies showing 8% higher risk of in-hospital mortality for each unit increase of NLR.[14,15,17] Thus, NLR seems to be a useful and easily approachable tool to predict the severity of COVID-19

disease. Different studies suggest NLR should be monitored starting from the first day of hospitalization to predict disease progression from mild to severe.[18-20]

Conclusion

Higher NLR is associated with severe COVID-19 and can be used as an effective tool to predict the progression of the non-severe disease to severe disease.

Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: KA; Study Design: KA; Supervision: KA; Materails: FA; Data Collection and/or Processing: FA; Statistical Analysis and/or Data Interpretation: KA, FA; Literature Review: FA; Manuscript Preparation: KA, FA; Critical Review: KA, FA.

References

1. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020 Oct;92(10):1733-4. doi: 10.1002/jmv.25819.
2. COVID-19 coronavirus pandemic. https://www.worldometers.info/coronavirus/.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
4. World Health Organization, Clinical Management of Severe Acute Respiratory Infection When Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection is Suspected: Interim Guidance, World Health Organization, Geneva, 2019.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-20. doi: 10.1056/NEJMoa2002032.
6. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, Li W, Tong Q, Yi J, Zhao L, Xiong L, Guo C, Tian J, Luo J, Yao J, Pang R, Shen H, Peng C, Liu T, Zhang Q, Wu J, Xu L, Lu S, Wang B, Weng Z, Han C, Zhu H, Zhou R, Zhou H, Chen X, Ye P, Zhu B, Wang L, Zhou W, He S, He Y, Jie S, Wei P, Zhang J, Lu Y, Wang W, Zhang L, Li L, Zhou F, Wang J, Dittmer U, Lu M, Hu Y, Yang D, Zheng X. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020 May;55:102763. doi: 10.1016/j.ebiom.2020.102763.
7. Xia XY, Wu J, Liu HL, Xia H, Jia B, Huang WX. Epidemiological and initial clinical characteristics of patients with family aggregation of COVID-19. J Clin Virol. 2020 Jun;127:104360. doi: 10.1016/j.jcv.2020.104360.
8. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, Zhang M, Tan J, Xu Y, Song R, Song M, Wang L, Zhang W, Han B, Yang L, Wang X, Zhou G, Zhang T, Li B, Wang Y, Chen Z, Wang X. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020 May 20;18(1):206. doi: 10.1186/s12967-020-02374-0.
9. Kerboua KE. NLR: A Cost-effective Nomogram to Guide Therapeutic Interventions in COVID-19. Immunol Invest. 2021 Jan;50(1):92-100. doi: 10.1080/08820139.2020.1773850.
10. Shang W, Dong J, Ren Y, Tian M, Li W, Hu J, Li Y. The value of clinical parameters in predicting the severity of COVID-19. J Med Virol. 2020 Oct;92(10):2188-92. doi: 10.1002/jmv.26031.
11. Sun S, Cai X, Wang H, He G, Lin Y, Lu B, Chen C, Pan Y, Hu X. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta. 2020 Aug;507:174-80. doi: 10.1016/j.cca.2020.04.024.
12. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020 Jul;84:106504. doi: 10.1016/j.intimp.2020.106504.
13. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020 May 5;172(9):577-82. doi: 10.7326/M20-0504.
14. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-42. doi: 10.1001/jama.2020.2648.
15. Faria SS, Fernandes PC Jr, Silva MJ, Lima VC, Fontes W, Freitas-Junior R, Eterovic AK, Forget P. The neutrophil-to-lymphocyte ratio: a narrative review. Ecancermedicalscience. 2016 Dec 12;10:702. doi: 10.3332/ecancer.2016.702.
16. Chan AS, Rout A. Use of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in COVID-19. J Clin Med Res. 2020 Jul;12(7):448-53. doi: 10.14740/jocmr4240.

17. Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med. 2016 May;42(5):829-40. doi: 10.1007/s00134-015-4095-4.
18. Xia H, Zhang Y, Deng W, Liu K, Xia X, Su CJ, Jeng US, Zhang M, Huang J, Huang J, Yan C, Wong WY, Lu X, Zhu W, Li G. Novel oligomer enables green solvent processed 17.5% ternary organic solar cells: synergistic energy loss reduction and morphology fine-tuning. Adv Mater. 2022 Jan 7:e2107659. doi: 10.1002/adma.202107659.
19. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M, Umberger R. . Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest. 2007 Apr;131(4):954-63. doi: 10.1378/chest.06-2100.
20. Ciccullo A, Borghetti A, Zileri Dal Verme L, Tosoni A, Lombardi F, Garcovich M, Biscetti F, Montalto M, Cauda R, Di Giambenedetto S; GEMELLI AGAINST COVID Group. Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: a report from the Italian front line. Int J Antimicrob Agents. 2020 Aug;56(2):106017. doi: 10.1016/j.ijantimicag.2020.106017.

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Original Article

The Positive Airway Pressure Therapy Compliance in Mild OSAS

Sezgi SAHIN DUYAR[1], Deniz CELIK[2], Funda AKSU[1], Selma FIRAT[1]

[1]Sleep Disorders Center, Health Sciences University Ataturk Chest Diseases and Thoracic Surgery Education and Research Hospital, Ankara, Turkey

[2]Department of Pulmonology, Health Sciences University Ataturk Chest Diseases and Thoracic Surgery Education and Research Hospital, Ankara, Turkey

ABSTRACT

Background This study is designed to determine the factors for predicting the PAP compliance in mild obstructive sleep apnea syndrome (OSAS) for improving the cost-effectiveness in the treatment choices of these patients.

Material and Methods The study group comprises 27 mild OSAS patients who underwent automatic positive airway pressure (APAP) titration between July 2016 and December 2017. Demographic, clinic and polysomnographic characteristics of the patients were retrospectively evaluated. Compliance with PAP treatment was defined as the usage of 5 nights/week and 4 hours/night at least. Data of compliant patients were statistically compared with non-compliant patients.

Results Most of the patients (23 patients, 85,2%) were prescribed APAP devices. Acceptable compliance at the end of the first year of therapy was achieved by 11 patients (40,2%) whereas 8 patients used PAP device 2 months at most (29,6%) The remaining 8 patients had not taken the device at all and were considered as non-adherent to PAP treatment (29,6%). The nonadherent/non-compliant group showed statistically the same demographic, clinic, and polysomnographic characteristics when compared to the compliant group. The level of maximum pressure during the titration test was lower in the compliant group (p=0,040).

Conclusions The sleep-related symptoms, scores of Epworth sleepiness scale or polysomnographic parameters can not be used to predict compliance for mild OSAS. The patients with mild OSAS, especially the ones who reach higher maximum pressure on titration test, must be followed up closely during the first 2 months of PAP treatment to detect nonadherence/non-compliance earlier.

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Address for Correspondence:
Deniz Celik, MD

Department of Pulmonology, Health Sciences University Ataturk Chest Diseases and Thoracic Surgery Education and Research Hospital, Ankara, Turkey
E-mail: drdenizcelik@hotmail.com

Introduction

Obstructive sleep apnea syndrome (OSAS) is considered mild if the apnea-hypopnea index (AHI) on all-night polysomnography (PSG) is 5-15/hour.[1] Despite the conflicting results about its necessity and efficacy, positive airway pressure (PAP) treatment is proposed as the main choice of treatment in mild OSAS patients with excessive daytime sleepiness, impaired sleep-related quality of life, or cardiovascular comorbidity.[2] This study is designed to determine the factors for predicting the PAP compliance in mild OSAS for improving the cost-effectiveness in the treatment choices of these patients.

Material and Methods

Patient Selection

Out of 3714 patients who underwent PSG in our tertiary hospital sleep center between 01 July 2016 and 31 December 2017, sleep efficiency was not sufficient in 312 patients during the test. Mild OSAS was detected in 493 of the remaining 3402 patients (14.5%). Thirty-six patients with mild OSAS were invited to the titration test due to symptomatic symptoms or accompanying cardiovascular comorbidities. Automatic positive airway pressure (APAP) device could be prescribed for 27 mild OSAS patients who completed the test successfully.

Examining the Data of the Patients Included in the Study

Demographic information (age and gender), disease duration, auto-antibody tests (rheumatoid factor [RF], anti-cyclic citrullinated peptide [anti-CCP]) were obtained from records of patients whose

Process

The study group comprises 27 mild OSAS patients who were prescribed PAP treatment after APAP titration with simultaneous PSG between July 2016 and December 2017. Age, gender, body mass index (BMI), symptoms, smoking status, comorbidities and scores on the Epworth Sleepiness Scale (ESS), pulmonary function tests, the results of diagnostic and titration PSG, recordings of PAP device during titration were retrospectively evaluated. Compliance with PAP treatment was defined as the usage of 5 nights/week and 4 hours/night at least. The patients with an ESS score ≥10 were considered to have excessive daytime sleepiness.[3]

The usage profile of the patients was based on either the records of their devices or the statement of the patient. The demographical, clinical, and polysomnographic characteristics of compliant patients were statistically compared with non-compliant patients.

Ethics

The study protocol was approved by the institutional review board of our education and research hospital. The study design was retrospective so ethical committee approval was not required. All procedures performed in this study were held according to the ethical standards of the institutional review board and the 1964 Helsinki declaration and its later amendments. Only the records of patients, who had signed the informed consent for the use of their data, were analyzed.

Measurements

Diagnostic and titration PSGs were performed as full night studies with the digital systems (Neuron-Spectrum EEG and EP neurophysiological system version 1.6.9.6, Neurosoft, Russia and Compumedics Voyager Digital Imaging E-series system Compumedics Ltd, Melbourne, Victoria, Australia) at our sleep laboratory.

For staging sleep four channels of the electroencephalogram, two channels of electrooculogram, one channel of chin electromyogram were used. Respiratory events were scored by using channels of the thermistor, airflow or thoracic and abdominal effort, pulse oximetry, and a microphone for snoring. All records were manually scored according to the criteria of the American Academy of Sleep Medicine (AASM) Scoring Manual Version 2.2[4] by a doctor who has a sleep medicine certificate from the Sleep Society in Turkey.

Different trademarks of APAP devices (ResMed, AutoSet T, Sydney, Australia, Weinman somnobalance, Hamburg, Germany, and Phillips Respironics Remstar Auto Aflex, Murrysville, USA) were used for the titration test. Excessive leak for the nasal mask was defined as the time spent with a large leak is ≥1% for Weinmann

devices, 95th or 90th percentile of nonintentional leakage is ≥24 L/min for Resmed and Phillips devices.

Statistical Analyses

Data analysis was performed using the SPSS software version 15. Descriptive statistics were presented as median (25^{th}-75^{th} percentile). Nominal variables were presented as the number and percentage of cases. Due to the small number of patients in the study group, a non-parametric test (Mann Whitney U test) was performed to compare the distribution of the aforementioned parameters between the groups for numerical data. A Chi-square test was used to examine the difference between groups for categorical variables and p-value <0.05 was accepted as statistically significant.

Results

Out of 28 mild OSAS patients who underwent APAP titration between July 2016 and December 2017, one patient was excluded due to antidepressant treatment. The remaining 27 patients were evaluated. Supine and/or REM predominancy for respiratory events was seen in 81.5% (22 patients) of the patients. Most of the patients (23 patients, 85.2%) were prescribed automated PAP devices. According to the records of the devices and/or oral statement of the patient, acceptable compliance at the end of the first year of therapy was achieved by 11 patients (40.2%) whereas 8 patients used PAP device 2 months at most (29.6%). The remaining 8 patients had not taken the device at all and were considered as non-adherent to PAP treatment (29.6%). As summarized in Table 1,

Table 1. Demographical and clinical characteristics

		All patients median (25.-75.percentile) %(n)	Compliant Median (25.-75.percentile) %(n)	Non-compliant/ Non-adherent Median (25.-75.percentile) %(n)	p value
Age (year)		54 (46-58)	57 (54-67)	51 (57.3-45.3)	0.060
Gender	Female	20 (74.1%)	10 (90.9%)	10 (62.5%)	0.183
	Male	7 (25.9%)	1 (9.1%)	6 (37.5%)	
BMI (n=26)		32.2 (27.8-37.2)	31.7 (28.3-37.5)	33.4 (26.1-37)	0.958
Comorbidities	Total	88.90%	81.80%	93.80%	0.549
Comorbidities	Cardiovascular	74.10%	81.80%	68.80%	0.662
	Metabolic	33.30%	27.30%	37.50%	0.692
	Respiratory	25.90%	36.40%	18.80%	0.391
Smoking status	None smoker	59.10%	62.50%	57.10%	1.000
	Ever-smoked	40.90%	37.50%	42.90%	
PFT (n=26)	FVC (%)	91% (73.8-108.3)	87% (66.3-107.5)	92% (76-111.8)	0.477
	FEV_1 (%)	92% (74.5-108.3)	84% (69.8-99.5)	100.5% (77-110.5)	0.196
	FEV_1/FVC	82.5 (77-86.3)	76.5 (73.8-88)	84 (81.3-85.8)	0.314
ESS		6 (3-7)	6 (2-7)	6 (3.3-10)	0.602
Symptoms	Snoring	92.60%	100%	87.50%	0.499
	EDS	55.60%	54.50%	56.30%	1.000
	Witnessed apnea	74.10%	63.60%	81.30%	0.391

BMI: body mass index, EDS: excessive daytime sleepiness, ESS: Epworth sleepiness scale, FVC: forced vital capacity, FEV_1: forced expiratory volume during the first second, PFT: pulmonary function test.

Table 2. The parameters of diagnostic PSG

		All patients median (25.-75.percentile) %(n)	Compliant Median (25.-75.percentile) %(n)	Non-compliant/ Non-adherent Median (25.-75.percentile) %(n)	p value
TRT (min)		472.2 (453-480.4)	453 (405.5-477.6)	475.5 (464.6-481.5)	0.093
TST (min)		366.5 (390.5-426)	304 (281.5-391.5)	388.5 (346.8-428.3)	0.16
Sleep efficiency (%)		78.2% (70.3-87.8)	72.7 (64.3-85.1)	81.6 (73.3-89.6)	0.256
Sleep latency (min)		12.5 (6-29)	14.5 (8-28)	10.3 (5.1-44.7)	0.639
REM latency (min)		108 (67.5-155.5)	108 (77.5-195)	100 (63-143)	0.199
WASO (min)		57.4 (40.5-102.6)	63.5 (46.7-125.3)	55.6 (38.4-88.5)	0.348
Sleep stages (%)	REM	17.4% (13.3-21.1)	13.8% (9.6-21.1)	19% (15.7-22.1)	0.103
	NREM1	3.5% (1.2-8.9)	5.2% (3.3-15.2)	1.7% (1-7.9)	0.072
	NREM2	56.9% (50.4-64.6)	56.9% (50.4-66.8)	57.3% (50-64.5)	0.961
	NREM3	18.7% (11.2-22)	18.7% (8.4-25.5)	18.9% (12.6-21.8)	0.98
AHI		12.4 (10.9-13.8)	12.4 (11.3-14)	12.5 (10.6-13.7)	0.693
Central AI		0.13 (0-0.21)	0 (0-0.34)	0.14 (0-0.18)	1
Obstructive AI		0 (0-0.98)	0 (0-0.21)	0.09 (0-1.55)	0.329
Hypopnea index		12.1 (9.8-12.9)	12.2 (9.8-13.7)	11.8 (8.6-12.9)	0.554
REM AHI		24.2 (8.7-28.7)	18.1 (4.5-28.2)	25.1 (10.9-28.9)	0.43
Non-REM AHI		9.9 (8.9-11.2)	10.3 (9.3-12.9)	9.8 (8-10.4)	0.132
Supine AHI		14.1 (12.2-20.5)	14.7 (12.7-19.4)	13.6 (11.9-23.4)	0.732
Non-supine AHI		3.2 (0-7.7)	5 (0-8.8)	1.5 (0-6.2)	0.381
Mean SpO_2		91% (90-92)	91% (90-92)	91% (89.3-94.3)	0.881
Minimum SpO_2		81% (75-84)	82% (77-87)	80% (74.3-82.8)	0.216

AHI: apnea-hypopnea index, AI: apnea index, REM: rapid eye movement; TRT: total recording time, TST: total sleep time, WASO: wake after sleep onset.

non-adherent/non-compliant group showed statistically same demographic-clinic characteristics including age, gender, BMI, symptoms, smoking status, comorbidities, and scores on ESS, The high scores of ESS were (ESS ≥11) recorded for only 22% of patients. However, 59.3% of the patients had a complaint of excessive daytime sleepiness (EDS). We could not show any statistically significant difference in the results of PFT, either. The results of diagnostic and titration PSG were also similar for the nonadherent/non-compliant group when compared to the compliant group *(Table 2-3)*. Although statistically insignificant, there were more female patients in the compliant group (p=0.183). As shown in Table 3, the maximum pressure during the titration test was lower in the compliant group (p=0.040). But the differences in an excessive leak, p95, or residue AHI recorded by the device during titration night were not substantial (p>0.05).

Discussion

Previous studies showed that the PAP compliance in mild/moderate OSAS varies between %43-64 for a follow-up lasting 3 weeks-6 months.[5-9] Our study comprised mild OSAS patients solely and we reported the results of a longer follow-up time (1 year). Due to these distinct features of this study, PAP compliance was lower in our study group. Approximately 60% of the patients had not taken the prescribed device or used the device for 2 months at most. This result reflects the accurate rate of compliance for mild OSAS and the importance of the close follow-up during the first two months of the PAP treatment.

In this study, the parameters of PSG including sleep and REM latencies, distribution of sleep stages, and AHI (total, positional, REM AHI, and index for each type of respiratory event),

Table 3. The parameters of titration PSG

		All patients median (25.-75.percentile) %(n)	Compliant Median (25.-75.percentile) %(n)	Non-compliant/ Non-adherent Median (25.-75.percentile) %(n)	p value
TRT (min)		471.4 (456-482.7)	477.4 (456-482.7)	468.3 (453.1-484)	0.459
TST (min)		361 (311-421)	355 (308.9-421)	371.3 (316.2-425.9)	0.844
Sleep efficiency (%)		78.6% (70.6-84)	75.5% (64.6-83.8)	79.8% (71.7-85.8)	0.402
Sleep latency (min)		23.5 (12.5-40.5)	25 (23.5-42.5)	16.3 (6.1-37)	0.109
	REM	16.3% (10.5-21)	14.4% (9.6-18.5)	16.9% (13.7-21.1)	0.348
	NREM1	1.4% (1-2.2)	1.3% (1.1-1.8)	1.5% (0.9-2.5)	0.711
Sleep stages (%)	NREM2	57.1% (52.4-64.7)	55.8% (52.4-68.8)	57.6% (63.8-52.2)	0.921
	NREM3	24.6% (17.3-29.3)	28.1% (23.3-30.3)	23.2% (14-27.9)	0.109
AHI		2.6 (1-3.9)	2.2 (0.9-4.6)	2.7 (1.3-3.9)	0.921
Central AI		0.4 (0-1.4)	0.4 (0-0.9)	0.8 (0.13-1.4)	0.383
Obstructive AHI		1.9 (0.6-3)	0.9 (0.6-3)	2 (0.4-2.8)	0.941
REM AHI		2.4 (0.8-9.2)	1.6 (0.8-4.9)	5 (0.2-9.4)	0.457
Non-REM AHI		2 (0.9-3.3)	2.2 (0.9-3.5)	1.9 (0.9-3)	0.57
Mean SpO_2		93% (91-94)	93% (92-94)	92.5% (90.3-93.8)	0.38
Minimum SpO_2		89% (84-90)	89% (82.90)	89.5% (84.3-90)	0.669
	RDI	(n=27) 1.9 (0.8-4)	(n=11) 1.6 (0.5-3.2)	(n=16) 2.2 (0.9-6.4)	0.256
	p95 (cmH_2O)	(n=23) 8.6 (7-11)	(n=9) 7.7 (6-11.7)	(n=14) 8.8 (7.5-10.6)	0.507
The recordings of PAP devices	Maximum presure (cmH_2O)	(n=23) 9.3 (7.3-11.6)	(n=10) 7.5 (6.9-10.2)	(n=13) 9.8 (8.6-11.8)	0.04
	Excessive mask leak	(n=27)	(n=11)	(n=16)	
	+	59.30%	54.50%	62.50%	0.71
	-	40.70%	45.50%	37.50%	

AHI: apnea-hypopnea index, AI: apnea index, REM: rapid eye movement, TRT: total recording time, TST: total sleep time, RDI: respiratory disturbance index.

wake after sleep onset time, minimum and mean oxygen saturations were also analyzed. But the compliant group did not show any statistical difference in means of these parameters either on diagnostic PSG or PSG during titration. We can conclude that PSG parameters can not be used for predicting compliance for patients with mild OSAS.

Despite the high rates of compliance in symptomatic patients with moderate/severe OSAS[10], our results also noted that sleep-related symptoms or scores of ESS can not be used for estimating the compliance for mild OSAS, either. Nevertheless, we showed that the level of maximum pressure during the titration test was the only parameter statistically promising for the estimation of the treatment compliance for mild OSAS.

The data from the Sleep Heart Health Study demonstrated that 28% of the patients with mild OSAS were sleepy and the quality of life was low.[11,12] The results from the Wisconsin Sleep Cohort Study revealed that the high level of sleepiness also affected the daily activities of snorers with AHI <5 when compared with non-snoring controls.[13] These two population studies also provided evidence for the significant effect of mild OSAS on blood pressure.[14,15] Peppard *et al.*[14] declared that the odds ratio for the 4-year incidence of developing hypertension was 2.03 (1.29-3.17) for AHI between 5 and 14.9. Although the incident risk for adverse

cardiovascular outcomes is unknown, the previous studies pointed out a link between mild OSAS and cardiovascular outcomes.[16,17] It is also known that the risk for endothelial dysfunction, atherosclerosis, and insülin resistance also starts with the mildest degree of OSAS.[18-20]

The outcomes of mild OSAS can be severe in means of cardiovascular and metabolic diseases. The characteristics of this group of patients with mild OSAS and cardiovascular and metabolic diseases must be clarified for selecting the patients who can benefit from the PAP treatment. The last guideline of AASM recommends PAP treatment for OSAS in adults with excessive sleepiness regardless of the severity. A lower degree of recommendation is also proposed for all OSAS patients with the impaired sleep-related quality of life and hypertension.[2] The previous studies published conflicting results for the benefits of APAP on cardiovascular risk, quality of life, and mortality in mild OSAS.[21] Some authors suggest that medical or conservative treatments including weight loss, positional therapy, or nasal corticosteroids may be more effective than PAP treatment in mild OSAS.[22] Additionally, even if the symptoms improve, the patients with mild OSAS are likely to abandon the PAP treatment.[23]

The sympathetic nervous system activation and hypoxia due to apnea/hypopnea and the oxidative stress due to reoxygenation are the main causes of cardiovascular and metabolic events for OSAS.[24]

Eventually, patients with mild OSAS tend for increased cardiovascular events and PAP treatment may lead to an increase in quality of life for a group of patients with mild OSAS.[16-25] We recommend that mild OSAS patients especially those who reach higher maximum pressure on titration test must be followed up closely during the first 2 months of PAP therapy to detect nonadherence and non-compliance earlier.

Our study has some limitations. First, the number of patients is small. The number of patients included in the previous studies range between 29-66 however the studies also include the patients with moderate OSAS.[5-9] Second, the adherence of 40.2% of patients in our study group was based on subjective data from patients' statements. Eventually as there is no benefit in making false statements, we found it trustable.

Conclusion

The number of patients diagnosed with mild OSAS requiring PAP treatment is quite less than moderate/severe OSAS. In the literature, mild OSAS is evaluated together with moderate OSAS. Uniquely, our study investigates mild OSAS solely and has a relatively long follow-up period of 1 year. Therefore, the results of this study will have a significant meaning for the clinicians dealing with sleep disorders.

The risk of complications increases if individuals with symptomatic mild OSAS patients with comorbidities are left untreated. However, parameters predicting poor compliance are needed for a better cost-effective approach, Our results show that the patients who require higher pressure during the titration test can be evaluated as the candidates of poor compliance/ adherence to PAP therapy.

Conflict of Interest

Authors have no conflict of interest to declare.

Authors' Contribution

Study Conception: SSD, DC, FA, SF; Study Design: SSD, DC, FA, SF; Supervision: SSD, DC, FA, SF; Data Collection and/or Processing: SSD, DC; Statistical Analysis and/or Data Interpretation: SSD, DC, FA, SF; Literature Review: SSD, DC; Manuscript Preparation: SSD, DC; Critical Review: SF.

References

1. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999 Aug 1;22(5):667-89.
2. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2019 Feb 15;15(2):335-43. doi: 10.5664/jcsm.7640.
3. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep Breath. 2008 May;12(2):161-8. doi: 10.1007/s11325-007-0145-7.
4. Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, Vaughn BV. The American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology

and Technical Specifications. 2015. Version 2.3. Darien, Illinois: American Academy of Sleep Medicine.
5. Marshall NS, Neill AM, Campbell AJ, Sheppard DS. Randomised controlled crossover trial of humidified continuous positive airway pressure in mild obstructive sleep apnoea. Thorax. 2005 May;60(5):427-32. doi: 10.1136/thx.2004.032078.
6. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, Pierce RJ. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med. 2004 Sep 15;170(6):656-64. doi: 10.1164/rccm.200311-1571OC.
7. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, Trinder J, Saunders NA, Douglas McEvoy R, Pierce RJ. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med. 2002 Mar 15;165(6):773-80. doi: 10.1164/ajrccm.165.6.2003166.
8. Engleman HM, McDonald JP, Graham D, Lello GE, Kingshott RN, Coleman EL, Mackay TW, Douglas NJ. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. Am J Respir Crit Care Med. 2002 Sep 15;166(6):855-9. doi: 10.1164/rccm.2109023.
9. Monasterio C, Vidal S, Duran J, Ferrer M, Carmona C, Barbé F, Mayos M, Gonzalez-Mangado N, Juncadella M, Navarro A, Barreira R, Capote F, Mayoralas LR, Peces-Barba G, Alonso J, Montserrat JM. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med. 2001 Sep 15;164(6):939-43. doi: 10.1164/ajrccm.164.6.2008010.
10. Qaseem A, Holty JE, Owens DK, Dallas P, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Management of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2013 Oct 1;159(7):471-83. doi: 10.7326/0003-4819-159-7-201310010-00704.
11. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5. doi: 10.1093/sleep/14.6.540.
12. Baldwin CM, Griffith KA, Nieto FJ, O'Connor GT, Walsleben JA, Redline S. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep. 2001 Feb 1;24(1):96-105. doi: 10.1093/sleep/24.1.96.
13. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993 Apr 29;328(17):1230-5. doi: 10.1056/NEJM199304293281704.
14. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000 May 11;342(19):1378-84.doi:10.1056/NEJM200005113421901.
15. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000 Apr 12;283(14):1829-36. doi: 10.1001/jama.283.14.1829. Erratum in: JAMA 2002 Oct 23-30;288(16):1985.
16. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001 Jan;163(1):19-25. doi: 10.1164/ajrccm.163.1.2001008.
17. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005 Mar 19-25;365(9464):1046-53. doi: 10.1016/S0140-6736(05)71141-7.
18. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med. 2005 Dec 15;172(12):1590-5. doi: 10.1164/rccm.200504-637OC.
19. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med. 2005 Sep 1;172(5):613-8. doi: 10.1164/rccm.200503-340OC.
20. Duchna HW, Stoohs R, Guilleminault C, Christine Anspach M, Schultze-Werninghaus G, Orth M. Vascular endothelial dysfunction in patients with mild obstructive sleep apnea syndrome. Wien Med Wochenschr. 2006 Nov;156(21-22):596-604. doi: 10.1007/s10354-006-0341-2.
21. Littner MR. Mild obstructive sleep apnea syndrome should not be treated. Con. J Clin Sleep Med. 2007 Apr 15;3(3):263-4.
22. Morgenthaler TI, Kapen S, Lee-Chiong T, Alessi C, Boehlecke B, Brown T, Coleman J, Friedman L, Kapur V, Owens J, Pancer J, Swick T; Standards of Practice Committee; American Academy of Sleep Medicine. Practice parameters for the medical therapy of obstructive sleep apnea. Sleep. 2006 Aug;29(8):1031-5.
23. Whitelaw WA, Brant RF, Flemons WW. Clinical usefulness of home oximetry compared with polysomnography for assessment of sleep apnea. Am J Respir Crit Care Med. 2005 Jan 15;171(2):188-93. doi: 10.1164/rccm.200310-1360OC.
24. Sağmen SB, Parmaksız ET, Cömert SŞ, Fidan A, Salepçi B. Liver functions in patients with obstructive sleep apnea syndrome. The European Research Journal. 2018;4(4):349-55. doi: 10.18621/eurj.381906.
25. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. Thorax. 1997 Feb;52(2):114-9. doi: 10.1136/thx.52.2.114.

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Original Article

The Outcome in Patients With Peripheral T-Cell Lymphoma Treated With Pralatrexate: A Single-Centre Experience

Aydan AKDENIZ[1], Nurcan YILMAZ CETIN[2], Mahmut Bakir KOYUNCU[3], Gulhan OREKICI[4], Pelin AYTAN[1], Anil TOMBAK[1]

[1]Division of Hematology, Department of Internal Medicine, Mersin University Hospital, Mersin, Turkey
[2]Department of Internal Medicine, Mersin University Hospital, Mersin, Turkey
[3]Department of Hematology, Adana City Hospital, Adana, Turkey
[4]Department of Statistics, Mersin University Hospital, Mersin, Turkey

ABSTRACT

Background Peripheral T-cell lymphoma (PTCL) accounts for 10-15% of all non-Hodgkin lymphomas. Five-year overall survival is very poor in all subtypes except in ALK positive anaplastic large cell lymphomas (ALCL). Patients in relapsed-refractory (RR) setting, treatment options are very limited, particularly in patients with poor performance or advanced age. Pralatrexate has been shown to improve remission and survival rates in RR PTCL. We aimed to evaluate the response rates, efficacy and adverse event profile of pralatrexate used in RR PTCL in our center.

Material and Methods Patients followed in hematology department of Mersin University with the diagnosis of RRPTCL and treated with pralatrexate were included in study. Their demographical and clinical data were documented. Response to treatment with pralatrexate was evaluated.

Results Median follow up time was 14 months and mean age at diagnosis was 50.6 (±17.9) in totally 11 patients. Patients received median 2 cycles of pralatrexate. Six patients were refractory to treatment while 5 patients achieved at least partial remission.

Conclusions PTCL has the worst prognosis among all types of lymphomas. Cure rates are still low and new therapeutic options are needed.

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Address for Correspondence:
Aydan Akdeniz, MD
Division of Hematology, Department of Internal Medicine,
Mersin University Hospital, Mersin, Turkey
E-mail: akdenizdr@hotmail.com

Introduction

Peripheral T-cell lymphoma (PTCL) accounts for 10-15% of all non-Hodgkin lymphomas (NHL). PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T cell lymphoma (AITL), NK/T cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), anaplastic large cell lymphoma (ALCL, ALK+, ALK-) are the most common subtypes.[1] Five-year overall survival is 70-79% in ALK+ ALCL, while it is quite poor in other subtypes (14% to 35%). Similar to B-cell lymphomas, anthracycline-based chemotherapies such as cyclophosphamide, doxorubicin, vincristine and prednisolone, etoposide (CHOP/CHOEP) or cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyperCVAD) are used in front-line treatment. Stem cell transplantation (SCT) should be planned as consolidation procedure after high-dose chemotherapy in patients who achieved remission and are eligible.[2] Allogenic SCT should be considered in patients in relapsed or refractory (RR) setting. In CD30-positive PTCL, brentuximab vedotin have been approved based on the randomized ECHELON-2 clinical trial.[3] In patients who are resistant or intolerant to first-line therapy or who have relapsed disease; alemtuzumab, bortezomib, gemcitabine, histone deacetylase inhibitors (romidepsin, belinostat), pralatrexate, monoclonal antibodies (brentuximab, mogamulizumab) are among the new treatment options.[4] Pralatrexate, a dihydrofolate reductase inhibitor, has been shown to improve remission and survival rates in PTCL patients both in early clinical studies and in the PROPEL study and got FDA approval in 2009, and its benefit has been proven by subsequent studies.[5-7] In our study, we aimed to evaluate the response rates, efficacy and adverse event profile of pralatrexate in patients with RR-PTCL in our center.

Material and Methods

Data of patients followed in hematology department of Mersin University Hospital between 1 January 2017 and 1 January 2021 with the diagnosis of PTCL were retrospectively analyzed. Patients treated with pralatrexate with this diagnosis were included in the study. The demographical data of the patients, pathological subtypes, follow-up periods, the number of cycles of pralatrexate they were treated, the number of chemotherapy lines before pralatrexate, side effects and reasons of death were documented. Response assessment was performed with positron emission tomography-computerized tomography (PET-CT) after 2 cycles of treatment. The proportion of patients with at least partial response was defined as overall response rate (ORR). Patients that responders and non-responders were compared in terms of demographics, age at diagnosis, follow-up time, stage, pathological subtypes, number of prior chemotherapy lines and cause of death. The data obtained were evaluated and compared with literature.

Shapiro-Wilk test was used for normality control of continuous variables. Standard deviation values were given for normally distributed variables, min-max and median values were given for non-conforming variables.

Results

Data of a total of 11 patients were accessed. Mean age at diagnosis, median follow-up time, median number of lines of treatment prior to pralatrexate, median number of cycles of pralatrexate, distribution of gender, histopathological subtypes and stage of patients are summarized in Table 1. Prior to pralatrexate, 8 patients received 2 lines and the others received 3 lines of treatment. First-line treatment was CHOP (cyclophosphamide, vincristine, cyclophosphamide, dexamethasone) in 8 patients, EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in 2 patients and dose adjusted EPOCH in 1 patient. No patient had stem cell transplantation prior to pralatrexate. Patients were treated with a median of 2 cycles of pralatrexate. ORR was 45% (4 patients; complete remission [CR], and 1 patient; partial remission [PR]). Two of 5 responder patients were relapsed. One of them was not eligible for SCT, and relapsed in fourth month of pralatrexate treatment, and the other relapsed with central nervous system involvement during the preparation for autologous SCT and has died. Patients treated with combination of pralatrexate and romidepsin were

Table 1. The characteristics of 11 patients.

Parameters	Values
Mean age at diagnosis (years) (mean±SD)	50.6±17.9
Male/Female	8/3
Median follow-up time (month) (min-max)	14 (8-40)
Pathological subtype, n (%)	
PTCL, NOS	5 (45)
ALCL (ALK+)	3 (27)
ALCL (ALK-)	1 (9)
AITL	2 (18)
Median stage (min-max)	4 (3-4)
Pralatrexate, n (%)	
Monotherapy	8 (72)
Combination with romidepsin	3 (27)
Number of patients who have died, n (%)	5 (45)
Median number of lines of treatment prior to pralatrexate (min-max)	4 (2-6)
Median follow-up time after relaps or progression (month) (min-max)	7 (3-25)
Median number of cycle of pralatrexate (min-max)	2 (1-6)
Overall response rate (%)	45

all refractory. As hematological adverse event: moderate neutropenia was seen in 5 of patients. One patient suffered from delayed wound healing. Patient who achieved PR died due to severe heart failure (ejection fraction; 20%) that occurred during the treatment. The mean age of the patients who were died was 68.6. In all three patients who were assessed, CD30 were positive. The responder and non-responder patients are compared in terms of mean age at diagnosis, gender, median follow up times, patological subtypes, stage, cause of death in Table 2.

Discussion

Based on reports presenting real life data, it is clear that RR-PTCL has quite poor outcome among the other RR-NHLs, In a study, 153 patients with RR-PTCL reported to have 5.5 months median overall survival, while it was 2.5 months in another report.[8,9] Although survival cannot be mentioned due to the small number of patients and the short follow-up period, relapsing rates and proportion of primary refractory patients in our study supports the information that the disease has poor prognosis.

Indeed, it is not exactly true to compare results of a clinical trail with large population with a real life data of a limited population. However we aimed to evaluate whether our results supported those in clinical trial. While the overall response rate was 29% in the PROPEL study, which accelerate the approval, it was 45% in our study.6 This supports the promising results of pralatrexate treatment in other studies.[10,11]

When the characteristics of the patients with or without response were compared, it was observed that 80% of patients with PTCL-NOS were refractory to pralatrexate treatment, this result is consistent with literature which mentioned that NOS subtype has worse prognosis.[2] Non-responder patients were younger than responder patients. Although Amengual *et al.*[12] reported better response rates with pralatrexate-romidepsin combination in a phase-1 study, none of the patients, treated with this combination responded in this study. Undoubtedly phase II, III study and real life data will yield more definitive and realistic

Table 1. Characteristics of responding and non-responding patients.

	Responders to pralatrexate (n=5)	Non-responders to pralatrexate (n=6)
Mean age at diagnosis (years) (mean±SD)	56.2±15.4	46±19.8
Male/Female (%)	60/40	84/16
Median follow-up time (month) (min-max)	22 (12-35)	12 (8-40)
Pathological subtype, n (%)		
PTCL, NOS		
ALCL (ALK+)	1 (20)	4 (66)
ALCL (ALK-)	3 (60)	1 (16)
AITL	1 (20)	1 (16)
Stage		
3	1	2
4	4	4
Primary refractory	4	2
Relapsed	1	4
Pralatrexate, n (%)		
Monotherapy	5 (100)	3 (50)
Combination with romidepsin		3 (50)
Number of patients who have died, n (%)	2 (40)	3 (50)
Cause of death	Progression after remission (n=1) Heart failure (n=1)	Progression (n=3)

results. On the other hand, the other combinations with bortezomib and gemcitabine are still under investigation and show promising.[13,14]

Mucositis is the most common adverse event in literature, but it is not detected in our patients so often.[15] All patients were received prophylaxis for mucositis, but we doubted about lack of documentation of side effects in our clinic during the treatment periods. As the most common hematological adverse event inconsistent with the multicenter study of Hong *et al.*[16], not thrombocytopenia but moderate neutropenia was seen in 5 of patients. While edema and tachycardia are the most common cardiac complications in literatüre, one of our patients who had no cardiac pathology except for left ventricular hypertrophy due to hypertension previously, got severe heart failure with treatment and died due to it.[10]

Limitations of the study includes small population of patients, shortness of follow-up duration, lack of assessment of CD30 marker in other 8 patients and lack of genetic assessment (such as mutations of TET2, IDH2, DNMT3A). Lack of documentation of adverse events is also the other limitation.

Conclusions

RR-PTCL has poor prognosis and there are few treatment options. Among these, pralatrexate has a proven efficacy. Despite all the positive and promising results, large population studies with long follow-up duration are needed and new mono and combined therapy modalities should be worked on.

Conflict of interest

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception: AA; Study Design: AA; Supervision: MBK; Data Collection and/or Processing: PA; Materials: NYC Statistical Analysis and/or Data Interpretation: PA; Literature Review: AA, PA; Manuscript Preparation: BY; and Critical Review: AT; Statistics: GO.

References

1. Bhurani M, Admojo L, Van Der Weyden C, Twigger R, Bazargan A, Quach H, Zimet A, Coyle L, Lindsay J, Radeski D, Hawkes E, Kennedy G, Irving I, Gutta N, Trotman J, Yeung J, Dunlop L, Hua M, Giri P, Yuen S, Panicker S, Moreton S, Khoo L, Scott A, Kipp D, McQuillan A, McCormack C, Dickinson M, Prince HM. Pralatrexate in relapsed/refractory Tcell lymphoma: a retrospective multicenter study. Leuk Lymphoma. 2021 Feb;62(2):330-6. doi: 10.1080/10428194.2020.1827241.
2. Sharma M, Pro B. Bone Marrow Transplantation for Peripheral T-Cell Non-Hodgkins' Lymphoma in First Remission. Curr Treat Options Oncol. 2015 Jul;16(7):34. doi: 10.1007/s11864-015-0347-3.
3. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, Bartlett NL, Christensen JH, Morschhauser F, Domingo-Domenech E, Rossi G, Kim WS, Feldman T, Lennard A, Belada D, Illés Á, Tobinai K, Tsukasaki K, Yeh SP, Shustov A, Hüttmann A, Savage KJ, Yuen S, Iyer S, Zinzani PL, Hua Z, Little M, Rao S, Woolery J, Manley T, Trümper L; ECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019 Jan 19;393(10168):229-40. doi: 10.1016/S0140-6736(18)32984-2.
4. Hong JY, Yoon DH, Yoon SE, Kim SJ, Lee HS, Eom HS, Lee HW, Shin DY, Koh Y, Yoon SS, Jo JC, Kim JS, Kim SJ, Cho SH, Lee WS, Won JH, Kim WS, Suh C. Pralatrexate in patients with recurrent or refractory peripheral T-cell lymphomas: a multicenter retrospective analysis. Sci Rep. 2019 Dec 30;9(1):20302. doi: 10.1038/s41598-019-56891-0.
5. O'Connor OA, Horwitz S, Hamlin P, Portlock C, Moskowitz CH, Sarasohn D, Neylon E, Mastrella J, Hamelers R, Macgregor-Cortelli B, Patterson M, Seshan VE, Sirotnak F, Fleisher M, Mould DR, Saunders M, Zelenetz AD. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. J Clin Oncol. 2009 Sep 10;27(26):4357-64. doi: 10.1200/JCO.2008.20.8470.
6. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, Lechowicz MJ, Savage KJ, Shustov AR, Gisselbrecht C, Jacobsen E, Zinzani PL, Furman R, Goy A, Haioun C, Crump M, Zain JM, Hsi E, Boyd A, Horwitz S. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011 Mar 20;29(9):1182-9. doi: 10.1200/JCO.2010.29.9024.
7. Advani RH, Ansell SM, Lechowicz MJ, Beaven AW, Loberiza F, Carson KR, Evens AM, Foss F, Horwitz S, Pro B, Pinter-Brown LC, Smith SM, Shustov AR, Savage KJ, Vose JM. A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial. Br J Haematol. 2016 Feb;172(4):535-44. doi: 10.1111/bjh.13855.
8. Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, Villa D, Gascoyne RD, Connors JM, Savage KJ. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol. 2013 Jun 1;31(16):1970-6. doi: 10.1200/JCO.2012.44.7524.
9. Biasoli I, Cesaretti M, Bellei M, Maiorana A, Bonacorsi G, Quaresima M, Salati M, Federico M, Luminari S. Dismal outcome of T-cell lymphoma patients failing first-line treatment: results of a population-based study from the Modena Cancer Registry. Hematol Oncol. 2015 Sep;33(3):147-51. doi: 10.1002/hon.2144.
10. Hong X, Song Y, Huang H, Bai B, Zhang H, Ke X, Shi Y, Zhu J, Lu G, Liebscher S, Cai C. Pralatrexate in Chinese Patients with Relapsed or Refractory Peripheral T-cell Lymphoma: A Single-arm, Multicenter Study. Target Oncol. 2019 Apr;14(2):149-58. doi: 10.1007/s11523-019-00630-y.
11. Maruyama D, Nagai H, Maeda Y, Nakane T, Shimoyama T, Nakazato T, Sakai R, Ishikawa T, Izutsu K, Ueda R, Tobinai K. Phase I/II study of pralatrexate in Japanese patients with relapsed or refractory peripheral T-cell lymphoma. Cancer Sci. 2017 Oct;108(10):2061-8. doi: 10.1111/cas.13340.
12. Amengual JE, Lichtenstein R, Lue J, Sawas A, Deng C, Lichtenstein E, Khan K, Atkins L, Rada A, Kim HA, Chiuzan C, Kalac M, Marchi E, Falchi L, Francescone MA, Schwartz L, Cremers S, O'Connor OA. A phase 1 study of romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma. Blood. 2018 Jan 25;131(4):397-407. doi: 10.1182/blood-2017-09-806737.
13. Lee SS, Jung SH, Ahn JS, Kim YK, Cho MS, Jung SY, Lee JJ, Kim HJ, Yang DH. Pralatrexate in Combination with Bortezomib for Relapsed or Refractory Peripheral T Cell Lymphoma in 5 Elderly Patients. J Korean Med Sci. 2016 Jul;31(7):1160-3. doi: 10.3346/jkms.2016.31.7.1160.
14. Toner LE, Vrhovac R, Smith EA, Gardner J, Heaney M, Gonen M, Teruya-Feldstein J, Sirotnak F, O'Connor OA. The schedule-dependent effects of the novel antifolate pralatrexate and gemcitabine are superior to methotrexate and cytarabine in models of human nonHodgkin's lymphoma. Clin Cancer Res. 2006 Feb 1;12(3 Pt 1):924-32. doi: 10.1158/1078- 0432.CCR-05-0331.
15. Zhu J, Yeoh EM, Maeda Y, Tobinai K. Efficacy and safety of single-agent pralatrexate for treatment of angioimmunoblastic T-cell lymphoma after failure of first line therapy: a pooled analysis. Leuk Lymphoma.2020 Sep;61(9):2145-52. doi: 10.1080/10428194.2020.1765232.
16. Hong JY, Yoon DH, Yoon SE, Kim SJ, Lee HS, Eom HS, Lee HW, Shin DY, Koh Y, Yoon SS, Jo JC, Kim JS, Kim SJ, Cho SH, Lee WS, Won JH, Kim WS, Suh C. Pralatrexate in patients with recurrent or refractory peripheral T-cell lymphomas: a multicenter retrospective analysis. Sci Rep. 2019 Dec 30;9(1):20302. doi: 10.1038/s41598-019-56891-0.

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Original Article

Relationship Between Familial Mediterranean Fever and Other Rheumatic Diseases: Coincidence or Coexistence?

Dilek TEZCAN[1], Semral GULCEMAL[1], Muhammet LIMON[1], Muslu Kazim KOREZ[2], Sema YILMAZ[1]

[1]Division of Rheumatology, Department of Internal Medicine, Selcuk University Faculty of Medicine, Konya, Turkey
[2]Department of Biostatistics, Selcuk University Faculty of Medicine, Konya, Turkey

ABSTRACT

Background Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease affecting mainly the ethnic groups of the Mediterranean basin. It has been reported that it can coexist with various systemic inflammatory diseases. This study aimed to obtain information on rheumatic diseases that accompany FMF and evaluate the relation between FMF and such diseases.

Material and Methods Eighty-four patients diagnosed with FMF and have rheumatic disease comorbidity in the rheumatology clinic between January 2018 - March 2020 were included in this study.

Results The most common accompanying rheumatic disease was spondyloarthritis (SpA) with 36 patients. Vasculitis was the second common disease accompanying FMF with 22, followed by connective tissue disease (CTD) in 18, juvenile idiopathic arthritis in 4, gout in 3, and hidradenitis suppurativa in 1 patients. The most common MEFV mutation observed was M694V. The rate of patients in the SPA group with signs of fever was significantly higher than those in the vasculitis group. The median C-reactive protein value of the patients in the vasculitis group was significantly higher than the CTD group. There was no statistically significant difference between disease groups regarding to other clinical manifestations and laboratory findings. There was no statistically significant association between disease groups and MEFV mutations regarding to genotype and allelic distribution.

Conclusions In this study, the relation between FMF and various rheumatic diseases was determined. Two new conditions, eosinophilic granulomatous polyangiitis and scleroderma were detected. The associations may be just coincidental or an extension of the common underlying pathology. To be aware of this association is important to early diagnosis and appropriate treatment.

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Address for Correspondence:
Dilek Tezcan, MD

Division of Rheumatology, Department of Internal Medicine, Selcuk University Faculty of Medicine, Konya, Turkey
E-mail: dr_dilekturan@hotmail.com

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic periodic fever syndrome characterized by recurrent polyserositis and fever attack.[1] FMF prevalence varies between 1:200-1,000 depending on geographic regions, and it mostly occurs in middle eastern and Mediterranean regions.[2] Several clinical diagnostic criteria sets have been proposed to diagnose FMF (Tel-Hashomer, Livneh, pediatric criteria, and new Eurofever/PRINTO classification criteria). The oldest and the most widely used criteria set is the Tel Hashomer.[3,4] It is considered an autosome recessive disease, but about one-fourth of patients are heterozygote, suggesting genetic heterogeneity. FMF is caused by mutations in the MEFV gene located on chromosome 16.

MEFV codes a protein termed pyrin. In the presence of MEFV gene mutations, as a result of uncontrolled pyrin activation, caspase 1 is activated, and IL-1β expression is enhanced, and hence an exaggerated inflammatory response arises.[5] Although the phenotype-genotype correlation of FMF remains to be elucidated, certain variants of the MEFV gene play an important part in pathogenesis. At present, all reported MEFV variants and the associated phenotypes are recorded in the INFEVERS database (http://fmf.igh.cnrs.fr/ISSAID/infevers/), and there are around 385 known sequence variants of MEFV.[5] The most common mutations are V726A, M680I, M694V, M694I in exon 10, and E148Q in exon 2. M694V prevalence is between 20% and 65%, and it is the most common and pathogenic variant of all FMF mutations.[6] The pathogenic effect of E148Q is uncertain and its presence in over 1% of the healthy population suggests that it may be a benign polymorphism. The most critical member of the inflammasome family plays an essential role in the etiopathogenesis of FMF is the nucleotide-binding domain-like receptor (NLRP3). When activated, NLRP3 leads to cleavage and activation of IL-1β in response to many inflammatory stimuli. It is also responsible for many other inflammatory conditions and diseases.[7,8] Whether increased inflammation in FMF patients sets the stage for some inflammatory and non-inflammatory conditions is still debatable. According to previous data, it has been reported that in %12-17, 2 of FMF patients, there may be coexisting systemic inflammatory conditions. The analysis of probable comorbidities is essential for understanding their effect on clinical presentation and if they share a common etiological pathway. This study aimed to obtain information on rheumatic diseases accompanying FMF and evaluate the relationship between these diseases and FMF.

Material and Methods

Study Population and Design

Among a group of 400 FMF patients followed up at one center, 84 patients were determined to have rheumatic disease comorbidity by reviewing their medical records. Eighty-four patients over 18 diagnosed with FMF and have rheumatic disease comorbidity in the rheumatology clinic between January 2018 - March 2020 were included in this study. The accompanying rheumatological diseases were spondyloarthritis (SpA) in 36 patients (ankylosing spondylitis [AS] 32, psoriatic arthritis [PSA] 3, and inflammatory bowel disease-associated SpA 1 patients), vasculitis in 23 patients (its distribution was as follows: Behçet's disease [BD] 12, leukocytoclastic vasculitis [LCV] 2, Henoch-Schoenlein purpura [HSP] 5, Takayasu arteritis [TA] 1, eosinophilic granulomatous polyangiitis [EGPA] 1, polyarteritis nodosa [PAN] 1 patient), connective tissue disease (CTD) present in 13 (Sjogren syndrome [SS] 6, systemic lupus erythematosus [SLE] 1, scleroderma [SSc] 3, mixed connective tissue disease [MCTD] 3, rheumatoid arthritis [RA] 5 patients, juvenile idiopathic arthritis [JIA] in 4, gout in 3, hidradenitis suppurativa [HS] in 1 patients). Sex, age, duration of disease, comorbidities, family history, clinical symptoms (fever, peritonitis, pleuritis, pericarditis, arthritis, myalgia, erysipelas-like rash), genotype data (if present), laboratory results, radiological findings, and treatment information were recorded. Data on accompanying rheumatic diseases were obtained from hospital records. All current and past rheumatic comorbidities were taken into consideration and supported by health system records. Patients with a diagnosis of FMF but without rheumatic disease were excluded. All the data were compared among a total of 5 groups (vasculitis, SpA, CTD, gout, and JIA)

This study was conducted by following the principles of the Helsinki Declaration, and written informed consent was obtained from all participants. Approval for the study was obtained from the ethics committee with the decision dated 22.04.2020 and numbered 2020/182.

Classification Criteria

FMF diagnosis was made according to The Tel-Hashomer criteria.[4] It is evaluated as major and minor criteria. Major criteria are fever with peritonitis, pleuritis, and synovitis attacks; AA-type amyloidosis, response to colchicine treatment; Minor criteria are recurrent episodes of fever, erysipelas-like erythema, and history of FMF in a first-degree relative. For the definitive diagnosis, two major or one major and two minor findings should accompany.

We included patients, as defined by accepted diagnostic criteria at the time studies were identified. Patients diagnosed with SSc according to 2013 classification criteria, SS according to 2016 ACR/EULAR SS classification criteria, SLE according to SLICC 2012 classification criteria, RA according to 2010 ACR/EULAR RA classification criteria, BD according to the International Working Group criteria, SpA according to the 2009 ASAS classification criteria were included. Other patients were also defined according to diagnostic criteria accepted at the time of the study. Organ involvement was evaluated according to clinical symptoms and the results of various diagnostic tests.

Laboratory Measurements

Blood was analyzed to obtain CBC results, including the leukocyte, hemoglobin, platelet, lymphocyte, neutrophil, and monocyte counts. Urine protein, erythrocyte sedimentation rate (ESR; 0–20 mm/hour), and C-reactive protein (CRP; 0-8 mg/L) of the patient were recorded.

Assessment of Genetic Analyses

Results of all MEFV gene whole gene sequence analyses were retrieved from the database of our hospital. HLA-B27 and HLA-B51 genetic analysis data were obtained retrospectively from the hospital database system.

Statistical Analysis

All statistical analysis was performed using R version 3.6.0 (the R Foundation of Statistical Computing, Vienna, Austria; https://www.r-project.org). To assess the normality of the data, Shapiro-Wilk's normality test and Q-Q plots were used, and also Levene's test was used to check the homogeneity of the variances. Numerical variables were presented as mean±standard deviation (minimum-maximum) or median with interquartile range. Categorical variables were described as count (n) and percentage (%). One–way ANOVA (analysis of variance) followed by Tukey HSD post-hoc test and Kruskal-Wallis test followed by Dunn post-hoc test with Bonferroni correction was run to determine whether there was a statistically significant difference between numerical variables and groups (SPA, vasculitis, and CTD). Moreover, the Pearson chi-square test followed by two proportions Z-test with Bonferroni correction and Fisher-Freeman-Halton exact test were conducted to examine whether there was a statistically significant association between categorical variables and groups. The allelic distribution of the mutations according to groups were compared using three sample proportion tests with and without continuity correction. The significance level was set at 5%.

Results

Eighty-four patients with comorbid FMF and rheumatic disease were included in this study. 32 (38.1%) males and 52 (61.9%) female participants with a mean age of 38.36±13.68 (17-78). There were 18 patients over the age of 40. Musculoskeletal involvement was predominant in these patients, and they had a low penetrating mutation, except for two homozygous patients for M694V mutation. The demographical characteristics, clinical manifestation and laboratory findings of the patients were given in Table 1. The duration of FMF disease is 8±5 (1-24) years. The most common symptoms were decreasing order of frequency recurrent abdominal pain 98.8%, fever 22.6%, arthritis 17.9%, lower back pain 9.5%, pleuritis 7.1%, erysipelas-like erythema 3.6%. A family history of FMF was found in 39 (46.4%) out of 84. Mean proteinuria was found to be

Table 1. Demographical characteristics, clinical manifestations and laboratory findings of the patients.

	All patients (n=84)	SPA (n=36)	Vasculitis (n=23)	CTD (n=18)	p-value†	Gout (n=3)	JIA (n=4)
Demographic characteristics							
Age (years)					<0.001[1]		
Mean±SD	38.36±13.68	34.72±11.37[a]	39.91±13.35	48.67±12.68[b]		30.33±17.10	21.75±3.40
Min-max	17-78	18-64	20-62	33-78		19-50	17-25
Gender					0.233[2]		
Female	52 (61.9)	20 (55.6)	16 (69.6)	14 (77.8)		1 (33.3)	1 (25)
Male	32 (38.1)	16 (44.4)	7 (30.4)	4 (22.2)		2 (66.7)	3 (75)
Clinical manifestations							
Fever	19 (22.6)	13 (36.1)[a]	1 (4.3)[b]	4 (22.2)	0.019[2]	0 (0)	1 (25)
Abdominal pain	83 (98.8)	35 (97.2)	23 (100)	18 (100)	>0.999[3]	3 (100)	4 (100)
Pleuritis	6 (7.1)	4 (11.1)	2 (8.7)	0 (0)	0.466[3]	0 (0)	0 (0)
Erysipelas-like erythema	3 (3.6)	0 (0)	2 (8.7)	1 (5.6)	0.139[3]	0 (0)	0 (0)
Arthritis	15 (17.9)	5 (13.9)	4 (17.4)	4 (22.2)	0.741[2]	0 (0)	2 (50)
Lower back pain	8 (9.5)	6 (16.7)	1 (4.3)	0 (0)	0.110[3]	1 (33.3)	0 (0)
Family history	39 (46.4)	13 (36.1)	10 (43.5)	11 (61.1)	0.234[3]	2 (66.7)	3 (75)
Laboratory findings							
Hemoglobin (g/dL)	13.60 (12.45-14.57)	13.80 (12.68-15.07)	13.30 (12.45-14.8)	12.80 (12.13-13.75)	0.177[4]	15.60 (15.05-15.8)	14.05 (13.53-14.43)
Leukocyte (10^9/L)	7.20 (5.88-9.33)	7.40 (6.22-9.35)	7.90 (6.10-9.45)	6.05 (5.50-6.95)	0.126[4]	8.10 (6.95-8.1)	9.95 (9.5-10.20)
Neutrophil (10^9/L)	3.90 (3.21-5.40)	3.90 (3.20-5.10)	5.05 (3.58-5.92)	3.30 (3.20-3.93)	0.067[4]	3.80 (3.65-4.35)	7.25 (6.43-7.75)
Lymphocyte (10^9/L)	2.09 (1.70-2.52)	2.20 (1.85-2.68)	1.97 (1.60-2.45)	1.92 (1.72-2.31)	0.318[4]	2.40 (1.95-2.85)	1.85 (1.73-2.67)
Monocytes (10^9/L)	0.50 (0.40-0.70)	0.53 (0.40-0.75)	0.51 (0.41-0.76)	0.43 (0.40-0.54)	0.151[4]	0.50 (0.50-0.60)	0.80 (0.65-1.20)
Platelet (10^9/L)	264.5 (205-326.75)	279 (206.5-340.25)	254 (205-318)	252.5 (203.5-293.5)	0.578[4]	260 (224.5-306.5)	327 (250.75-397.25)
CRP (mg/L)	5.35 (3-12.05)	5.80 (3-12.40)	10 (4.5-17.5)[a]	3.75 (2.32-6.72)[b]	0.040[4]	4 (3.45-5.70)	15.25 (4.47-32.75)
ESR (mm/h)	14.5 (7-27)	11 (6.75-25.25)	18 (12.5-28.5)	15 (8-22.75)	0.370[4]	5 (3.5-5.5)	27.5 (16.25-37.25)
Urine protein (mg/day)	116 (68.75-173)	100 (50.75-173)	134 (75-175.5)	106.5 (76.38-167)	0.404[4]	101 (83-107)	185 (140-229)

Data were presented as mean±standard deviation (minimum-maximum), median (interquartile range: 25th percentile-75th percentile) or count (n), and percentage (%). p values <0.05 indicate that statistically significant.
p-value† shows a comparison of SPA, vasculitis, and STD groups (gout and JIA were excluded from statistical analysis due to the small sample size).
Different small superscript letters in each column denote that statistically significant difference between groups.
[1]One-Way ANOVA followed by Tukey HSD multiple comparison tests.
[2]Pearson chi-square test followed by Two proportion Z-test with Bonferroni correction.
[3]Fisher-Freeman-Halton exact test.
[4]Kruskal-Wallis test followed by Dunn multiple comparison test with Bonferroni correction.
SPA: spondyloarthropathy, CTD: connective tissue disease, SD: standard deviation, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

239 mg/day. In three patients, proteinuria at the level of 500 mg or over was observed.

The most common accompanying rheumatological disease was SpA in 36 (43%) patients. AS was detected in 32 (38.9%), PSA in 3 (3.6%), and inflammatory bowel disease-associated SpA in 1 (1.2%) patient. Vasculitis was the second most common comorbid disease group in FMF with a rate of 26.2%. Its distribution was as follows: BD 12, LCV 2, HSP 5, TA 1, EGPA 1, PAN 1 patients. CTD present in 18 (21.4%) (SS 6, SLE 1, SSc 3, MCTD 3, RA in 5 [6%]), JIA in 4 (4.8%), gout in 3 (3.6%), HS in 1 (1.2%) patient *(Table 2)*. 17 patients who had comorbid AS underwent HLA-B27 analysis and it was found to be positive in two patients. FMF patients with radiographically detected sacroiliitis, the rate of M694V mutation was high. Enthesitis is present in 11.9% of FMF patients accompanying SPA. Eleven patients with comorbid BD underwent HLA-B51 analysis, with positive results in 4 patients. One patient had neuro-BD, four vascular involvement, two joint and eye involvement, four isolated mucocutaneous involvement, and no gastrointestinal involvement in BD patients. Thrombosis was present in 30% of patients with BD, and of these, all but one had M694V mutation. Coexistence with SS was detected in six patients.

Table 2. Comorbidities in patients with familial Mediterranean fever.

Diseases	n=84	(%)
Spondyloarthropathy		
Ankylosing spondylitis	32	38.1
Psoriatic arthritis	3	3.6
Inflammatory bowel disease-associated spondyloarthritis	1	1.2
Vasculitides		
Behcet's disease	12	14.3
Henoch-Schönlein purpura	5	6
Leukocytoclastic vasculitis	3	3.6
Eosinophilic granulomatous polyangiitis	1	1.2
Polyarteritis nodosa	1	1.2
Takayasu arteritis	1	1.2
Connective Tissue Disease		
Sjogren syndrome	6	7.1
Systemic lupus erythematosus	1	1.2
Scleroderma	3	3.6
Mixed connective tissue disease	3	3.6
Rheumatoid arthritis	5	6
Juvenile idiopathic arthritis	4	4.8
Gout	3	3.6

In five of these patients, there was a MEFV mutation in exon 10 without any life-threatening organ involvement. No serositis was detected in MCTD patients with M694V mutation. One SSc patient had limited, and two patients had widespread skin involvement. There was no interstitial lung disease and pulmonary hypertension. Two patients had M694V mutations in SSc patients. As a medical treatment, all patients used colchicine. Azathioprine was used in 11 (13.1%), anakinra in 1 (1.2%), anti-TNF in 7 (8.3%), DMARD in 45(53.6%), allopurinol in 2 (2.4%), cyclosporin in 1 (1.2%) patients.

There was a statistically significant difference between disease groups as determined by One-way ANOVA (F=7.741, p=0.001). A Tukey post hoc test revealed that the mean age of the patients in the CTD group was statistically significantly higher than the patients in the SPA group (48.67±12.68 vs. 34.72±11.37, p=0.001), but there was no significant difference between the mean age of the patients in the vasculitis group (39.91±13.35, p=0.067). There was no statistically significant difference between the vasculitis and SPA groups (p=0.260). The gender distribution of the groups was similar (Pearson $\chi^2$2=2.911, p=0.233). A Pearson chi-square test found that there was a statistically significant association between the disease groups and fever (Pearson χ^2=7.922, p=0.019). Post-hoc two proportions Z-test with Bonferroni adjustment show that the rate of patients in the SPA group with signs of fever was significantly higher than those in the Vasculitis group (n=13 [36.1%] vs. n=1 [4.3%]). A Kruskal-Wallis test showed that there was a statistically significant difference in CRP value between the different disease groups (χ^2=6.447, p=0.040). Post-hoc Dunn tests using a Bonferroni-adjusted alpha level of 0.016 were used to compare all pairs of groups. The median CRP value of the patients in the vasculitis group was significantly higher than the patients in the CTD group (10 [IQR, 4.5-17.5] vs. 3.75 [IQR, 2.32-6.72], p=0.011). The other comparisons were not statistically significant after the Bonferroni adjustment (all p=0.016). There was no statistically significant difference between disease groups regarding to other clinical manifestations and laboratory findings (all p>0.05) *(Table 1)*.

The genotype and allele frequency of FMF according to the MEFV mutations were given in Table 3. MEFV gene mutation was investigated in 70 (83.33%) patients. In these patients, the most common mutation was M694V heterozygote, which was found in 30 (42.85%) patients. M694V homozygote was found in 15 (21.42%), M680I heterozygote in 10 (14.28%), M680I homozygote in 2 (2.85%), E148Q homozygote in 1(1.42%), E148Q heterozygote in 1(1.42%), V726A homozygote in 0 (0%), V726A heterozygote in 5 (7.14%), the normal mutation in 1 (1.42%), others in (E520V, R761H, P369S, R202Q, M801) 9 (12.85%) patients, also were not tested from 13 (18.57%) patients *(Table 3)*. Among the detected mutations, 13 (15.5%) of the patients were defined as compound heterozygous. A Fisher-Freeman-Halton exact test and a three-sample proportion test with and without continuity correction test showed that there was no statistically significant association between disease groups and MEFV mutations regarding to genotype and allelic distribution (all p>0.05) *(Table 3)*.

Table 3. Comparison of genotype and allele frequency of FMF according to the MEFV mutations.

	All patients (n=84)	SPA (n=36)	Vasculitis (n=23)	CTD (n=18)	p-value	Gout (n=3)	JIA (n=4)
No. patients included in the calculation‡	70	27	21	15			
M694V gene mutation					0.776[1]		
Homozygote	15 (33.3)	6 (31.6)	6 (40)	3 (27.3)		-	1 (25)
Heterozygote	30 (66.7)	13 (68.4)	9 (60)	8 (72.7)		3 (100)	3 (75)
Allelic distribution	60/140 (42.86)	25/54 (46.3)	21/42 (50)	14/30 (46.67)	0.930[2]	3/6 (50)	5/8 (62.50)
M680I gene mutation					0.455[1]		
Homozygote	2 (16.7)	2 (33.3)	0 (0)	0 (0)		-	-
Heterozygote	10 (83.3)	4 (66.7)	3 (100)	3 (100)		-	1 (100)
Allelic distribution	14/140 (10)	8/54 (14.82)	3/42 (7.14)	3/30 (10)	0.483[2]	-	1/8 (12.50)
E148Q gene mutation					NA		
Homozygote	1 (50)	1 (100)	0 (0)	0 (0)		-	-
Heterozygote	1 (50)	0 (0)	1 (100)	0 (0)		-	-
Allelic distribution	3/140 (2.14)	2/54 (3.7)	1/2 (2.38)	0/30 (0)	0.566[2]	-	-
V726A gene mutation					>0.999[1]		
Homozygote	0 (0)	0 (0)	0 (0)	0 (0)		-	-
Heterozygote	5 (100)	0 (0)	2 (100)	3 (100)		-	-
Allelic distribution	5/140 (3.57)	0/54 (0)	2/42 (4.76)	3/30 (10)	0.076[2]	-	-
Others					0.286[1]		
Homozygote	4 (44.4)	1 (20)	2 (66.7)	1 (100)		-	-
Heterozygote	5 (55.6)	4 (80)	1 (33.3)	0 (0)		2 (100)	-
Allelic distribution	13/140 (9.29)	6/54 (11.11)	5/42 (11.9)	2/30 (6.67)	0.747[2]	2/6 (33.33)	-
Normal	1 (1.2)	1 (2.8)					
No test	13 (15.5)	8 (22.2)	2 (8.7)	3 (16.7)			

Data were described as number (n) and percentage (%).
p-value[1] shows the comparison of SPA, vasculitis, and STD groups (gout and JIA were excluded from statistical analysis due to the small sample size) and was calculated using Fisher-Freeman-Halton exact test.
p-value[2] shows comparison of SPA, vasculitis, and CTD groups (gout and JIA were excluded from statistical analysis due to the small sample size) and was calculated using a 3-sample proportion test with and without continuity correction.
‡Patients who did not show mutations and were not tested were excluded from the analysis for allelic distribution.
SPA: spondyloarthropathy, CTD: connective tissue disease, NA: not applicable.

Discussion

FMF, which is the most common inherited autoinflammatory disease, still has many unknown aspects, despite much information. In a few FMF patient series, there was a slight male predominance. In this study females were preponderant. Although FMF usually arises at young ages, it may rarely emerge after 40. Patients with late-onset have lower rates of mutation in exon 2 and exon 10 of the MEFV gene. They display higher rates of musculoskeletal system

symptoms and a lower rate of serositis during attacks; therefore, they are associated with milder disease responding to lower doses of colchicine.[9] Consistent with the literature, in this study, in 18 patients diagnosed after 40, there were low penetrating mutations except for 2 cases who were M694V homozygote and musculoskeletal findings predominant.

In FMF, inflammation is not restricted to severe inflammation during periodic attacks, and chronic subclinical inflammation may continue between attacks. This chronic proinflammatory condition may play a triggering role in the development of some diseases. The coexistence of FMF with diseases such as SpA, BD, RA, SS, JIA, IBD, and PAN has been reported. Some of these inflammatory conditions may be regarded as coincidental, but some have reached important figures, suggesting an association between them. The exact mechanism of this association is unknown; however, it may be due to predisposing effects of impaired immune pathways in FMF. Mutations in NLR proteins are strongly associated with autoimmune diseases. In FMF, pyrin, which has undergone mutation, interacts with the inflammasome, activating caspase-1, which leads to overexpression of many cytokines, including IL-1β, IL-6, and IL-18. IL-1β upregulates IL-2 receptors, prolongs T cells' lifespan, and plays an important role in the proliferation of B cells and antibody production. IL-1β also has a key role in the differentiation of Th17 cells, essential in the adaptive immune system.[10,11]

The SpA was the most common comorbid inflammatory condition in this study, with a rate of 43%. The SpA is a well-known MHC-I-apathy with a strong relation with HLA-B27 and completely overlaps with typical characteristics of neither autoimmune nor autoinflammatory diseases. SpA prevalence increases in FMF patients and their first-degree relatives. It has been reported that the prevalence of SpA is as high as 7% in FMF patients.[12] The articular symptoms of FMF have characteristics overlapping with SpA, and the increased prevalence of SpA in FMF patients suggests a relation between the two disorders. Furthermore, it has been reported that sacroiliitis, which is the hallmark of SpA, are higher than expected rates in FMF patients with musculoskeletal symptoms. In a recent study, the incidence of sacroiliitis in FMF patients was established to be 2.6%.

Nevertheless, current data on HLA-B27 in the development of sacroiliitis in FMF patients are controversial. HLA-B27 was positive merely in 11% of our patients with SpA. This finding indicates that HLA-B27 does not have an essential role in the pathogenesis of FMF-associated SpA and that other pathophysiological mechanisms are required to explain the relation between SpA and FMF. A new study demonstrated the relationship between the IL1R2 gene and AS. Therefore, candidate gene and genome-wide association studies suggest that in addition to the IL-17 pathway associated with IL-23R, there is also an increased risk of AS in association with the IL-1 cytokine pathway.[11,13] SpA associated endoplasmic reticulum-associated aminopeptidase 1 plays a role in the modulation of IL-1, IL-6, and TNF.[14,15] There is some evidence that M694V variation may be more common in FMF patients with sacroiliitis.[16-18] A common result of the present study and the aforementioned studies is that the prevalence of M694V mutation is high among FMF and SpA patients. In this study, of 36 FMF patients with SpA, MEFV mutation analysis was performed in 28 patients. Besides, in FMF patients with radiographically detected sacroiliitis, the rate of M694V mutation was higher, similar to the literature. Furthermore, enthesitis, which is the hallmark of SpA, has been reported in FMF. Compared to AS, in FMF patients with SpA, peripheral arthritis and enthesitis occurred more commonly, and uveitis and syndesmophyte less commonly in the previous study.[19] In this study, the rate of enthesitis was 11.9%.

Inflammasomes play a crucial role in the development of various skin diseases such as psoriasis and HS.[20] In a recent population-based study by Hodak *et al.*[19], a strong relationship between HS and FMF has been reported. In this study, there was one HS, one enteropathic arthritis, and three PSA patients. Ashida *et al.*[21] demonstrated Th17 cells in the upper dermis of lesions similar to psoriasis in a patient with FMF. It is estimated that high IL-1 levels in FMF patients may lead to Th17 activation and direct stimulation of keratinocytes. The level

of IL-1 produced by active T lymphocytes is high in psoriasis lesions.[21] FMF and IBD have many similar clinical and biological properties and may accompany FMF. MEFV mutation has been detected in IBD as well, making diagnosis more challenging.[22]

Vasculitis is the second most common inflammatory disease occurring in FMF patients, with a rate of 26%.[23] The relation between FMF and vasculitis has long been debated. The risk of vasculitis development seems to be increased in FMF patients. High serum IL-6 levels, which remain elevated even during relapse-free periods, have been reported. Although the exact pathogenesis of FMF-associated vasculitis remains unknown, an increase in serum levels of all pro-inflammatory cytokines, including IL-1β, IL-6, IL-18, IL-33, and INF-γ and resulting in endothelial cell dysfunction (ECD), seems to be important. IL-1 is the most predominant among these cytokines, and high IL-1β activity may promote vasculitis in FMF patients. It has been demonstrated that IL-1β and TNF-α mediate type II activation of endothelial cells and cause ECD by leading to the long-term inflammatory response. As reported in a recent comprehensive review, ECD, increased atherosclerotic burden, and thrombocyte activation are important characteristics of FMF and are maintained even in attack-free periods of FMF. A few reports have been published in the last few years, which relate subclinical inflammation to hypercoagulopathy and thrombosis in FMF. MEFV gene mutations associated with FMF may contribute to vasculitis in some FMF patients by producing high proinflammatory cytokine levels. The role played by environmental factors, especially streptococcal infections, seems to be important.[24,25] Studies report the increased prevalence of HSP or PAN in both pediatric and adult FMF patients was published. The prevalence of HSP in FMF patients ranged from 2.7% and 7.2% in four studies in Turkey and Israel. In this study, 22 patients were diagnosed with vasculitis and FMF, and four of them had HSP. HSP findings emerged after the diagnosis of FMF, and the male/female ratio was 3/1. The literature demonstrated that most FMF patients reported having HSP or PAN as well had homozygote or compound heterozygote M694V mutations; our findings agreed with the literature.[24,26] It has been reported that patients with HSP with MEFV mutations are younger and have higher rates of edema and acute phase responses than those without such mutations. Can *et al*.[27] stated that 45% of patients with HSP had MEFV mutations, but these mutations were unrelated to the clinical course and complications. Some authors suggested that HSP-like vasculitis in FMF is a specific feature of FMF.[25] In agreement with Ben Chetrit *et al*.[28], we established LCV in our patients, but no IgA accumulation was detected. PAN is the second most common FMF-associated vasculitis, involving 0.9–1.4% of patients.[28] It has been reported that compared to other PAN patients, FMF-associated PAN arises at younger ages, has lower HBS antigen positivity, and peripheral nerve involvement is absent. However, myalgia, perirenal hematoma, and central nervous system involvement were more common, and the prognosis was more favorable.[24,25] There is still no consensus on whether PAN occurring in FMF is coincidental or directly associated with it. M694 V is the most common mutation in patients with FMF and PAN. Consistent with the literature, symptoms of our 32-year-old male patient with M694V mutation, were mild. After HSP and PAN, BD is the third most common vasculitis encountered in FMF patients. Due to the absence of T and B cells in its pathogenesis, the episodic pattern of disease course, and abnormally increased inflammatory response, BD is a polygenic autoinflammatory disease. MEFV gene, IL-1, is an important cytokine in BD. BD and FMF share some common characteristics, such as geographical distribution and clinical symptoms. Tunca *et al*.[29] reported the prevalence of BD to be 0.5% among 2,838 FMF patients in Turkey. In 2017, it was stated by Watad *et al*.[30] that in patients with BD, the prevalence of FMF increases considerably. The male/female ratio in FMF and patients with BD varied between different studies. Watad *et al*.[30] reported a male/female ratio of 0.4 in FMF-BD. In or series, the M/F ratio was 1/3, with female predominance. FMF patients with or without accompanying BD presented with a similar FMF phenotype. In the literature, in BD accompanying FMF, the rate of gastrointestinal

and CNS involvement was found to be higher. In our patient series, one patient had neuro-BD, four vascular involvement, two joint and eye involvement, four isolated mucocutaneous involvement, and no GIS involvement. Whether FMF and BD are separate clinical entities or have common characteristics which cannot be ascribed to coincidence is still disputed. According to Ben-Chetrit and Yazıcı[28,31], there is no association between FMF and BD. Schwartz *et al*.[32] concluded that FMF and BD coexisted in the same people more frequently than expected, and BD should be incorporated into other vasculitides widespread in FMF. Therefore, the overlapping of some disease features has suggested a common genetic susceptibility in BD and FMF, and both disorders suggest that there is a common genetic susceptibility in BD and FMF. Both disorders may represent the opposite poles of the same disease axis. It was also observed that MEFV mutations increased susceptibility to BD and increased the risk of venothrombotic events in patients with BD patients, suggesting that pyrin, which has undergone mutation, plays suggesting that pyrin, which has undergone mutation, may play a direct role in the pathogenesis of BD. In our series, thrombosis was present in 30% of patients with BD, and of these, all but one had M694V mutation. It has been proposed that these mutations may be associated with the pathogenesis of BD. In the study of Yazıcı *et al*.[31] evaluating 100 patients with BD, MEFV mutations (M694V, E148Q, M680I, V726A) were detected in 27% of patients. The most common mutation was M694V. They also evaluated the relation between MEFV mutations and clinical data of BD, finding no relation. In the study of Taşliyurt *et al*.[33], it was established that the rate of MEFV mutations in Turkish patients with BD was 39%, and it was thought that E148Q and M680I mutations might play a part in the pathogenesis of BD. The rates of uveitis were found to be significantly lower in patients with BD with MEFV mutations.[34] Nevertheless, in this study, MEFV mutation was detected in two patients with uveitis. Livneh *et al*.[35] determined that despite a single MEFV allele with mutation, BD was present in 10 out of 11 patients with clinical expression of FMF. There were four heterozygote patients in our series. However, studies with a larger sample size are warranted to demonstrate the role of MEFV mutations in the pathogenesis of BD.

In addition to these widespread vasculitis symptoms, some case reports on FMF patients with central nervous system vasculitis, coronary vasculitis, TA, Cogan syndrome, and cutaneous vasculitis.[36,37] In this study, FMF coexisted with cutaneous vasculitis in four patients, with TA in one patient and EGPA in one patient. As far as we know, no association between FMF and EGPA has been reported so far. Although these cases are considered FMF-associated vasculitis, we believe that there is no adequate evidence to rule out a coincidental relationship with FMF.

Gout arthritis and FMF share some clinical and pathological characteristics such as classification as autoinflammatory disease, relations with the inflammasome short-term intermittent arthritis, and good response to colchicine and anti-interleukin-1 treatment. It has commonly been accepted that mono-sodium urate activates the NLRP3 inflammasome, leading to the production and release of proinflammatory cytokines.[38] Sari *et al*.[39] investigated the frequency of MEFV gene mutation in patients with gout arthritis and established that E148Q was the most commonly encountered mutation. However, this finding should be cautiously interpreted owing to the high prevalence of this mutation in the normal population (18.3%). Karaarslan *et al*.[40] demonstrated high rates of MEFV gene mutation in 93 patients and concluded that MEFV gene mutations might play an essential part in the pathogenesis of the disease. In 3 patients with gout arthritis in this study, the most common MEFV mutation was M694V.

Although acute, non-erosive arthritis is one of the most important clinical findings of FMF, chronic arthritis may also occur in FMF patients. Pyrin may function as a sensor for the inactivation of Rho GTPase caused by pathogens in the impaired intestinal flora. Dysbiosis may lead to post-translational modification of autoantibodies and subsequently to RA development, and it was established in patients with RA. Therefore, dysbiosis of intestinal bacteria may trigger natural and adaptive immunity leading to RA and FMF. Anti-citrullinated protein antibodies (ACPA)

were found to be markedly more common in FMF patients.[41] In three of our five cases with RA, ACPA levels were found to be high. In various studies, the prevalence of JIA in FMF patients varies between 3.6% and 8%. JIA was present in 5% of our patients. The rate of M694V mutation was found to be around 10% in JIA, and these cases were more severe and recalcitrant to treatment.[37] In this study, in JIA cases, M694V mutation was present one patient as homozygote and three patients as heterozygote. Hence, in children assumed to have JIA, it is recommended that MEFV gene mutations be screened.

Although CTD and FMF coexist very rarely, there are a few cases reported in the literature. In this study, there were six cases of SS, one case of SLE, three cases of SSc, and three cases of MCTD. In a large Turkish cohort with 32,716 FMF patients, four cases of SLE were detected.[11] In patients with SLE with pericardial/pleural effusion, MEFV gene variants were more common. In a multi-center study including 3,000 Turkish FMF patients, no case of SLE was detected. A recent study demonstrated carrier status of MEFV mutation protected from more severe kidney involvement while enhancing excessive inflammatory symptoms such as fever and pleuritis.[42] In contrast, Deniz *et al*.[43] showed that exon 10 mutations were associated with SLE nephritis. In our cases with lupus, there was no nephritis and pleuritis. Some evidence regarding the relation between FMF and SS.[44] Tanaka *et al*.[45] found higher IL-18 levels in patients with concurrent SS and FMF and suggested that FMF-associated irregular IL-18 production and chronic inflammation are related to the development of SS. Coexistence with SS was detected in six patients in our cohort. In five of these patients, there was a MEFV mutation in exon 10 without any life-threatening organ involvement. It has been stated that MEFV mutation may contribute to the clinical symptoms of MCTD, including serositis, through the alteration in pyrin inflammasome function.[46] No serositis was detected in our MCTD patients with M694V mutation. There was no concurrence with SSc in the literature reported so far. One SSc patient had limited, and two patients had widespread skin involvement. There was no interstitial lung disease and pulmonary hypertension. Two patients had M694V mutations. In countries where FMF is endemic, in connective tissue disease patients with atypical clinical symptoms such as unexplained acute phase response, intermittent abdominal and back pain, and inadequate response to treatment, FMF should be borne in mind. The number of patients was too few to conclude the relationship between MEFV gene mutation and CTD development.

This study has some limitations. As it is a single-center cross-sectional study, it is not possible to generalize these results to the general population. Moreover, the research included a relatively small number of patients (n=84). In this regard, the results and conclusions should be interpreted with caution. Finally, there were patients without any genetic analysis.

Conclusion

A wide range of other rheumatic diseases associated with FMF has been described. The high correlation reported between them reflects the similarities in clinical presentation in conjunction with probable common genetic and ethnic background. We also established two new conditions, i.e., EGPA and scleroderma, which may be associated with FMF. This concurrence may only be coincidental or reflect an extension of the underlying pathology of FMF. The determination of pathological pathways connecting FMF to these diseases requires further investigations to be conducted.

Learning Points

FMF can coexist with various rheumatic diseases. Related diseases might have a causality relationship with FMF. They can be due to common genetic predisposition, immune dysfunction, or autoinflammation itself. The healthcare provider must be aware of these associations to detect them timely, treat them appropriately, and improve the prognosis.

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Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: DT, SY, ML; Study Design: DT, SY, ML; Supervision: DT, SG, ML; Materails: DT, SG; Data Collection and/or Processing: DT, SG; Statistical Analysis and/or Data Interpretation: DT, SY; Literature Review: DT; Manuscript Preparation: DT; Critical Review: DT, SY.

References

1. Ozdogan H, Ugurlu S. Familial Mediterranean fever. Presse Med. 2019 Feb;48(1 Pt 2):e61-e76. doi: 10.1016/j.lpm.2018.08.014.
2. Tufan A, Lachmann HJ. Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. Turk J Med Sci. 2020; 50(SI-2):1591-1610. doi: 10.3906/sag-2008-11.
3. Tanatar A, Sönmez HE, Karadağ ŞG, Çakmak F, Çakan M, Demir F, Sözeri B, Ayaz NA. Performance of Tel-Hashomer, Livneh, pediatric and new Eurofever/PRINTO classification criteria for familial Mediterranean fever in a referral center. Rheumatol Int. 2020 Jan;40(1):21-7. doi: 10.1007/s00296-019-04463-w.
4. Demirkaya E, Saglam C, Turker T, Koné-Paut I, Woo P, Doglio M, Amaryan G, Frenkel J, Uziel Y, Insalaco A, Cantarini L, Hofer M, Boiu S, Duzova A, Modesto C, Bryant A, Rigante D, Papadopoulou-Alataki E, Guillaume-Czitrom S, Kuemmerle-Deschner J, Neven B, Lachmann H, Martini A, Ruperto N, Gattorno M, Ozen S; Paediatric Rheumatology International Trials Organisations (PRINTO); Eurofever Project. Performance of different diagnostic criteria for familial Mediterranean fever in children with periodic fevers: Results from a Multicenter International Registry. J Rheumatol. 2016 Jan;43(1):154-60. doi: 10.3899/jrheum.141249.
5. Skendros P, Papagoras C, Mitroulis I, Ritis K. Autoinflammation: Lessons from the study of familial Mediterranean fever. J Autoimmun. 2019 Nov;104:102305. doi: 10.1016/j.jaut.2019.102305.
6. Sönmez HE, Batu ED, Özen S. Familial Mediterranean fever: current perspectives. J Inflamm Res. 2016 Mar 17;9:13-20. doi: 10.2147/JIR.S91352.
7. Kasifoglu T, Bilge SY, Sari I, Solmaz D, Senel S, Emmungil H, Kilic L, Oner SY, Yildiz F, Yilmaz S, Bakirli DE, Tufan MA, Yilmaz S, Yazisiz V, Pehlivan Y, Bes C, Cetin GY, Erten S, Gonullu E, Temel T, Sahin F, Akar S, Aksu K, Kalyoncu U, Direskeneli H, Erken E, Kisacik B, Sayarlioglu M, Korkmaz C. Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. Rheumatology (Oxford). 2014 Apr;53(4):741-5. doi: 10.1093/rheumatology/ket400.
8. Yasar Bilge NS, Sari I, Solmaz D, Senel S, Emmungil H, Kilic L, Yilmaz Oner S, Yildiz F, Yilmaz S, Ersozlu Bozkirli D, Aydin Tufan M, Yilmaz S, Yazisiz V, Pehlivan Y, Bes C, Yildirim Cetin G, Erten S, Gonullu E, Sahin F, Akar S, Aksu K, Kalyoncu U, Direskeneli H, Erken E, Sayarlioglu M, Cınar M, Kasifoglu T. Comparison of early versus late onset familial Mediterranean fever. Int J Rheum Dis. 2018 Apr;21(4):880-4. doi: 10.1111/1756-185X.13259.
9. Bouomrani S, Masmoudi I, Teber SB. Familial Mediterranean fever: What associations to screen for? Reumatologia. 2020;58(3):150-4. doi: 10.5114/reum.2020.96688.
10. Atas N, Armagan B, Bodakci E, Satis H, Sari A, Bilge NSY, Salman RB, Yardımcı GK, Babaoglu H, Guler AA, Karadeniz H, Kilic L, Ozturk MA, Goker B, Haznedaroglu S, Kalyoncu U, Kasifoglu T, Tufan A. Familial Mediterranean fever is associated with a wide spectrum of inflammatory disorders: results from a large cohort study. Rheumatol Int. 2020 Jan;40(1):41-8. doi: 10.1007/s00296-019-04412-7.
11. Akar S, Soysal O, Balci A, Solmaz D, Gerdan V, Onen F, Tunca M, Akkoc N. High prevalence of spondyloarthritis and ankylosing spondylitis among familial Mediterranean fever patients and their first-degree relatives: further evidence for the connection. Arthritis Res Ther. 2013 Jan 28;15(1):R21. doi: 10.1186/ar4154.
12. Akkoc N, Gul A. Familial Mediterranean fever and seronegative arthritis. Curr Rheumatol Rep. 2011 Oct;13(5):388-94. doi: 10.1007/s11926-011-0191-9.
13. Watad A, Bragazzi NL, Adawi M, Shoenfeld Y, Comaneshter D, Cohen AD, McGonagle D, Amital H. FMF is associated with a wide spectrum of MHC class I- and allied SpA disorders but not with classical MHC class II-associated autoimmune disease: Insights from a large cohort study. Front Immunol. 2019 Nov 26;10:2733. doi: 10.3389/fimmu.2019.02733.
14. Haj-Yahia S, Ben-Zvi I, Lidar M, Livneh A. Familial Mediterranean fever (FMF)-response to TNF-blockers used for treatment of FMF patients with concurrent inflammatory diseases. Joint Bone Spine. 2021 Apr 28;88(5):105201. doi: 10.1016/j.jbspin.2021.105201.
15. Kaşifoğlu T, Calişir C, Cansu DU, Korkmaz C. The frequency of sacroiliitis in familial Mediterranean fever and the role of HLA-B27 and MEFV mutations in the development of sacroiliitis. Clin Rheumatol. 2009 Jan;28(1):41-6. doi: 10.1007/s10067-008-0980-3.
16. Yıldırım DG, Fidan HK, Gönen S, Söylemezo□lu O. Sacroiliitis associated with familial Mediterranean fever in childhood: a case series and review of literature. Turk J Pediatr. 2020;62(2):175-81. doi: 10.24953/turkjped.2020.02.002.
17. Li Z, Akar S, Yarkan H, Lee SK, Çetin P, Can G, Kenar G, Çapa F, Pamuk ON, Pehlivan Y, Cremin K, De Guzman E, Harris J, Wheeler L, Jamshidi A, Vojdanian M, Farhadi E, Ahmadzadeh N, Yüce Z, Dalkılıç E, Solmaz D, Akın B, Dönmez S, Sarı İ, Leo PJ, Kenna TJ, Önen F, Mahmoudi M, Brown MA, Akkoc N. Genome-wide association study in Turkish and Iranian populations identify rare familial Mediterranean fever gene (MEFV) polymorphisms associated with ankylosing spondylitis. PLoS Genet. 2019 Apr 4;15(4):e1008038. doi: 10.1371/journal.pgen.1008038.
18. Yazici A, Ozdemir Isik O, Temiz Karadag D, Cefle A. Are there any clinical differences between ankylosing spondylitis patients and familial Mediterranean fever patients with ankylosing spondylitis? Int J Clin Pract. 2021 Jan;75(1):e13645. doi: 10.1111/ijcp.13645.
19. Hodak E, Atzmony L, Pavlovsky L, Comaneshter D, Cohen

AD. Hidradenitis suppurativa is associated with familial Mediterranean fever-a population-based study. J Invest Dermatol. 2017 Sep;137(9):2019-21. doi: 10.1016/j.jid.2017.04.024.
20. Erden A, Batu ED, Seyhoglu E, Sari A, Sönmez HE, Armagan B, Demir S, Bilgin E, Kilic L, Karadag O, Akdogan A, Bilginer Y, Ertenli I, Kiraz S, Apras Bilgen S, Kalyoncu U. Increased psoriasis frequency in patients with familial Mediterranean fever. Ups J Med Sci. 2018 Mar;123(1):57-61. doi: 10.1080/03009734.2017.1423425.
21. Ashida M, Koike Y, Kuwatsuka S, Ichinose K, Migita K, Sano S, Utani A. Psoriasis-like lesions in a patient with familial Mediterranean fever. J Dermatol. 2016 Mar;43(3):314-7. doi: 10.1111/1346-8138.13068.
22. Beşer ÖF, Çokuğraş FÇ, Kutlu T, Erginöz E, Gülcü D, Kasapçopur Ö, Erkan T. Association of familial Mediterranean fever in Turkish children with inflammatory bowel disease. Turk Pediatri Ars. 2014 Sep 1;49(3):198-202. doi: 10.5152/tpa.2014.1998..
23. Aksu K, Keser G. Coexistence of vasculitides with familial Mediterranean fever. Rheumatol Int. 2011 Oct;31(10):1263-74. doi: 10.1007/s00296-011-1840-z.
24. Abbara S, Grateau G, Ducharme-Bénard S, Saadoun D, Georgin-Lavialle S. Association of vasculitis and familial Mediterranean fever. Front Immunol. 2019 Apr 12;10:763. doi: 10.3389/fimmu.2019.00763.
25. Salehzadeh F, Enteshari Moghaddam A. Coexisting diseases in patients with familial Mediterranean fever. Open Access Rheumatol. 2020 May 28;12:65-71. doi: 10.2147/OARRR.S252071.
26. Yildiz M, Adrovic A, Tasdemir E, Baba-Zada K, Aydin M, Koker O, Sahin S, Barut K, Kasapcopur O. Evaluation of co-existing diseases in children with familial Mediterranean fever. Rheumatol Int. 2020 Jan;40(1):57-64. doi: 10.1007/s00296-019-04391-9.
27. Can E, Kılınç Yaprak Z, Hamilçıkan Ş, Erol M, Bostan Gayret Y Özgül Yigit Ö. MEFV gene mutations and clinical course in pediatric patients with Henoch-Schönlein purpura. Arch Argent Pediatr. 2018 Jun 1;116(3):e385-91. doi: 10.5546/aap.2018.eng.e385.
28. Ben-Chetrit E, Yazici H. Non-thrombocytopenic purpura in familial Mediterranean fever-comorbidity with Henoch-Schönlein purpura or an additional rare manifestation of familial Mediterranean fever? Rheumatology (Oxford). 2016 Jul;55(7):1153-8. doi: 10.1093/rheumatology/kev378.
29. Tunca M, Ozdogan H. Molecular and genetic characteristics of hereditary autoinflammatory diseases. Curr Drug Targets Inflamm Allergy. 2005 Feb;4(1):77-80. doi: 10.2174/1568010053622957.
30. Watad A, Tiosano S, Yahav D, Comaneshter D, Shoenfeld Y, Cohen AD, Amital H. Behçet's disease and familial Mediterranean fever: Two sides of the same coin or just an association? A cross-sectional study . Eur J Intern Med. 2017 Apr;39:75-8. doi: 10.1016/j.ejim.2016.10.011.
31. Yazici A, Cefle A, Savli H. The frequency of MEFV gene mutations in Behcet's disease and their relation with clinical findings. Rheumatol Int. 2012 Oct;32(10):3025-30. doi: 10.1007/s00296-011-2011-y.
32. Schwartz T, Langevitz P, Zemer D, Gazit E, Pras M, Livneh A. Behcet's disease in Familial Mediterranean fever: characterization of the association between the two diseases. Semin Arthritis Rheum. 2000 Apr;29(5):286-95. doi: 10.1016/s0049-0172(00)80015-3.
33. Tasliyurt T, Yigit S, Rustemoglu A, Gul U, Ates O. Common MEFV gene mutations in Turkish patients with Behcet's disease. Gene. 2013 Nov 1;530(1):100-3. doi: 10.1016/j.gene.2013.08.026.
34. Zerkaoui M, Laarabi FZ, Ajhoun Y, Chkirate B, Sefiani A. A novel single variant in the MEFV gene causing Mediterranean fever and Behçet's disease: a case report. J Med Case Rep. 2018 Mar 1;12(1):53. doi: 10.1186/s13256-017-1552-4.
35. Livneh A, Aksentijevich I, Langevitz P, Torosyan Y, G-Shoham N, Shinar Y, Pras E, Zaks N, Padeh S, Kastner DL, Pras M. A single mutated MEFV allele in Israeli patients suffering from familial Mediterranean fever and Behçet's disease (FMF-BD). Eur J Hum Genet. 2001 Mar;9(3):191-6. doi: 10.1038/sj.ejhg.5200608.
36. Limon M, Tezcan D, Gülcemal S, Yilmaz S, Nayman A. Takayasu's arteritis with familial Mediterranean fever. Clin Exp Rheumatol. 2020 Sep-Oct;38 Suppl 127(5):118.
37. Ayaz NA, Tanatar A, Karadağ ŞG, Çakan M, Keskindemirci G, Sönmez HE. Comorbidities and phenotype-genotype correlation in children with familial Mediterranean fever. Rheumatol Int. 2021 Jan;41(1):113-20. doi: 10.1007/s00296-020-04592-7.
38. Salehzadeh F, Mohammadikebar Y, Haghi RN, Asl SH, Enteshary A. Familial Mediterranean fever gene mutations and gout as an auto-inflammatory arthropathy. Med Arch. 2019 Feb;73(1):55-7. doi: 10.5455/medarh.2019.73.55-57.
39. Sari I, Simsek I, Tunca Y, Kisacik B, Erdem H, Pay S, Cay HF, Gul D, Dinc A. Is there a relationship between gouty arthritis and Mediterranean fever gene mutations?. Rev Bras Reumatol. 2015 Jul-Aug;55(4):325-9 (in Portuguese). doi: 10.1016/j.rbr.2014.10.008.
40. Karaarslan A, Kobak S, Kaya I, Intepe N, Orman M, Berdeli A. Prevalence and significance of MEFV gene mutations in patients with gouty arthritis. Rheumatol Int. 2016 Nov;36(11):1585-9. doi: 10.1007/s00296-016-3560-x.
41. Yago T, Asano T, Fujita Y, Migita K. Familial Mediterranean fever phenotype progression into anti-cyclic citrullinated peptide antibody-positive rheumatoid arthritis:a case report. Fukushima J Med Sci. 2020 Dec 10;66(3):160-6. doi: 10.5387/fms.2020-07.
42. Kokubu H, Ida H, Tanaka T, Fujimoto N. Systemic lupus erythematosus with familial Mediterranean fever: Case report and review of literature. Acta Derm Venereol. 2019 Jul 1;99(9):822-3. doi: 10.2340/00015555-3197.
43. Deniz R, Ozen G, Yilmaz-Oner S, Alibaz-Oner F, Erzik C, Aydin SZ, Inanc N, Eren F, Bayalan F, Direskeneli H, Atagunduz P. Familial Mediterranean fever gene (MEFV) mutations and disease severity in systemic lupus erythematosus (SLE): implications for the role of the E148Q MEFV allele in inflammation. Lupus. 2015 Jun;24(7):705-11. doi: 10.1177/0961203314560203.
44. Dörtbas F, Garip Y, Güler T, Karci AA. Coexistence of familial Mediterranean fever with ankylosing spondylitis and Sjogren's syndrome: A rare occurrence. Arch Rheumatol. 2015 Nov 3;31(1):87-90. doi: 10.5606/ArchRheumatol.2016.5671.
45. Tanaka M, Migita K, Miyashita T, Maeda Y, Nakamura M, Komori A, Ishibashi H, Eguchi K, Kikuchi M, Hirayama K, Yasunami M. Coexistence of familial Mediterranean fever and Sjögren's syndrome in a Japanese patient. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):792.
46. Fujita Y, Asano T, Sato S, Furuya MY, Temmoku J, Matsuoka N, Kobayashi H, Watanabe H, Suzuki E, Koga T, Endo Y, Kawakami A, Migita K. Coexistence of mixed connective tissue disease and familial Mediterranean fever in a Japanese patient. Intern Med. 2019 Aug 1;58(15):2235-40. doi: 10.2169/internalmedicine.2376-18.

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Original Article

Five Years' Experience of Multidisciplinary Approach to Chronic Inflammatory Diseases by Rheumatology, Dermatology and Gastroenterology Departments

Burcu YAGIZ[1], Belkis Nihan COSKUN[1], Tugba OCAK[1], Altug GUNER[2], Asli Ceren MACUNLUOGLU[3], Yavuz PEHLIVAN[1], Murat KIYICI[4], Serkan YAZICI[5], Emel BULBUL BASKAN[5], Ediz DALKILIC[1]

[1]Department of Internal Medicine, Division of Rheumatology, Bursa Uludag University, Faculty of Medicine, Bursa, Turkey
[2]Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Bursa Uludag University, Faculty of Medicine, Bursa, Turkey
[3]Department of Biostatistics, Bursa Uludag University, Faculty of Medicine, Bursa, Turkey
[4]Department of Internal Medicine, Division of Gastroenterology, Bursa Uludag University, Faculty of Medicine, Bursa, Turkey
[5]Department of Dermatology, Bursa Uludag University, Faculty of Medicine, Bursa, Turkey

ABSTRACT

Background Chronic inflammatory diseases (CIDs) are lifelong complex disorders that affect quality of life, and this study aimed to summarize five years of experience with a multidisciplinary approach for these complex diseases as a result of medical council meetings.

Material and Methods Hospital-based, medical records review study was conducted. A total of 45 monthly medical council meetings were held between 2014-2019 with the participation of the rheumatology, dermatology and gastroenterology departments of the same university. Patients with complex conditions that were seen in each department's own polyclinic composed the council. This study only included 308 patients referred by the rheumatology group.

Results Females made up 66.5% of the 308 patients. The median age was 45 (19-77) years. Psoriatic arthritis (PsA) and other spondyloarthritis (SPA) patients composed 49.3% of the total. A total of 68.18% of the patients were presented only to consult with the dermatology department. The most common reason for presenting patients was to discuss options for treatment (41.5%). The diagnosis of psoriasis was confirmed in 48 of 67 (71.6%) patients who presented with a pre-diagnosis. The diagnosis was changed in 34.74% of the patients, whereas the diagnosis became completely different in 11.36% of the patients.

Conclusions Many patients with challenging diagnosis and treatment processes are encountered in daily practice. The combination of different disciplines makes it possible to provide more rapid and effective solutions. In this study, we aimed to emphasize the increasing importance of such multidisciplinary approaches.

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Address for Correspondence:
Burcu Yagiz, MD
Department of Internal Medicine, Division of Rheumatology, Bursa Uludag University, Faculty of Medicine, Bursa, Turkey
E-mail: ozlemtfl@hotmail.com

Introduction

Chronic inflammatory diseases (CIDs) have a profound effect on populations because CIDs are lifelong diseases, leading to a considerable impact on the quality of life of patients and families.[1,2] Common treatment agents that are used in the management of CIDs, such as psoriasis, psoriatic arthritis (PsA), spondyloarthritis (SPA), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), suggest a similar pathogenesis and underscore the importance of a multidisciplinary approach.[3]

PsA is a chronic, inflammatory and progressive type of arthritis that affects 10-30% of patients with psoriasis.[4,5] Although dermatologists have sufficient knowledge to identify and treat the cutaneous symptoms of psoriasis, the diagnosis of PsA generally requires specialization in rheumatology.[6] Effective management of PsA should encompass both skin and joint involvement. Early diagnosis is critical since 40-60% of patients exhibit joint damage within the first year of disease onset.[7-9] Therefore, the collaboration of dermatologists and rheumatologists is essential to provide an extensive and holistic approach.

In addition to psoriasis and PsA, skin problems are also among the common extraintestinal manifestations of IBDs. Apart from disease-related skin manifestations, it is also possible to observe paradoxical psoriasis, cutaneous infection, malignancy, and vasculitis.[10] A dermatology perspective is of importance in identifying these lesions.

Recently, we have come to understand that CIDs constitute a systemic inflammatory process associated with important comorbidities, such as diabetes, obesity, nonalcoholic fatty liver disease (NAFLD), coronary artery disease and depression, as a result of our expanding knowledge of biological pathways and epidemiological data.[11-17] These comorbidities, as well as the primary conditions with which they coexist, increase the need for a multidisciplinary approach. A collaboration with gastroenterologists provides advantages in terms of the early diagnosis of comorbidities, such as obesity and NAFLD, and in decreasing the disease burden.

In addition to comorbidities, the increased use of immunosuppressants has rendered prophylaxis for hepatitis B more important. Moreover, collaboration between gastroenterologists and rheumatologists is essential for the proper management of SPA and IBD.[18]

A collaboration between different departments is also essential in identifying noninflammatory symptoms. In this way, it becomes easier to reduce the clinical and polyclinic patient burden and to provide better quality health care to patients.

In the literature, there are various studies underlining the importance of collaborations between dermatology and rheumatology for PsA and between gastroenterology and rheumatology for IBD. However, to the best of our knowledge, no studies provide data from patient evaluations conducted by three departments holding monthly meetings. This study is important in that the mentioned three disciplines convened to create solutions for challenging cases and shared clinical experiences with each other.

Material and Methods

Study Design

This is hospital-based, medical records review study. 45 monthly medical council meetings were held between May 2014 and June 2019, with participation of the rheumatology, dermatology and gastroenterology departments of a tertiary university hospital. Two clinicians from rheumatology, two clinicians from dermatology and one clinician from gastroenterology departments took part in the multidisciplinary medical council; during this five-year follow-up period, the same clinicians always joined the council. To perform the present research, the approval was obtained from the Ethics Committee in June 2020 (2011-KAEK-26/332).

Data Collection

Patients with complex problems, such as diagnosis and care issues affecting one of the three departments, who were seen in each department's own polyclinic were chosen for the council. The average number of patients evaluated per session in the council, where all three divisions bring their own challenging cases, was thirteen. This study included only data from the patients who were presented to the multidisciplinary medical council by rheumatology and did not

include the patients presented by gastroenterology and dermatology departments

The patients were evaluated and examined along with their medical histories presented. Demographic and clinical data of the patients as well as the council decisions were recorded in the hospital's information system. The electronic medical records were retrospectively screened for data. Decisions about the diagnosis were grouped as follows: patients whose existing diagnosis was completely changed, patients who received another diagnosis in addition to the existing one and patients who were undiagnosed before the council meetings and could or could not be diagnosed afterwards. Treatment decisions were classified as the following: patients who had and did not have a change of treatment. Of those who had a change in treatment, patients who were started on biologics for the first time and those who were switched to another biologic were also noted.

Table 1. General characteristics of the patients presented to the council (n=308)

Number of councils, n (%)	1	241 (78.25%)
	2	42 (13.64%)
	≥3	25 (8.12%)
Age		
Median (minimum: maximum)		45 (19:77)
Gender, n (%)	Female	205 (66.56%)
	Male	103 (33.44%)
Current diagnosis, n (%)	Psoriatic arthritis	85 (27.60%)
	Other spondyloarthritis	67 (21.75%)
	Rheumatoid arthritis	23 (7.47%)
	Vasculitis	17 (5.52%)
	Connective tissue disease	47 (15.26%)
	Other	37 (12.01%)
	Undiagnosed	32 (10.39%)
Classification according to consultation, n (%)	Gastroenterology only (G)	57 (18.51%)
	Dermatology only (D)	210 (68.18%)
	G+D	41 (13.31%)
Classification by diagnosis and treatment, n (%)	Diagnosis only	99 (32.14%)
	Treatment only	128 (41.5%)
	Diagnosis+Treatment	81 (26.2%)
Coexisting condition, n (%)		72 (23.37%)†
	Renal	2 (2.77%)
	Gastrointestinal	48 (66.66%)
	Pregnancy and desire to become pregnant	4 (5.55%) and 2 (2.77%)
	Breastfeeding	2 (2.77%)
	Malignancy	3 (4.16%)
	Other‡	16 (22.2%)
Drug side effect		20 (6.49%)
Diagnosis changed, n (%)		107 (34.74%)
Diagnosis completely changed		35 (11.36%)
Diagnosis added		50 (16.23%)
Among the undiagnosed, n (%)		
Diagnosed		22 (7.14%)
Undiagnosed		9 (2.9%)
Change of treatment, n (%)		221 (71.75%)
Started on biologics, n (%)		39 (12.66%)
Switched to another biologics, n (%)		27 (8.76%)

†The total number is lower due to the presence of those with both renal and gastrointestinal pathologies.
‡Herpes zoster (n=1), pyoderma gangrenosum (n=1), systemic sclerosis digital ulcer (n=1), photocontact dermatitis (n=1), anemia (n=1), allergies (n=2), oral aphthae (n=1), tuberculosis (n=1), thrombophilia (n=1), cervical furuncle (n=1), onychomycosis (n=1), breast fat necrosis (n=1), IgG4-related disease (n=2), hidradenitis suppurativa (n=1).

Statistical Analysis

SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis. The distribution of the variables was analyzed with the Kolmogorov-Smirnov test. Descriptive statistics are expressed as the means, standard deviations, medians, ratios and frequency values.

Results

Overall, 758 patients were evaluated during 45 meetings held by the multidisciplinary medical council. The rheumatology department presented 308 patients, accounting for 40.6% of all patients. The council evaluated 241 patients once, 42 patients twice, 21 patients three times, and four patients four times, for a total of 404 visits *(Table 1)*.

A total of 68.18% of the patients presented to the multidisciplinary medical council only to consult with the dermatology and gastroenterology departments, respectively. 41 (13.31%) patients were presented to consult with both departments, wherein these patients were under follow-up with PsA (n=13), enteropathic arthritis (n=7), ankylosing spondylitis (n=7), Behcet's syndrome (n=3), IgG4-related disease (n=3), RA (n=1), familial Mediterranean fever (n=1), antiphospholipid syndrome (n=1) and dermatomyositis (n=1), whereas four patients were undiagnosed. The most common cause of presenting patients to the multidisciplinary medical council was the need for treatment planning (41.55%).

The number of patients who presented to the multidisciplinary medical council with suspected "side effects of medications used" was 20 (6.49%). These side effects consisted of: herpes zoster (n=2), skin infection (n=1), drug rash (n=7), aphthae (n=1), drug-induced diarrhea (n=1), drug-induced lupus (n=1), elevated liver enzymes (n=6) and fulminant hepatitis (n=1).

Psoriasis was considered in 67 of 140 patients (47.85%) who presented to the medical council by rheumatologists with rash and prediagnosis of psoriasis was confirmed by the council in 48 patients (71.64%) (pathological confirmation: 21). Nine (18.75%) of these patients were diagnosed with paradoxical psoriasis. Dermatitis was detected in nine (47.3%) of the remaining 19 patients *(Figure 1)*. The total number of patients who underwent a skin biopsy was 73 (52.14%).

After the multidisciplinary council meetings, the diagnosis was completely changed in 11.36% of the patients, which constituted 26.26% of

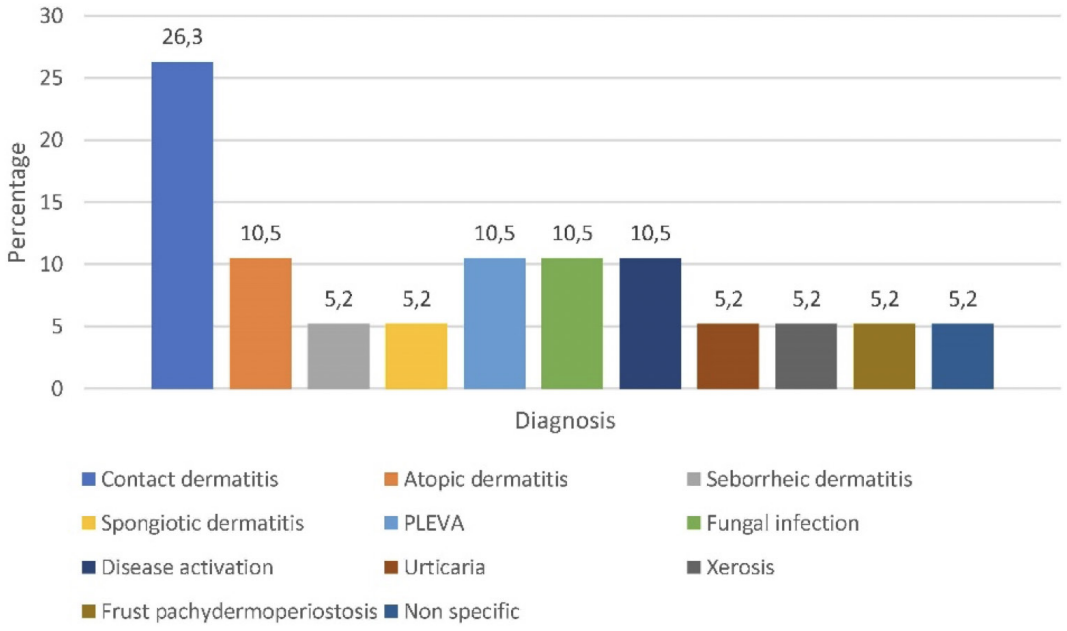

Figure 1. Other diagnosis in patients presented to the multidisciplinary medical council with the preliminary diagnosis of psoriasis.

Table 1. NLR values of those operated on according to Bethesda groups

Diagnosis (percentage, %)	Spondyloarthritis	4
	Spondyloarthritis+Behcet's syndrome	1
	Spondyloarthritis+Familial Mediterranean Fever	1
	Psoriatic arthritis	16
	Enteropathic arthritis	4
	Rheumatoid arthritis	3
	Sjogren's syndrome	1
	Mixed connective tissue disease	1
	Undifferentiated arthritis	1
	Discoid lupus	1
	Psoriasis	3
	Granuloma annulare	2
	Hidradenitis suppurativa	1
Prescribed biologics (percentage, %)	Adalimumab	15
	Etanercept	9
	Infliximab	3
	Golimumab	1
	Ustekinumab	4
	Secukinumab	2
	Rituximab	3
	Tofacitinib	2
Reason for prescription	Disease activation	39
	Disease activation only	32
	+ Inability to use NSAIDs§ secondary to entropathic arthritis	3
	+ Side effects of the conventional drugs	4

§NSAID: non-steroidal anti-inflammatory drugs.

those who were presented to the council for problems concerning the diagnosis. Of the 31 patients who were undiagnosed, 22 (7.14%) received a diagnosis. Considering all patients who presented at the multidisciplinary medical council meetings, 2.9% of the patients remained undiagnosed.

In 11 (31.42%) of the 35 patients whose diagnoses were completely changed, noninflammatory diseases replaced inflammatory diseases. Among those, PsA was the most common diagnosis made after the council (48.57%). In the group of patients who received an additional diagnosis, 80 percent were diagnosed with dermatologic diseases, while the remaining 10 patients were diagnosed with PsA, IgG4-related disease, fibromyalgia syndrome, autoimmune hepatitis, AA amyloidosis, gout, primary biliary cirrhosis (PBC), portal hypertension (HT), Crohn's disease, and tuberculosis.

Conventional disease modifying antirheumatic drugs, immunosuppressants and immunoregulatory drugs were added to the treatment regimen in 44 patients (14.28%). The added drugs were as follows: methotrexate (n=21), leflunomide (n=1), hydroxychloroquine (n=5), azathioprine (n=12), cyclosporine (n=2), acitretin (n=2), cyclophosphamide (n=1) and intravenous immunoglobulin (n=1). Before the multidisciplinary medical council meetings, 71 patients (23.05%) were on biologics. 39 patients (12.66%) were started on biologics *(Table 2)*, and 27 patients (8.76%) were switched to another biologic. The causes of switching to another biologic were as follows: paradoxical psoriasis (n=2), switching to rituximab not requiring the use of isoniazid due to elevated liver enzymes (n=2), drug allergies (n=1), need for a different pathway due to change of diagnosis (PsA→Gout and TNFi→IL-1 inhibitor, n=1) and resistance to the prescribed biologic (n=21).

Discussion

CIDs are lifelong conditions that are challenging to manage, and their management requires a multidisciplinary approach. In such diseases, early and accurate diagnosis as well as effective treatment are highly valuable for increasing treatment success and preventing complications. We evaluated 308 patients with challenging conditions throughout their follow-up between 2014 and 2019 in the mentioned council meetings.

Patients diagnosed with PsA constituted the most frequently presented patient group to the multidisciplinary medical council. Nearly half of patients with PsA exhibit a chronic progressive course.[8] There is evidence suggesting that early intervention provides better outcomes.[19] Effective treatment should be aimed at both skin and joint involvement.[20] The goal here was to prevent this progressive course with a multidisciplinary approach provided by the council.

Rheumatologists' recognition of psoriasis is as important as the recognition of PsA. As a result of the multidisciplinary medical council meetings, psoriasis was accurately identified by rheumatologists in 71.64% of the cases and was most frequently confused with dermatitis (47.3%). In the literature, psoriasis is most frequently confused with seborrheic dermatitis, atopic dermatitis and contact dermatitis in terms of the clinical picture, and biopsy is beneficial for the differential diagnosis.[21,22] A biopsy was performed in 52.14% of the patients who presented to the multidisciplinary medical council for the differential diagnosis of rash, and council meetings were important for determining which patients should undergo biopsy, accurate interpretation of pathology results and rapid diagnosis.

IBD has various extraintestinal manifestations consisting of arthralgia, arthritis, erythema nodosum (EN), pyoderma gangrenosum (PG), primary sclerosing cholangitis (PSC), autoimmune hepatitis, episcleritis and uveitis. Other diseases, such as psoriasis and multiple sclerosis, have also been associated with IBD.[23] Seven patients with enteropathic arthritis presented by us exhibited involvement, such as PG, psoriasis, EN and cutaneous infection. Extraintestinal manifestations are important indicators of morbidity.[24] Therefore, management of such challenging cases by a multidisciplinary team is ideal instead of evaluation only by gastroenterologists.

Patients with rheumatic diseases are at risk of liver damage due to drug-induced hepatotoxicity, exacerbation of underlying chronic viral hepatitis and possible coexisting liver disease.[25] NAFLD is also common in these patients, with a prevalence of nearly 20%.[26] In our patients, the most common reason for consulting the gastroenterology department was elevated liver enzymes. Diagnoses, such as PBC, PSC, portal HT, autoimmune hepatitis and NAFLD, were made by imaging and biopsies planned by the medical council, wherein the multidisciplinary approach was important for revealing the underlying cause as well as rapid and effective management of the medications used.

In 31.42% of the patients whose diagnoses were completely changed as a result of the council meetings, inflammatory diagnoses for which the patients were followed were replaced with noninflammatory diagnoses. A collaboration between departments is also essential for enabling the recognition of noninflammatory symptoms. Therefore, patients are prevented from receiving unnecessary treatments.

The limitation of this study was that it was a single-center experience and did not include comparisons with other sites that had similar multidisciplinary medical council activities. Such comparisons are challenging, particularly due to the lack of studies combining the three mentioned disciplines. In addition, the absence of patients presented by dermatology and gastroenterology departments is another limitation. However, council meetings revealed the importance of collaboration, especially in the diagnosis and treatment of challenging cases, as well as contributing to the education of subspecialists, assistants and students participating in the council.

Conclusions

Multiple disciplines may provide a holistic approach to inflammatory diseases by using each other's experience and strategies. Such collaborations reduce disease activity and

morbidity by ensuring a high-quality management process in early diagnosis and treatment. Therefore, such collaborations should be standardized and become more common, particularly in academic centers.

Thus, teams working together at such multidisciplinary medical councils that address challenging cases provide an extensive evaluation of high-risk patients, increase collaboration between departments and provide guidance for accurate diagnosis and effective treatment. The experience gained from this study can set an example for other centers, particularly in terms of enhancing the collaboration between rheumatology, dermatology and gastroenterology departments.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: BY, BNC; Study Design: YP, ED; Supervision: BY; Data Collection and/or Processing: TO, AG, SY; Statistical Analysis: ACM; Data Interpretation: MK, EBB; Literature Review: BY, BNC; Manuscript Preparation: BY; and Critical Review: MK, EBB, YP, ED.

References

1. Daniel C Baumgart, William J Sandborn. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007;369(9573):1641-57. doi: 10.1016/S0140- 6736(07)60751-X.
2. Strober W, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. J Clin Investig. 2007;117(3):514-21. doi: 10.1172/JCI30587.
3. Andersen V, Holmskov U, Sørensen SB, Jawhara M, Andersen KW, Bygum A, Hvid L, Grauslund J, Wied J, Glerup H, Fredberg U, Villadsen JA, Kjær SG, Fallingborg J, Moghadd SAGR, Knudsen T, Brodersen J, Frøjk J, Dahlerup JF, Nielsen OH, Christensen R, Bojesen AB, Sorensen GL, Thiel S, Færgeman NJ, Brandslund I, Stensballe A, Schmidt EB, Franke A, Ellinghaus D, Rosenstiel P, Raes J, Heitmann B, Boye M, Nielsen CL, Werner L, Kjeldsen J, Ellingsen T. A proposal for a study on treatment selection and lifestyle recommendations in chronic inflammatory diseases: A danish multidisciplinary collaboration on prognostic factors and personalised medicine. Nutrients. 2017 May 15;9(5):499. doi: 10.3390/nu9050499.
4. Ibrahim G, Waxman R, Helliwell PS. The prevalence of psoriatic arthritis in people with psoriasis. Arthritis Rheum. 2009 Oct 15;61(10):1373-8. doi: 10.1002/art.24608.
5. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. Arthritis Rheum. 2009 Feb 15;61(2):233-9. doi: 10.1002/art.24172.
6. Velez NF, Wei-Passanese EX, Husni ME, Mody EA, Qureshi AA. Management of psoriasis and psoriatic arthritis in a combined dermatology and rheumatology clinic. Arch Dermatol Res. 2012 Jan;304(1):7-13. doi: 10.1007/s00403-011-1172-6.
7. Gladman DD, Stafford-Brady F, Chang CH, Lewandowski K, Russell ML. Longitudinal study of clinical and radiological progression in psoriatic arthritis. J Rheumatol. 1990 Jun;17(6):809-12.
8. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology (Oxford). 2003 Dec;42(12):1460-8. doi: 10.1093/rheumatology/keg384.
9. McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. Rheumatology (Oxford). 2003 Jun;42(6):778-83. doi: 10.1093/rheumatology/keg217.
10. Hindryckx P, Novak G, Costanzo A, Danese S. Disease-related and drug-induced skin manifestations in inflammatory bowel disease. Expert Review of Gastroenterology and Hepatology. 2017;11(3):203-214. doi: 10.1080/17474124.2017.1283985.
11. Bansback NJ, Ara R, Barkham N, Brennan A, Fraser AD, Conway P, Reynolds A, Emery P. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology (Oxford). 2006 Aug;45(8):1029-38. doi: 10.1093/rheumatology/kel147.
12. Fowler JF, Duh MS, Rovba L, Buteau S, Pinheiro L, Lobo F, Sung J, Doyle JJ, Swensen A, Mallett DA, Kosicki G. The impact of psoriasis on health care costs and patient work loss. J Am Acad Dermatol. 2008 Nov;59(5):772-80. doi: 10.1016/j.jaad.2008.06.043.
13. Gottlieb AB, Dann F. Comorbidities in Patients with Psoriasis. Am J Med. 2009;122(12):1150. doi: 10.1016/j.amjmed.2009.06.021.
14. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: A population-based cohort study. Arch Dermatol. 2010;146(8):891-5. doi: 10.1001/archdermatol.2010.186.
15. Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. Arch Dermatol. 2009;145(6):700-3. doi: 10.1001/archdermatol.2009.94.
16. Solomon DH, Love TJ, Canning C, Schneeweiss S. Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. Ann Rheum Dis. 2010;69(12):2114-7. doi: 10.1136/ard.2009.125476.
17. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol. 2010;146(7):721-6. doi: 10.1001/archdermatol.2010.141.

18. Felice C, Leccese P, Scudeller L, Lubrano E, Cantini F, Castiglione F, Gionchetti P, Orlando A, Salvarani C, Scarpa R, Vecchi M, Olivieri I, Armuzzi A; Italian SpA-IBD Expert Panel Group. Red flags for appropriate referral to the gastroenterologist and the rheumatologist of patients with inflammatory bowel disease and spondyloarthritis. Clin Exp Immunol. 2019 Apr;196(1):123-38. doi: 10.1111/cei.13246.
19. Kirkham B, de Vlam K, Li W, Boggs R, Mallbris L, Nab HW, Tarallo M. Early treatment of psoriatic arthritis is associated with improved patient-reported outcomes: findings from the etanercept PRESTA trial. Clin Exp Rheumatol. 2015 Jan-Feb;33(1):11-9.
20. Boehncke WH, Anliker MD, Conrad C, Dudler J, Hasler F, Hasler P, Häusermann P, Kyburz D, Laffitte E, Michel BA, Möller B, Navarini AA, Villiger PM, Yawalkar N, Gabay C. The dermatologists' role in managing psoriatic arthritis: results of a Swiss Delphi exercise intended to improve collaboration with rheumatologists. Dermatology. 2015;230(1):75-81. doi: 10.1159/000367688.
21. Silverberg JI. Adult-Onset Atopic Dermatitis. J Allergy Clin Immunol Pract. 2019;7(1):28-33. doi: 10.1016/j.jaip.2018.09.029.
22. Park JH, Park YJ, Kim SK, Kwon JE, Kang HY, Lee ES, Choi JH, Kim YC. Histopathological Differential Diagnosis of Psoriasis and Seborrheic Dermatitis of the Scalp. Ann Dermatol. 2016 Aug;28(4):427-32. doi: 10.5021/ad.2016.28.4.427.
23. Ghosh S. Multidisciplinary teams as standard of care in inflammatory bowel disease. Can J Gastroenterol. 2013 Apr;27(4):198. doi: 10.1155/2013/710671.
24. Siebert U, Wurm J, Gothe RM, Arvandi M, Vavricka SR, von Känel R, Begré S, Sulz MC, Meyenberger C, Sagmeister M; Swiss IBD Cohort Study Group. Predictors of temporary and permanent work disability in patients with inflammatory bowel disease: results of the swiss inflammatory bowel disease cohort study. Inflamm Bowel Dis. 2013 Mar-Apr;19(4):847-55. doi: 10.1097/MIB.0b013e31827f278e.
25. Tung CH, Lai NS, Lu MC, Lee CC. Liver cirrhosis in selected autoimmune diseases: a nationwide cohort study in Taiwan. Rheumatol Int. 2016 Feb;36(2):199-205. doi: 10.1007/s00296-015-3369-z.
26. Abraham S, Begum S, Isenberg D. Hepatic manifestations of autoimmune rheumatic diseases. Ann Rheum Dis. 2004 Feb;63(2):123-9. doi: 10.1136/ard.2002.001826.

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Case Report

A Case of Acute Pancreatitis Following Computed Tomography Scan

Basak SAYINALP[1], Lale OZISIK[1], Erkan PARLAK[2]

[1]Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey
[2]Division of Gastroenterology, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Background Acute pancreatitis is a common cause of hospitalization among gastrointestinal disorders and its frequency has been rising in the past few years. The majority of cases are due to alcohol use, gallstones and hypertriglyceridemia. However, there still remain a significant number of cases in which no causative factor can be found and therefore called idiopathic. Contrast induced pancreatitis is a rare cause pancreatitis and there are only a few cases reported so far. Here we presented a case of mild acute pancreatitis following iodinated contrast exposure.

Case Report A 42-year-old female patient with a history of lymphoma was admitted to our clinic with severe abdominal pain and nausea. Her blood tests revealed elevated pancreatic enzyme levels and mildly elevated liver function tests. Upper abdomen magnetic resonance imaging revealed pancreatic inflammation without any sign of necrosis. Since her complaints began after a computed tomography scan that she had earlier that day for the evaluation of lymphoma and no other cause could be found, iodinated contrast was thought to be the cause of acute pancreatitis in this patient.

Conclusions Contrast agents seem to be a rare cause of acute pancreatitis, however taking the increasing availability of procedures involving radiocontrast agents into consideration, it is important to keep in mind that clinicians may come across more cases of contrast-induced acute pancreatitis in the future.

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Address for Correspondence:
Basak Sayinalp, MD

Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey
E-mail: bsayinalp@gmail.com

Introduction

Acute pancreatitis (AP) is a common cause of hospitalization among gastrointestinal disorders and its frequency has been rising in the past few years. Pathophysiology of AP involves both the localized destruction of pancreas and systemic inflammatory response. The severity of AP varies widely and it is classified based on Revised Atlanta Classification 2013 as mild, moderately severe and severe AP. Severe AP results in persistent organ failure and death in approximately 20% of the cases.[1] The majority of cases are due to alcohol use, gallstones and hypertriglyceridemia. However, there still remain a significant number of cases in which no causative factor can be found and therefore called idiopathic. Although the frequency of drug induced pancreatitis is very low, it should be considered when other common causes of pancreatitis are ruled out and therefore a detailed history of drug intake should be taken from every AP patient.[2] Contrast induced pancreatitis is a rare cause of drug induced pancreatitis and there are only a few cases reported so far. Here we presented a case of mild acute pancreatitis following iodinated contrast exposure.

Case Report

A 42-year-old female patient was admitted to our clinic with severe abdominal pain and nausea. She had a history of non-Hodgkin lymphoma (NHL) that had been diagnosed last year and she had received 4 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) so far. She received the fourth cycle approximately 20 days ago. Her pain began a few hours ago and was first located in the epigastrium and right upper quadrant. It progressively increased in severity and began to radiate towards her lower back.

Upon admission, her vital signs were normal with a body temperature of 36.5 °C, a heart rate of 83 beats per minute, a blood pressure of 125/70 mmHg and a respiratory rate of 16 breaths per minute. Mild tenderness was present in her epigastrium and right upper quadrant. Her blood tests revealed elevated pancreatic enzyme levels (amylase: 2,672 U/L, pancreatic amylase: 1,896 U/L, lipase: 3,781 U/L) and mildly elevated liver function tests (ALT: 128 U/L, AST: 196 U/L, ALP: 72 U/L, GGT: 109 U/L) *(Table 1).*

A diagnosis of acute pancreatitis was made, and the patient was hospitalized. Intravenous hydration was initiated while her oral intake was discontinued. Upper abdomen magnetic resonance imaging along with magnetic resonance cholangiopancreatography was conducted and pancreatic inflammation was detected without any sign of necrosis *(Figure 1).* No gallstones were present. The patient did not have a history of alcohol consumption. Neither hypercalcemia nor hypertriglyceridemia was detected in her blood tests. She has not recently used any new drugs except for the iodinated contrast that was administered to her earlier that day, for the computed tomography scans that were performed to evaluate the status of her NHL. Abdominal

Table 1. Laboratory parameters of the patient at admission, in 48 hours and at discharge

Parameter	At admission	In 48 hours	At discharge
Hematocrit (%)	37.3	35.7	36.4
Leukocyte count (x10^3/μL)	5.9	3.3	7.2
Creatinine (mg/dL)	0.7	0.54	0.5
Blood urea nitrogen (mg/dL)	13.31	5.24	9.1
ALT (U/L)	128	63	28
AST (U/L)	196	32	14
Amylase (U/L)	2,672	276	88
Pancreatic amylase (U/L)	1,896	190	52.7
Lipase (U/L)	3,781	96	28
Calcium (mg/dL)	8.7	9.78	8.69
Triglyceride (mg/dL)	60		

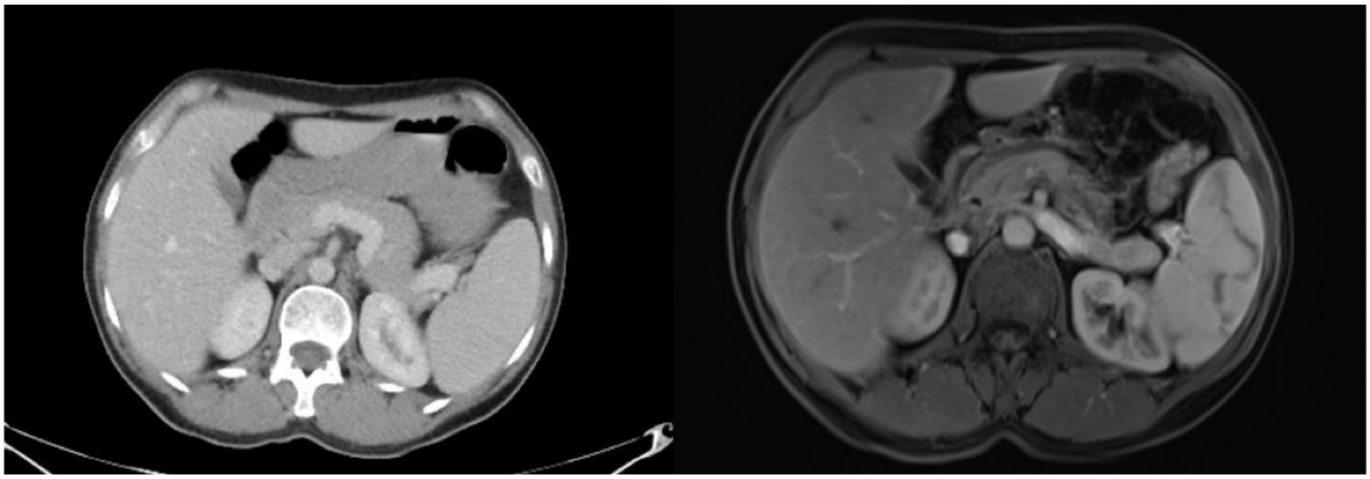

Figure 1. Magnetic resonance cholangiopancreatography images showing pancreatic inflammation without any sign of necrosis.

CT scan was examined, and no sign of pancreatic inflammation was noted. Since her complaints began only a few hours after the iodinated contrast administration, it was thought to be the most likely cause of acute pancreatitis in this patient. On follow up, her pain began to resolve, and pancreatic enzyme levels began to decrease. Her pain resolved completely on the third day of hospitalization and oral intake was initiated. She didn't have any further complaints and was discharged on the next day.

Discussion

Contrast agents are used for a variety of diagnostic and therapeutic procedures in medicine. Their usage is associated with various complications, contrast induced nephropathy being the most significant. Contrast induced pancreatitis has also been reported in the literature, but there aren't many cases. Since such procedures are becoming increasingly available worldwide, it is important for the clinicians to be aware of even the rarest complications in order to make suitable interventions.

Cases of contrast induced AP date back to 1956 when Robinson reported a case with autopsy findings of AP following translumbar aortography.[3] After that, there were several other AP cases reported following aortography and a more recent case following ventriculography in 1981 by Chin *et al.*[4] More recently, cases of AP following coronary angiography and thrombectomy have been published.[5-7] In February 2020, Mui *et al.*[8] reported a case of mild contrast induced AP, whose symptoms began right after being transferred to ward after uncomplicated coronary angiography. It has also been shown that contrast enhanced CT performed immediately after the onset of AP symptoms may further damage the pancreas.[9]

The pathophysiology of contrast induced AP is not well understood. The most recognized hypothesis is the impaired microcirculation in pancreatic tissue due to contrast exposure, similar to contrast induced nephropathy. In 1995, Schmidt *et al.*[10] examined rats with acute pancreatitis and demonstrated that contrast infusion induced a significant decrease of total pancreatic capillary flow and concluded that contrast exposure aggravated the impairment of pancreatic microcirculation in experimental pancreatitis. However, in 2005 Plock *et al.*[11] conducted a meta analysis to review whether the application of contrast enhanced CT worsens the course of AP due to impaired microcirculation in humans and found out that there were not enough data to support this hypothesis in humans.

In 2014, Jin *et al.*[12] investigated the effects of pancreas exposure to contrast in mice and human cell lines at the molecular level. They found out that incubation of mouse and human acinar cells with iohexol led to increased intracellular release

of calcium and activation of nuclear factor-kappa B. They also showed that iohexol did not result in pancreatic inflammation in calcineurin Aβ-deficient mice and concluded that calcineurin inhibitors might be used to prevent post-endoscopic retrograde cholangiography (ERCP) pancreatitis, which is a finding that needs to be studied in human models.

It is also possible to hypothesize that, chemotherapeutic agents such as cyclophosphamide and doxorubicin or corticosteroids could be the cause of AP in our patient, or they might had induced a pancreatic inflammation at first and later, AP was triggered by the iodinated contrast administration. There are several case reports in the literature that assume there is a relation between the use of these therapeutic agents and AP.[13,14] However, the diagnosis of contrast induced AP cannot still be ruled out in this patient.

Since AP is one of the leading causes for hospitalization among gastrointestinal disorders and is associated with significant morbidity and mortality, it is important to define the causative factors and take precautions against them. Contrast agents seem to be a rare cause of AP, however taking the increasing availability of procedures involving radiocontrast agents into consideration, it is important to keep in mind that clinicians may come across more cases of contrast induced AP in the future. Studies are needed to find ways to prevent this phenomenon, such as using lower volumes or lower osmolality contrast.

Conflict of Interests

Authors declare that there are none.

Authors' Contribution

Study Conception: BS, LO; Study Design: BS; Supervision: LO, EP; Analysis and Data Interpretation: BS, LO, EP; Literature Review: BS; Manuscript Preparation: BS; Critical Review: LO, EP.

References

1. Fu CY, Yeh CN, Hsu JT, Jan YY, Hwang TL. Timing of mortality in severe acute pancreatitis: experience from 643 patients. World J Gastroenterol. 2007 Apr 7;13(13):1966-9. doi: 10.3748/wjg.v13.i13.1966.
2. Zheng J, Yang QJ, Dang FT, Yang J. Drug-induced pancreatitis: An update. Arab J Gastroenterol. 2019 Dec;20(4):183-188. doi: 10.1016/j.ajg.2019.11.005.
3. Robinson AS. Acute pancreatitis following translumbar aortography; case report with autopsy findings seven weeks following aortogram. AMA Arch Surg. 1956 Feb;72(2):290-4.
4. Chin WS, Ng R. Acute fulminant pancreatitis following ventriculography. Cardiovasc Intervent Radiol. 1981;4(2):108-9. doi: 10.1007/BF02552388.
5. Kheda MF, Szerlip HM. Two cases of iodixanol-induced pancreatitis. NDT Plus. 2008 Oct;1(5):296-9. doi: 10.1093/ndtplus/sfn063.
6. Gorges R, Ghalayini W, Zughaib M. A case of contrast-induced pancreatitis following cardiac catheterization. J Invasive Cardiol. 2013 Oct;25(10):E203-4.
7. Farooq AU, Amjad W, Yasin H. Rare Complication of Coronary Angiography: Contrast-Induced Acute Pancreatitis. Am J Ther. Nov/Dec 2017;24(6):e771-e772. doi: 10.1097/MJT.0000000000000626.
8. Mui JJ, Shamavonian R, Thien KCP. Acute pancreatitis following coronary angiography: case report and review of contrast-induced pancreatitis. Int Surg J. 2020 Feb;7(3):870-2. doi: 10.18203/2349-2902.isj20200836.
9. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013 Jan;62(1):102-11. doi: 10.1136/gutjnl-2012-302779.
10. Schmidt J, Hotz HG, Foitzik T, Ryschich E, Buhr HJ, Warshaw AL, Herfarth C, Klar E. Intravenous contrast medium aggravates the impairment of pancreatic microcirculation in necrotizing pancreatitis in the rat. Ann Surg. 1995 Mar;221(3):257-64. doi: 10.1097/00000658-199503000-00007.
11. Plock JA, Schmidt J, Anderson SE, Sarr MG, Roggo A. Contrast-enhanced computed tomography in acute pancreatitis: does contrast medium worsen its course due to impaired microcirculation? Langenbecks Arch Surg. 2005 Apr;390(2):156-63. doi: 10.1007/s00423-005-0542-y.
12. Jin S, Orabi AI, Le T, Javed TA, Sah S, Eisses JF, Bottino R, Molkentin JD, Husain SZ. Exposure to Radiocontrast Agents Induces Pancreatic Inflammation by Activation of Nuclear Factor-□B, Calcium Signaling, and Calcineurin. Gastroenterology. 2015 Sep;149(3):753-64.e11. doi: 10.1053/j.gastro.2015.05.004.
13. Yoshiwaza Y, Ogasa S, Izaki S, Kitamura K. Corticosteroid-induced pancreatitis in patients with autoimmune bullous disease: case report and prospective study. Dermatology. 1999;198(3):304-6. doi: 10.1159/000018137.
14. Salvador VB, Singh M, Witek P, Peress G. Cyclophosphamide and doxorubicin-induced acute pancreatitis in a patient with breast cancer. BJMP. 2014;7(3):a727.

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Case Report

Kaposi's Sarcoma in an Ankylosing Spondylitis Patient Treated With Anti-Tumor Necrosis Factor-Alpha Therapy

Selda HAKBILEN[1], Dilek TEZCAN[1], Semra YILMAZ[1]

[1]Division of Rheumatology, Department of Internal Medicine, Selcuk University Faculty of Medicine, Konya, Turkey

ABSTRACT

Tumor necrosis factor-alpha (TNF-α) inhibitors are immunosuppressive agents used in a variety of inflammatory diseases, including rheumatoid arthritis (RA), spondyloarthritis, psoriasis, and inflammatory bowel disease (IBD). Kaposi's sarcoma (KS) is an angioproliferative disease associated with the human herpes virus 8 (HHV-8). We present a 46-year-old male patient with ankylosing spondylitis (AS) treated with TNF-α inhibitor and developed KS during follow-up. The coexistence of anti-TNF-α treatment with KS is a rare condition. This case is presented to address this rare association. Therefore, keeping in mind KS, which is a type of skin tumor, in such HIV-negative patients in whom immunosuppressive agents are initiated, is essential in terms of early diagnosis, treatment, and prevention of complications.

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Keywords: *Tumor necrosis factor-alpha inhibitors, Kaposi's sarcoma, ankylosing spondylitis.*

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that damages the spine by causing structural changes, including bone growth and fusion. Anti-tumor necrosis factor (TNF) agents use has greatly improved the AS treatment, with anti-TNFs are now routinely recommended by clinical practice guidelines for AS patients with persistently high disease activity following first-line therapy with nonsteroidal anti-inflammatory drugs' (NSAIDs) description added to introduction section.[1] Tumor necrosis factor-alpha (TNF-α) is synthesized by activated macrophages and T cells. TNF-α is important for macrophage activation, phagosome activation, differentiation of monocytes to macrophages, recruitment of neutrophils and macrophages, and granuloma formation and function.[2] TNF-α, a pleiotropic inflammatory cytokine, is now

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Address for Correspondence:
Selda Hakbilen, MD
Division of Rheumatology, Department of Internal Medicine, Selcuk University Faculty of Medicine, Konya, Turkey
E-mail: seldahakbilen@gmail.com

recognized as a key pathogenic mediator of infectious and inflammatory diseases.[3] TNF-α with monoclonal antibodies or soluble receptors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) has been developed novel treatment options for certain rheumatic diseases. During the past decades, biological agents in rheumatic diseases resulted in better control of disease activity and improved quality of life. However, TNF-α inhibitors are potentially associated with severe side effects. Injection site reactions, infusion reactions, neutropenia, infections, demyelinating disease, heart failure, skin reactions, autoimmunity induction, malignancy.[4] Kaposi's sarcoma (KS) is divided into four types according to the clinical conditions in which it develops: classical (the type originally defined by Kaposi that typically occurs in middle age and old age), endemic (various forms identified in sub-Saharan indigenous Africans), epidemic type immunodeficiency syndrome (AIDS), iatrogenic type (the form associated with immunosuppressive drug therapy typically seen in renal allograft recipients).[5] The iatrogenic variant of KS is classically reported in organ transplant patients undergoing immunosuppressive therapy or those receiving long-term steroids. However, over the past few decades, the use of biological agents such as TNF-α inhibitors has led to an increase in KS cases. Herein, we report a case of iatrogenic KS caused by adalimumab in AS patients receiving TNF-α inhibitor therapy.

Case Report

A 46-year-old male patient, who was followed up in our clinic for 4 years with a diagnosis of AS. The patient had grade 3 bilateral sacroiliitis. Spinal involvement and enthesitis were not present. As a result of genetic analysis, HLA-B27 was found to be negative. The patient who was unresponsive to NSAID treatment received etanercept treatment for 1 year, and then adalimumab treatment was started due to secondary unresponsiveness to etanercept. Adalimumab treatment was interrupted due to coronavirus disease 2019 (COVID-19) infection. He had not been using adalimumab for the last year. While using adalimumab one year ago, purple-black patch-like lesions developed in a limited area on his hand *(Figure 1)*. The patient, who did not come for follow-ups, presented to our outpatient clinic when new lesions developed in both hands and feet in the last 2 months, similar to those at the beginning *(Figure 2)*. There was a history of lobectomy due to tuberculosis 20 years ago in his medical history. No signs of disease activation were detected in the patient, who was followed up regularly for pulmonologist. There was no known systemic disease except AS.

In the physical examination of the patient, vital signs were stable. Head and neck examinations were normal. Respiratory system examination did not reveal respiratory sounds in the upper lobe of the right lung. Cardiovascular system, abdominal and rheumatological examination

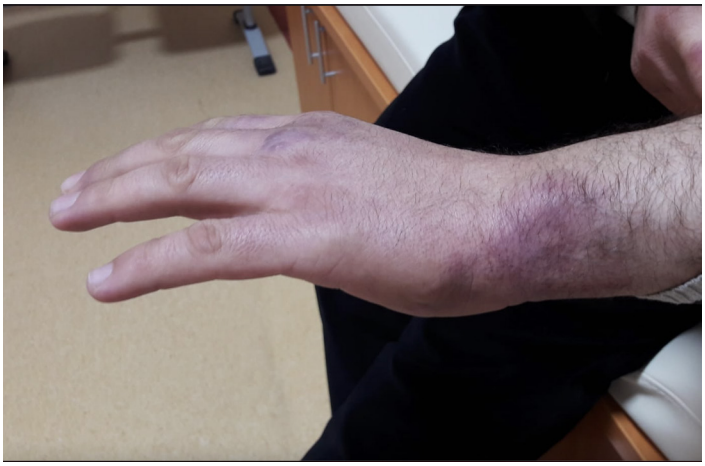

Figure 1. Purple-black patch-like on the patient's hand.

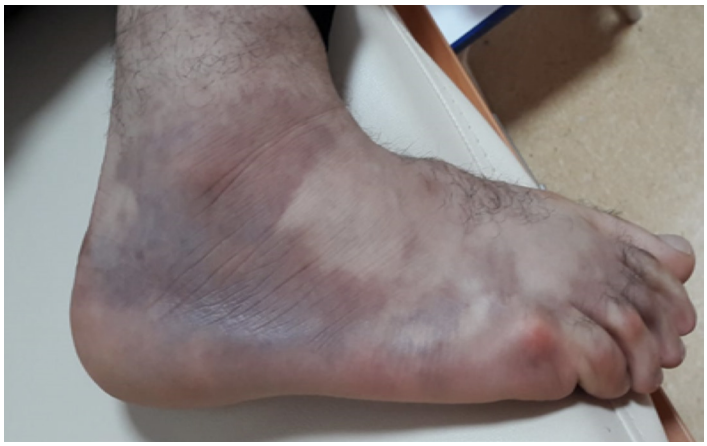

Figure 2. Purple-black patch-like on the patient's foot.

were normal. In the dermatological examination, there were bilateral livingoid patches on the hands and feet; no lesions were found elsewhere on the body. Laboratory parameters; leukocyte 4.0 K/uL, neutrophil 2.6 K/uL hemoglobin 14.2 g/dL, platelet 185 K/uL, blood urea nitrogen 41 mg/dL, creatinine 1.2 mg/dL, alanine aminotransferase 28 U/L, aspartate aminotransferase 29 U/L, lactate dehydrogenase 164 U/L, vitamin B12 642 pg/mL, folic acid 6.03 ng/mL, TSH 1.93 µIU/mL and ferritin 23.6 ng/mL, C-reactive protein (CRP) 8 mg/L, erythrocyte sedimentation rate 11 mm/hour. ANA, RF, anti-CCP, F-ANCA, anti-dsDNA, cold agglutinins, HBsAg, anti-HCV, anti-HIV ELISA tests were found to be negative. The patient was diagnosed with iatrogenic KS as a result of the skin biopsy performed from the foot lesion. Histopathological examination showed expansion of spindle cell vascular processes, and the tissue was stained positive for human herpes virus 8 (HHV8) *(Figure 3)*. The patient did not report any family history of endemic KS. No involvement was observed in the endoscopy and tomography of the neck, thorax, and abdomen in terms of possible involvement. Chemotherapy was initiated for the patient, and he was followed up in the outpatient clinic.

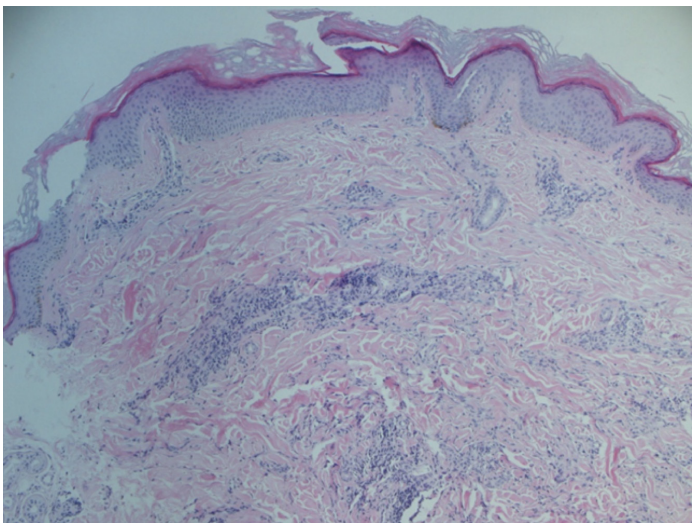

Figure 3. Images of pathology preparations showing Kaposi's sarcoma and images of human herpesvirus 8 stainings.

Discussion

KS is an angioproliferative disease associated with HHV-8.[6] Immunosuppression is a well-defined risk factor for KS. This indicates the presence of cofactors that affect the risk of KS after infection with HHV-8. The iatrogenic variant of KS has traditionally been reported in organ transplant patients receiving immunosuppressive therapy or taking steroids for a long time.[7,8] Iatrogenic CS due to TNF-α inhibitor therapy is rare.[9] Although some meta-analyses of clinical trial data found an increased risk of cancer using TNF-α inhibitor, observational data, especially from registries, generally did not confirm these findings.[10] Overall, there is evidence that TNF-α inhibitors do not increase the risk of most solid tumors, except for some skin cancers. However, uncertainty persists, and study design may affect findings. There is evidence of an increased risk of non-melanoma skin cancer among patients treated with TNF-α inhibitors compared with those who do not receive these agents, including meta-analyses of data from registries, prospective observational studies randomized data.[11-14] In the study, there was no difference in the incidence of malignancy between the three TNF-α inhibitors (infliximab, adalimumab, etanercept) or between different forms of AS, but a significant increase in overall cancer risk was seen. The age at the beginning of treatment with TNF-α inhibitors and the presence and number of comorbidities are also associated with the risk of malignancy, demonstrating that previous malignancy is a significant predictor for a new malignancy. The type of drug was not associated with the risk of malignancy. The data provided by this study are insufficient to determine whether this effect is due to TNF-α inhibitor therapy or other factors.[15] Cancer risk in patients with spondyloarthritis treated with TNF-α inhibitors: a joint study from ARTIS and DANBIO registries In patients with AS, treatment with TNF-α inhibitors was not associated with an increased risk of cancer.[16]

To our knowledge, five KS cases were identified with the use of infliximab, three cases with adalimumab, one with golimumab, and one with certolizumab pegol.[9,17-26] Despite this and the previous report, a casual connection between TNF-α blockade and KS development is still

unclear and should be addressed by appropriate studies. In most of the cases, KS was notably localized to the skin. Except for an ulcerative colitis patient with gastrointestinal involvement of KS.[24] All patients tested negative for HIV. Similar to our patient, in all of the reported cases, KS developed during the use of the biologic agent. Cohen *et al.*[20] described the case of a rheumatoid arthritis patient who developed a typical KS lesion a few weeks after starting infliximab therapy. Kuttikat *et al.*[21] described a case of an older woman with giant cell arteritis (GCA) who developed KS while on a double-blind trial for GCA with an anti-TNF medication. As in the early stages of treatment, cases emerging months and years later, as in our case, have been reported. A close relationship between adalimumab and KS has been emphasized in previous studies.[9,22,23] These patients consisted of rheumatoid arthritis patients. No patients with AS were reported. This AS case is presented to share the association with anti-TNF therapy and KS.

Conclusions

As far as we know, in coincidence with the initiation of TNF-α inhibitory therapy in AS patients, KS has not been reported previously. Due to the rarity of the disease in this patient population, the diagnosis can often be missed or delayed. Therefore, it is significant for patients receiving biologic agents, including anti-TNF-α therapy, to have a close follow-up and receive routine skin evaluation for malignancy. Clinicians should have a high suspicion for KS in such HIV-negative patients starting immunosuppressive agents.

Conflict of Interests

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception: SH, DT, SY; Study Design: BS; Supervision: SH, DT, SY; Analysis and Data Interpretation: SH, DT, SY; Literature Review: SH, DT, SY; Manuscript Preparation: SH, DT, SY; Critical Review: SH, DT, SY.

References

1. Acurcio FA, Guerra Junior AA, da Silva MRR, Pereira RG, Godman B, Bennie M, Nedjar H, Rahme E. Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. Curr Med Res Opin. 2020 Apr;36(4):677-86. doi: 10.1080/03007995.2020.1722945.
2. Koo S, Marty FM, Baden LR. Infectious complications associated with immunomodulating biologic agents. Hematol Oncol Clin North Am. 2011 Feb;25(1):117-38. doi: 10.1016/j.hoc.2010.11.009.
3. Beutler B. TNF, immunity and inflammatory disease: lessons of the past decade. J Investig Med. 1995 Jun;43(3):227-35.
4. García-Doval I, Hernández MV, Vanaclocha F, Sellas A, de la Cueva P, Montero D; BIOBADADERM and BIOBADASER study groups. Should tumour necrosis factor antagonist safety information be applied from patients with rheumatoid arthritis to psoriasis? Rates of serious adverse events in the prospective rheumatoid arthritis BIOBADASER and psoriasis BIOBADADERM cohorts. Br J Dermatol. 2017 Mar;176(3):643-9. doi: 10.1111/bjd.14776.
5. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med. 1998 Apr 2;338(14):948-54. doi: 10.1056/NEJM199804023381403.
6. Gao SJ, Kingsley L, Hoover DR, Spira TJ, Rinaldo CR, Saah A, Phair J, Detels R, Parry P, Chang Y, Moore PS. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. N Engl J Med. 1996 Jul 25;335(4):233-41. doi: 10.1056/NEJM199607253350403.
7. Baykal C, Atci T, Buyukbabani N, Kutlay A. The Spectrum of Underlying Causes of Iatrogenic Kaposi's Sarcoma in a Large Series: A Retrospective Study. Indian J Dermatol. 2019 Sep-Oct;64(5):392-399. doi: 10.4103/ijd.IJD_217_18.
8. Klepp O, Dahl O, Stenwig JT. Association of Kaposi's sarcoma and prior immunosuppressive therapy: a 5-year material of Kaposi's sarcoma in Norway. Cancer. 1978 Dec;42(6):2626-30.
9. Mariappan AL, Desai S, Locante A, Desai P, Quraishi J. Iatrogenic Kaposi Sarcoma Precipitated by Anti-Tumor Necrosis Factor-Alpha (Anti-TNF-α) Therapy. Cureus. 2021 Feb 16;13(2):e13384. doi: 10.7759/cureus.13384.
10. Askling J, van Vollenhoven RF, Granath F, Raaschou P, Fored CM, Baecklund E, Dackhammar C, Feltelius N, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Rantapää-Dahlqvist S, Saxne T, Klareskog L. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum. 2009 Nov;60(11):3180-9. doi: 10.1002/art.24941.
11. Mariette X, Matucci-Cerinic M, Pavelka K, Taylor P, van Vollenhoven R, Heatley R, Walsh C, Lawson R, Reynolds A, Emery P. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis. 2011 Nov;70(11):1895-904. doi: 10.1136/ard.2010.149419.
12. Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf. 2011 Feb;20(2):119-30. doi: 10.1002/pds.2046.

13. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007 Sep;56(9):2886-95. doi: 10.1002/art.22864.
14. Amari W, Zeringue AL, McDonald JR, Caplan L, Eisen SA, Ranganathan P. Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis. Rheumatology (Oxford). 2011 Aug;50(8):1431-9. doi: 10.1093/rheumatology/ker113.
15. Atzeni F, Carletto A, Foti R, Sebastiani M, Panetta V, Salaffi F, Bonitta G, Iannone F, Gremese E, Govoni M, Marchesoni A, Favalli EG, Gorla R, Ramonda R, Sarzi-Puttini P, Ferraccioli G, Lapadula G; GISEA group. Incidence of cancer in patients with spondyloarthritis treated with anti-TNF drugs. Joint Bone Spine. 2018 Jul;85(4):455-9. doi: 10.1016/j.jbspin.2017.08.003.
16. Hellgren K, Dreyer L, Arkema EV, Glintborg B, Jacobsson LT, Kristensen LE, Feltelius N, Hetland ML, Askling J; ARTIS Study Group, For the DANBIO Study Group. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis. 2017 Jan;76(1):105-11. doi: 10.1136/annrheumdis-2016-209270.
17. Martínez-Martínez ML, Pérez-García LJ, Escario-Travesedo E, Ribera-Vaquerizo PA. Kaposi sarcoma associated with infliximab treatment. Actas Dermosifiliogr. 2010 Jun;101(5):462-4 (in Spanish).
18. Ursini F, Naty S, Mazzei V, Spagnolo F, Grembiale RD. Kaposi's sarcoma in a psoriatic arthritis patient treated with infliximab. Int Immunopharmacol. 2010 Jul;10(7):827-8. doi: 10.1016/j.intimp.2010.04.016.
19. Vural S, Gündogdu M, Akay BN, Korkmaz P, Sanli H, Heper AO, Kundakçi N. Aggressive Kaposi's Sarcoma Associated With Golimumab Therapy. Arch Rheumatol. 2018 Jan 29;33(3):384-6. doi: 10.5606/ArchRheumatol.2018.6695.
20. Cohen CD, Horster S, Sander CA, Bogner JR. Kaposi's sarcoma associated with tumour necrosis factor alpha neutralising therapy. Ann Rheum Dis. 2003 Jul;62(7):684. doi: 10.1136/ard.62.7.684.
21. Kuttikat A, Joshi A, Saeed I, Chakravarty K. Kaposi sarcoma in a patient with giant cell arteritis. Dermatol Online J. 2006 Oct 31;12(6):16.
22. Amadu V, Satta R, Montesu MA, Cottoni F. Kaposi's sarcoma associated with treatment with adalimumab. Dermatol Ther. Nov-Dec 2012;25(6):619-20. doi: 10.1111/j.1529-8019.2012.01523.x.
23. Bret J, Hernandez J, Aquilina C, Zabraniecki L, Fournie B. Kaposi's disease in a patient on adalimumab for rheumatoid arthritis. Joint Bone Spine. 2009 Dec;76(6):721-2. doi: 10.1016/j.jbspin.2009.10.006.
24. Hamzaoui L, Kilani H, Bouassida M, Mahmoudi M, Chalbi E, Siai K, Ezzine H, Touinsi H, Azzouz MM, Sassi S. Iatrogenic colorectal Kaposi sarcoma complicating a refractory ulcerative colitis in a human immunodeficiency negative-virus patient. Pan Afr Med J. 2013 Aug 29;15:154. doi: 10.11604/pamj.2013.15.154.2988.
25. Windon AL, Shroff SG. Iatrogenic Kaposi's Sarcoma in an HIV-Negative Young Male With Crohn's Disease and IgA Nephropathy: A Case Report and Brief Review of the Literature. Int J Surg Pathol. 2018 May;26(3):276-82. doi: 10.1177/1066896917736610.
26. Bergler-Czop B, Brzezińska-Wcisło L, Kolanko M. Iatrogenic Kaposi's sarcoma following therapy for rheumatoid arthritis. Postepy Dermatol Alergol. 2016 Apr;33(2):149-51. doi: 10.5114/ada.2016.59163.

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https://dergipark.org.tr/tr/pub/tjim