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Is the visceral adiposity index associated with the presence of cardiovascular risk scores and comorbidity in psoriatic disease?

Psöriyatik hastalıkta viseral yağlanma indeksi kardiyovasküler risk skorları ve komorbidite ile ilişkili mi?

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Abstract

Objective: The aim of this study was to evaluate the relationship between cardiovascular risk scores and the visceral adiposity index (VAI) in patients with psoriatic disease (PsD).

Methods: A total of 101 PsD patients meeting psoriatic arthritis (CASPAR) criteria and 98 healthy individuals were included in this study. Systematic coronary risk evaluation index (SCORE), Framingham risk score (FS), and VAI values in patients and VAI values in healthy individuals were calculated.

Results: The mean body mass index (BMI) (kg/m²) of the patients was 29.63±5.66. According to the SCORE measurements, the patients were classified as low risk, moderate risk, and high risk-53 (52.5%), 45 (44.6%), and 3 (3%), respectively. No patient was found to be at very high risk. According to the FS, the low-risk, moderate-risk, and high-risk patient rates were 72 (71.3%), 22 (21.8%), and 7 (6.9%), respectively. Statistically significantly higher rates of metabolic syndrome, obesity (BMI >30), and VAI levels were found in the PsA group compared to the healthy control group ($p<0.05$). Statistically significantly higher VAI levels were observed in PsA patients with metabolic syndrome, BMI >30 (obesity), diabetes mellitus, and hypertension compared to patients without these comorbidities ($p<0.05$). A statistically significant correlation was found between low- and moderate-risk FS and VAI levels of PsA patients.

Conclusion: Since VAI can be easily calculated using routine tests, it can provide information about cardiometabolic risks and comorbidities in newly diagnosed PsD patients.

Keywords: Psoriatic disease, psoriatic arthritis, metabolic syndrome, visceral adiposity index, cardiovascular risk

Öz

Amaç: Bu çalışmanın amacı, psöriyatik artriti (PsA) olan hastaların viseral yağlanma indeksi (VAI) ile kardiyovasküler risk skorları arasındaki ilişkiyi değerlendirmektir.

Yöntem: Bu çalışma, PsA sınıflandırma kriterlerini (CASPAR) karşılayan 101 PsA hastası ve 98 sağlıklı gönüllü ile yapılmıştır. Hastaların SCORE, Framingham indeksi (FS) ve VAI değerleri ile sağlıklı bireylerin VAI değerleri hesaplandı.

Bulgular: Ortalama vücut kitle indeksi (VKİ) (kg/m²) 29,63±5,66 olarak hesaplandı. SCORE ölçümlerine göre 53 (%52,5) hasta düşük risk, 45 (%44,6) hasta orta risk ve 3 (%3) hasta yüksek risk altında idi. Hiçbir hasta çok yüksek risk altında değildi. FS'ye göre 72 hasta (%71,3) düşük risk, 22 hasta (%21,8) orta risk ve 7 hasta (%6,9) yüksek risk altındaydı. Metabolik sendrom, obezite (VKİ >30) ve VAI düzeyleri ($p<0,05$) açısından PsA grubunda sağlıklı kontrol grubuna göre risk istatistiksel olarak anlamlı derecede yüksek bulundu. Metabolik sendromlu, (VKİ >30), diabetes mellitus ve hipertansiyonu olan PsA hastalarında, bu komorbiditelerin olmadığı durumlarla karşılaştırıldığında önemli ölçüde daha yüksek VAI seviyeleri saptandı ($p<0,05$). Düşük ve orta riskli FS ile PsA'nın VAI düzeyleri arasında istatistiksel olarak anlamlı bir ilişki belirlendi.

Sonuç: VAI rutin olarak alınan verilerden basitçe hesaplanabildiğinden VAI düzeyi kardiyovasküler riski belirlemek için kullanılabilir ve VAI ayrıca yeni tanı konmuş PsA hastalarında komorbiditeler hakkında ipuçları sağlayabilir.

Anahtar Kelimeler: Psöriyatik hastalık, psöriyatik artrit, metabolik sendrom, viseral yağlanma indeksi, kardiyovasküler risk

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Introduction

Psoriasis (PsD) is an immune-mediated, inflammatory, chronic disease that primarily affects the skin and joints. Although the global incidence and prevalence of PsD are not fully known and vary according to demographic, regional, age, and genetic factors, it is estimated to affect approximately 1-3% of the general population. Despite advances in etiology and treatment, many studies have long shown an association between the severity of PsD and certain comorbidities, such as metabolic syndrome, cardiovascular disease, and obesity. These findings suggest that PsD is not just a skin or joint disease but also a multi-system disease associated with increased morbidity and mortality in the general population.[1,2] Adipose tissue is an active organ with metabolic and endocrine effects, producing adipocytokines such as adiponectin, leptin, resistin, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), plasminogen activator inhibitor-1, and various growth factors. It interacts with all other organs via adipocytokines.[3,4] Some of these adipokines are anti-inflammatory, while others are pro-inflammatory.[5] Changes in adipokine levels play a role in regulating events such as metabolic balance, immune response to infection and inflammation, and ischemia-induced damage.[6,7] Obesity stimulates the production of certain cytokines, such as IL-6, IL-8, and TNF-α, in adipose tissue. Serum levels of IL-6, IL-8, and TNF-α are known to be elevated in PsD and are associated with disease severity.[8] Levels of adiponectin, an antagonist cytokine against TNF-α, are reduced in obesity and insulin resistance. Recent reports have shown that obesity, insulin resistance, hypertension, and hyperlipidemia are important risk factors for cardiovascular disease and diabetes mellitus.[9,10]

The visceral adiposity index (VAI) is an important sex-specific marker of insulin resistance, adipose tissue function, and distribution. Although visceral fat can be measured using imaging techniques such as magnetic resonance imaging and computed tomography, these techniques are expensive and may not be easily accessible. VAI is easier to use as it is based on anthropometric and metabolic parameters.[11,12]

The aim of this study was to investigate the relationship between disease severity and activity, VAI, Framingham risk score (FS), and systematic coronary risk evaluation index (SCORE) in patients with PsD. In addition, the correlation between disease activity scores and VAI was assessed.

Materials and Methods

This study was conducted with 101 patients with PsA who met the criteria for the Classification of Psoriatic Arthritis (CASPAR).[13] Patients with a history of acute or chronic renal failure, chronic liver disease, cardiovascular disease or heart failure, symptomatic carotid artery disease (CAD) or peripheral artery disease, abdominal aortic aneurysm, nonalcoholic fatty liver disease, malignancy, pregnancy, active infection, chronic obstructive pulmonary disease, or obstructive sleep apnea were excluded from the study. A control group was formed, consisting of 98 age- and gender-matched healthy individuals (31 males, 67 females) who applied to the rheumatology outpatient clinic. The study was approved by the Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (decision no: 1636/2017, date: 06.12.2017). All participants signed a written informed consent form. Demographic and clinical data were recorded. Disease activity was assessed with the health assessment questionnaire (HAQ), disease activity index for psoriatic arthritis (DAPSA), PsD severity index (PASI), bath ankylosing spondylitis disease activity index (BASDAI), and bath ankylosing spondylitis functional index (BASFI). After a 12-hour fasting period, fasting blood glucose (FBG), ESR, C-reactive protein (CRP), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were analyzed in morning venous blood. Participants' anthropometric measurements, including height, weight, and waist circumference (WC), were taken with light clothing and no shoes, using standard devices. WC was measured at the midpoint between the lowest rib margin and the top of the iliac crest at the end of light expiration. Body mass index (BMI) was calculated by dividing weight (in kilograms) by height squared (in meters). VAI was calculated as follows:

- For men: $VAI=WC/[39.68+(1.88\times BMI)]\times(TG/1.03)\times(1.31/HDL)$
- For women: $VAI=WC/[36.58+(1.89\times BMI)]\times(TG/0.81)\times(1.52/HDL)$.[14]

The updated harmonized diagnostic criteria of the International Diabetes Federation (IDF) were used to diagnose metabolic syndrome (MetS). Participants were considered to have MetS if at least three of the following five criteria were present: 1) abdominal obesity according to population- and country-specific definitions, 2) hypertriglyceridemia (≥150 mg/dL) or use of antilipidemic drugs, 3) low HDLc (≤40 mg/dL in men and ≤50 mg/dL in women) or use of antilipidemic drugs, 4) mean blood pressure ≥130/85 mm Hg or use of antihypertensive drugs, and 5) high fasting glucose (≥100 mg/dL) or use of antidiabetic drugs.[15] To estimate the 10-year risk of a cardiovascular disease event, the FS and the SCORE were used.[16,17] The FS includes age, sex, smoking, blood pressure, and cholesterol concentrations and divides individuals into

three risk categories: low (less than 10% 10-year event risk), intermediate (10% to 20%), and high (greater than 20%). The SCORE equation, calculated from age, gender, smoking, total cholesterol, and systolic blood pressure values, identifies patients at very high CV risk (SCORE >10% with documented CV disease), high CV risk (5%< SCORE < 10%), intermediate CV risk (1%< SCORE <5%), or low CV risk (SCORE <1%).

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 11.0 for Windows software (SPSS Inc., Chicago, IL, USA). The conformity of the data to a normal distribution was assessed using visual and analytical methods and the Shapiro-Wilk test. The distribution of measurable (quantitative) data was given as mean ± standard deviation, and variables that did not show normal distribution were given as median and minimum-maximum values. Student's t-test was used to evaluate the difference between data with a normal distribution, and the Mann-Whitney U test was used for parameters that did not conform to a normal distribution. The chi-square test was used to evaluate categorical variables. Quantitative data were expressed as number (n) and percentage (%). Correlations between numerical data were analyzed using the Spearman correlation coefficient. A p-value <0.05 was considered statistically significant.

Results

The patient group of 101 cases comprised 71 females (70.3%) and 30 males (29.7%) with a mean age of 45.15±13.01 years. The control group of 98 cases comprised 67 females (68.4%) and 31 males (31.6%) with a mean age of 39.3±13.02 years. The demographic and clinical data of the PsA patients are shown in Tables 1 and 2. The PsD duration was 159.10±140.37 months, and PsA disease duration was 64.14±72.75 months. Nail involvement was seen in 46 (45.5%) patients, and 20 (19.8%) patients were tobacco users. In the evaluation of comorbidities, 13 PsA patients had diabetes mellitus, 3 dyslipidemia, 26 hypertension, and 36 metabolic syndrome. No diabetes mellitus, dyslipidemia, or hypertension was determined in the control group. The mean BMI (kg/m²) values of the patient and control groups were 29.63±5.66 and 26.82±6.05, respectively (p<0.001). According to the SCORE measurements, the patients were classified as low risk, moderate risk, and high risk-53 (52.5%), 45 (44.6%), and 3 (3%), respectively. No patient was found to be at very high risk. According to the FS, the low-risk, moderate-risk, and high-risk patient rates were 72 (71.3%), 22 (21.8%), and 7 (6.9%), respectively. In the PsA group, 28 (27.7%) patients had axial involvement, and 89 (88.1%) had peripheral involvement. Dactylitis was determined in 44 (43.6%) patients, and enthesitis in 18 (17.8%).Statistically significantly higher rates of metabolic syndrome, obesity (BMI >30), and VAI levels were found in the PsA group than in the healthy control group (p<0.05) (Table 3).

No correlation was determined between the VAI values of PsA patients and healthy control group subjects with metabolic syndrome and BMI >30 (obesity) (Table 4).The mean age of the patient with MS is older than those without MS and is statistically significant. The number of women in the patient with MS is higher than those without MS

Table 1. Demographic data of patients with PsA

Parameters	PsA (n=101)
Age (mean ± SD)	45.15±13.01
Female/male, n (%)	71 (70.3%) / 30 (29.7%)
PsA disease duration (mean ± SD)	64.14±72.75
Psoriasis disease duration (mean ± SD)	159.10 ± 140.37
BMI (kg/m²) (mean ± SD)	29.63±5.66
Tobacco user, n (%)	20 (19.8%)
Diabetes mellitus, n (%)	13 (12.9%)
Dyslipidemia, n (%)	3 (3%)
Hypertension, n (%)	26 (25.7%)
Metabolic syndrome, n (%)	36 (35.6%)
Disease involvement	
Axial involvement, n (%)	28 (27.7%)
Peripheral involvement, n (%)	89 (88.1%)
Dactylitis, n (%)	44 (43.6%)
Nail involvement, n (%)	46 (45.5%)
Enthesitis, n (%)	18 (17.8%)

BMI: Body mass index, PsA: Psoriatic arthritis, SD: Standard deviation

and is statistically significant. There aren't any differences in disease duration and clinical subtypes of patients with and without MS. VAI levels were found to be statistically significantly higher in PsA patients with BMI >30 (obesity), metabolic syndrome, diabetes mellitus, and hypertension compared to patients without these comorbidities (p<0.05) (Table 5). There was a statistically significant difference in median VAI levels between PsA patients with and without metabolic syndrome [3.37 (1.45-7.81) vs. 1.51 (0.57-5.90), p<0.0001]. No correlation with VAI levels was observed in PsA patients with and without dyslipidemia or smokers and non-smokers.As seen in Table 6, there was a statistically significant correlation between low- and medium-risk FS and VAI levels in PsA patients, but no significant correlation was found with the SCORE index. Correlations were determined between disease activity and cardiovascular and metabolic risks. A weak correlation was found between FS and VAI levels (Table 7). The medications used by patients were recorded. Glucocorticoids were used by 42 (42.6%) patients, non-steroidal anti-inflammatory drugs by 62 (61.4%), methotrexate by 59 (58.4%), leflunomide by 6 (5.9%), salazopyrin by 19 (18.8%), topical steroids by 23 (22.8%), cyclosporine by 1 (1%), and biological agents by 15 (14.9%).

Table 2. Clinical features of patients with PsA

SCORE, n (%)	
Low CV risk SCORE <1%	53 (52.5%)
Moderate CV risk 1% < SCORE <5%	45 (44.6%)
High CV risk 5% < SCORE <10%	3 (3%)
Very high CV risk SCORE >10%	0
Framingham risk score	
Low <10%	72 (71.3%)
Intermediate 10% to 20%	22 (21.8%)
High >20%	7 (6.9%)
ESR (mean ± SD)	19.85±15.21
CRP (mean ± SD)	9.9±15.59
DAPSA (mean ± SD)	22.1±20.6
PASI (mean ± SD)	5.8±10.98
BASDAI (mean ± SD)	3.41±2.52
BASFI (mean ± SD)	1.86±2.18
HAQ (mean ± SD)	0.53±0.56

BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, CV: Cardiovascular, CRP: C-reactive protein, DAPSA: Disease activity index for psoriatic arthritis, ESR: Erythrocyte sedimentation rate, HAQ: Health assessment questionnaire, PASI: Psoriasis area severity index, SCORE: Systematic Coronary risk evaluation index

Discussion

In recent years, the relationship between PsD and cardiovascular comorbidities has been extensively studied. This study assessed demographics, disease characteristics, and cardiovascular risk factors, which aligns with findings from other studies while diverging in some areas.

There is an increasing global trend toward obesity for many reasons, including sedentary lifestyles and excessive consumption of fast food. In patients with moderate and severe PsD, psychosocial issues can be as severe as physical problems, affecting quality of life and leading to avoidance of routine activities, resulting in social exclusion and stigmatization. Stigmatized individuals become trapped in a vicious cycle of preferring a sedentary lifestyle, which makes them more susceptible to obesity. Recent studies have shown that people with PsD are not only more prone to obesity but also to metabolic syndrome, insulin resistance, diabetes, dyslipidemia, and cardiovascular disease. While the prevalence of metabolic syndrome in the general population varies from 0.2% to 43.9%, population-based studies have shown a 5-fold increase in patients with PsD.[18] BMI and abdominal obesity have also been reported to increase in PsA and PsD patients.[13,15,16,19,20] In Turkiye, the prevalence of metabolic syndrome has been found to be 33.9% in the general population, 40.6% in patients with PsA, and 53.0% in patients with PsD.[17,21,22]

Table 3. Evaluation of metabolic syndrome, BMI, and VAI levels in PsA and healthy control groups

Parameters		PsA (n=101)	Healthy (n=98)	p
Metabolic syndrome (n/%)	Yes	36 (35.6%)	15 (15.4%)	0.001
	No	65 (64.4%)	83 (84.6%)	
BMI >30 (n/%)	Yes	45 (44.6%)	22 (22.4%)	0.001
	No	56 (55.4%)	76 (77.6%)	
VAI, Median (minimum-maximum)		1.9 (0.57-7.81)	1.5 (0.38-11.08)	0.022

BMI: Body mass index, PsA: Psoriatic arthritis, VAI: Visceral adiposity index

Table 4. Evaluation of VAI in PsA and healthy control groups with metabolic syndrome and obesity

Parameters	VAI value (PsA)	VAI value (healthy control)	p
Presence of metabolic syndrome, mean (± SD)	3.62 (1.72)	4.67 (2.39)	0.08
BMI >30 (obesity), median (minimum-maximum)	2.16 (0.70-7.65)	2.36 (0.7-11.08)	0.3

BMI: Body mass index, PsA: Psoriatic arthritis, SD: Standard deviation, VAI: Visceral adiposity index

In a study by Fernández-Torres et al.[23], obesity was observed in 35.4% of PsD patients. A study by Baeta et al.[24] found an obesity rate of 33.2% among PsD patients, while the current study found that 44.6% of patients were obese. Thus, a high rate of obesity can be seen in this patient group. Therefore, as indicated in many studies, control of body weight is important for the management of this disease.

Table 5. VAI levels in PsA patients with and without comorbidities

Parameters	VAI Median (minimum-maximum)	p
PsA with metabolic syndrome (n=36)	3.37 (1.45-7.81)	<0.0001
PsA without metabolic syndrome (n=65)	1.51 (0.57-5.90)	
PsA with BMI >30 (obesity) (n=45)	2.1 (0.79-7.65)	0.03
PsA without BMI >30 (obesity) (n=56)	1.63 (0.57-7.81)	
PsA with dyslipidemia (n=3)	1.60 (1.48-4.85)	0.82
PsA without dyslipidemia (n=98)	1.91 (0.57-7.81)	
PsA with hypertension (n=26)	2.30 (0.83-7.81)	0.013
PsA without hypertension (n=75)	1.64 (0.57-7.65)	
PsA with diabetes mellitus (n=13)	2.33 (1.48-7.81)	0.024
PsA without diabetes mellitus (n=88)	1.73 (0.57-7.65)	
PsA with smokers (n=20)	1.53 (0.57-4.40)	0.15
PsA without smokers (n=81)	1.94 (0.79-7.81)	

BMI: Body mass index, PsA: Psoriatic arthritis, VAI: Visceral adiposity index

Table 6. VAI levels according to Framingham and SCORE in PsA patients

Parameters	VAI median (minimum-maximum)	p
Framingham score		
Low (n=72)	1.62 (0.57-6.45)	0.03
Intermediate (n=22)	2.89 (1-7.81)	<0.0001
High (n=7)	2.33 (0.83-4.18)	0.388
SCORE		
Low CV risk (n=53)	1.64 (0.79-7.81)	0.058
Moderate CV risk (n=45)	2.15 (0.57-7.65)	0.172
High CV risk (n=3)	1.13 (0.83-1.37)	

CV: Cardiovascular, PsA: Psoriatic arthritis, SCORE: Systematic coronary risk evaluation index, VAI: Visceral adiposity index

In recent years, VAI has emerged as an important gender-dependent marker of insulin resistance, adipose tissue function, and distribution. A high VAI leads to peripheral hyperinsulinemia and insulin resistance. Adipose tissue-derived pro-inflammatory cytokines, including TNF-α, IL-6, and IL-8, play an important role in the pathogenesis of PsD. Production of these pro-inflammatory cytokines increases secondary to obesity and hyperinsulinemia.[3,9,10] In studies related to VAI, it has been used to evaluate polycystic ovary syndrome (PCOS), patients with cardiac or cerebrovascular risk, and chronic hepatitis C.In a study by Androulakis et al.[25], 193 PCOS women were divided into 4 groups according to the severity of menstrual irregularities, and VAI was found to be associated with hyperandrogenism and anovulation. In patients with high VAI levels, an increase in metabolic profile disorders, ovulation disorders, and inflammation was observed.

Petta et al.[26] evaluated 236 patients with genotype 1 chronic hepatitis C and reported that the VAI score increased in association with an increased HCV-RNA burden, steatosis, and inflammation grade. Furthermore, in that study, 44 (18.7%) patients were classified as obese. Based on these data, a high VAI was found to be a marker predictive of higher viral load and severity of inflammation. Another study found that VAI was an important marker of adipose tissue function and distribution and that high VAI levels were an indicator of cardiometabolic risk.[14]

In the present study, the VAI values of PsA patients were found to be statistically significantly higher than those of the control group. However, the VAI values of all patients with metabolic syndrome and BMI >30 (obesity) were found to be higher than the VAI values of the control group. Furthermore, when comparing PsA patients with or without metabolic syndrome, BMI >30 (obesity), hypertension, and DM, VAI values were significantly higher in patients with these comorbidities. In particular, a striking difference in VAI levels was observed in PsA patients with

Table 7. Correlations (r) between disease activity and metabolic and cardiovascular risks of patients

Parameters	BASDAI	PASI	DAPSA	BASFI	HAQ	VAI	SCORE	Framingham risk score
Framingham risk score	0.02	0.095	0.285**	0.202**	0.067	0.299**	0.523	1
SCORE	-0.079	-0.026	0.095	0.065	-0.01	0.058	1	0.523**
VAI	0.128	0.192	0.101	0.105	0.019	1	0.058	0.299**
HAQ	0.129	0.135	0.421**	0.284**	1	0.019	-0.01	0.067
BASFI	0.764**	0.14	0.484**	1	0.284**	0.105	0.065	0.202*
DAPSA	0.462**	0.341**	1	0.484**	0.421**	0.101	0.095	0.285**
PASI	0.092	1	0.341**	0.140	0.135	0.192	-0.026	0.095
BASDAI	1	0.092	0.462**	0.764**	0.129	0.128	-0.079	0.024

**:p<0.05, **:p<0.001*

BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, DAPSA: Disease activity index for psoriatic arthritis, HAQ: Health assessment questionnaire, PASI: Psoriasis area severity index, SCORE: Systematic coronary risk evaluation index, VAI: Visceral adiposity index

metabolic syndrome compared to PsA patients without metabolic syndrome. Therefore, VAI may be an indicator of comorbidities (especially metabolic syndrome) in patients with newly diagnosed PsA.

Patients with PsA have an increased risk of atherosclerosis due to endothelial dysfunction resulting from chronic systemic inflammation. Consequently, cardiovascular mortality and morbidity are higher than in the general population. When individual risk factors are added, this risk increases significantly.[27]

In a study by Ernste et al.[28], evaluating the cardiovascular risk profile at the onset of psoriatic arthritis, approximately half of the patients were obese, which aligns with the current study. Additionally, 41 (33%) of 126 patients had FS ≥10%. This study suggested that cardiovascular risk in PsA patients may be higher than anticipated.

In the study by Martinez Vital et al.[27], 3.9% and 25.5% of patients were at very high and high risk, respectively, according to the SCORE index. After carotid ultrasound, the percentage of patients at true very high and high risk changed to 29.4% and 18.6%, respectively, suggesting that the SCORE index may not be sufficient to assess the true cardiovascular risk.

A study by Gisondi et al.[29], involving 234 adult patients with PsD, found that the FS score was significantly higher in PsD patients, although there was no correlation with the severity or duration of PsD.

Another study by Fernández-Torres et al.[23], involving 395 patients with PsD, examined the relationship between cardiovascular risk and PsD characteristics. According to Framingham scoring, 58.2%, 30.5%, and 11.4% of patients were at low, intermediate, and high risk, respectively. There was no correlation between higher risk and severity of PsD and FS. Using the SCORE index, low risk was calculated as 77.9% and high risk as 22.1%.

In the current study, similar to other studies, no association was found between the PsD disease activity score and FS or SCORE. However, as this was a cross-sectional study and patients were receiving treatment, this may explain the lack of association.

Study Limitations

The main limitations of the current study were the small number of patients and the cross-sectional design. Longitudinal studies are needed to obtain more accurate and reliable results.To the best of our knowledge, there are no studies in the literature on VAI in patients with PsD. Since VAI can be easily calculated using routine tests, it can provide valuable information about cardiometabolic risks and comorbidities in newly diagnosed PsD patients.

Conclusion

VAI scores were associated with low and intermediate FS, but the correlations were weak. In addition to the SCORE index and FS, the VAI score can be used to determine cardiovascular risk. The VAI is a parameter that can be easily calculated using simple measurements in the detection of visceral fat, which poses an increased cardiovascular risk beyond being overweight. This index can be suggested as a reliable tool in the assessment of cardiometabolic risk, especially in the absence of overt metabolic syndrome.[30]

Ethics

Ethics Committee Approval: The study was approved by the Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (decision no: 1636/2017, date: 06.12.2017).

Informed Consent: Informed consent form was obtained from all participants in the study.

Footnotes

Authorship Contributions

Concept: A.O., S.Y.Ç., A.Ö., A.E., Design: A.O., S.Y.Ç., S.C.S.,, A.Ö., A.E., Data Collection and Processing: A.O., F.E., S.Y.Ç., S.C.S.,, T.O., A.Ö., Analysis or Interpretation: A.O., S.C.S.,, İ.K., Literature Search: A.O., F.E., S.Y.Ç., S.C.S.,, T.O., İ.K., A.Ö., A.E., Writing: A.O., F.E., İ.K., A.Ö., A.E.

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Juvenil idiyopatik enflamatuvar miyopati hastalarında hastalık seyri ve ciddi komplikasyonların değerlendirilmesi

Evaluation of disease course and major complications in juvenile idiopathic inflammatory myopathy patients

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Öz

Amaç: İdiyopatik enflamatuvar miyopatiler (İİM), esas olarak deri ve proksimal kasların etkilendiği, kronik, multisistemik, otoimmün hastalıklardır. Bu çalışmada juvenil İİM hastalarında, hastalık seyrini öngörebilecek faktörlerin belirlenmesi ve ciddi komplikasyonların hastalık seyri üzerine etkisinin araştırılması amaçlanmıştır.

Yöntem: Bu retrospektif, gözlemsel çalışma, 2009-2019 yılları arasında Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesi ve 2019-2022 yılları arasında Sağlık Bilimleri Üniversitesi, Ankara Bilkent Şehir Hastanesi'nde İİM tanısıyla en az 6 ay takip edilen hastalarla yapıldı. Demografik, klinik, laboratuvar bulguları, miyozit spesifik antikorlar, tedaviler, hastalık seyri ve komplikasyonlar kaydedildi.

Bulgular: İİM tanısı ile takipli 30 hasta çalışmaya dahil edildi. Hastaların 18'i (%60) kızdı. Ortanca tanı yaşı 118,5 [çeyrekler açıklığı (ÇA): 76,5-139,5] aydı. Hastaların 26'sında (%86,7) kas güçsüzlüğü, 27'sinde (%90,0) deri bulgusu, 11'inde (%36,7) artrit, 4'ünde (%13,3) gastrointestinal sistem tutulumu, 2'sinde (%6,6) yaygın ödem, 1'inde (%3,3) akciğer tutulumu, 1'inde (%3,3) kardiyak tutulum mevcuttu. Ortanca takip süresi 25 (ÇA: 17,7-72,5) aydı. Hastaların 15'inde (%50,0) monosiklik, 4'ünde (%13,3) polisiklik, 11'inde (%36,6) persistan seyir gözlendi. Dördünde (%13,3) kalsinozis, 3'ünde (%10) ciddi steroid yan etkisi gelişti. Altıncı ay çocukluk çağı miyozit değerlendirme ölçeği (CMAS) skoru ile monosiklik hastalık seyri arasında anlamlı istatiksel ilişki mevcuttu (p=0,027). Kalsinozis ile persistan hastalık seyri arasında anlamlı istatistiksel ilişki mevcuttu (p=0,05).

Abstract

Objective: Idiopathic inflammatory myopathies (IIM) are chronic, multisystemic, autoimmune diseases affecting mainly the skin and proximal muscles. In this study, we aimed to determine the factors that may predict the disease course and to investigate the effect of major complications on the disease course in juvenile IIM patients.

Methods: This retrospective, observational study was conducted in Ankara Pediatrics Hematology Oncology Training and Research Hospital between 2009 and 2019 and University of Health Sciences Turkiye, Ankara Bilkent City Hospital between 2019 and 2022 with patients who were followed up for at least 6 months with a diagnosis of IIM. Demographic, clinical, laboratory findings, myositis-specific antibodies, treatments, disease course and complications were recorded.

Results: Thirty patients with IIM were included in the study. Eighteen (60%) of the patients were female. The median age at diagnosis was 118.5 [inter quartile range (IQR): 76.5-139.5] months. Twenty-six (86.7%) patients had muscle weakness, 27 (90.0%) had skin manifestations, 11 (36.7%) had arthritis, 4 (13.3%) had gastrointestinal system involvement, 2 (6.6%) had generalized edema, 1 (3.3%) had pulmonary involvement, and 1 (3.3%) had cardiac involvement. The median follow-up period was 25 (IQR: 17.7-72.5) months. Monocyclic course was observed in 15 (50.0%), polycyclic in 4 (13.3%) and persistent in 11 (36.6%) patients. Calcinosis developed in 4 (13.3%) patients and severe steroid side effects in 3 (10%) patients. The 6th month Childhood Myositis Assessment Scale (CMAS) score was significantly correlated with monocyclic disease course.

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Öz

Sonuç: İİM olgularında CMAS skoru hastalık seyri öngörüsünde önemlidir. Altıncı ay CMAS skoru düşük olan hastalarda polisiklik/persistan seyir ihtimalinin arttığı göz önünde bulundurularak bu hasta grubu yakından izlenmelidir.

Anahtar Kelimeler: İdiyopatik enflamatuvar miyopati, jüvenil dermatomiyozit, prognoz, komplikasyon

Abstract

Conclusion: CMAS score is useful tool in predicting the disease course in patients with IIM. Patients with low 6th month CMAS score should be carefully followed up considering the increased possibility of polycyclic/persistent course.

Keywords: Idiopathic inflammatory myopathy, juvenile dermatomyositis, prognosis, complications

Giriş

İdiyopatik enflamatuvar miyopatiler (İİM), dermatomiyozit (DM), polimiyozit (PM), amiyopatik DM (ADM), inklüzyon cisimcikli miyozit ve immün aracılı nekrotizan miyopatiyi (İMNM) içeren bir grup nadir otoimmün hastalıktır.[1] Ağırlıklı olarak kasları ve cildi etkiler ancak akciğerler, kalp, bağırsaklar ve merkezi sinir sistemi dahil olmak üzere mortalite üzerine etkili diğer organları da tutabilir.[2] Kalsinozis, lipodistrodi, osteoporoz, fonksiyonel kısıtlılıklar ve büyüme gelişme geriliği hem kontrolsüz enflamasyon hem de İİM tedavisinde kullanılan ilaçların yan etkilerine bağlı olarak gelişebilecek morbiditeyi etkileyebilen komplikasyonlardır.[3-5]

Hastalığın seyri değişkendir. Hastaların yaklaşık %30'unda monosiklik, %3-30'unda polisiklik ve %30-60'ında persistan seyir görülür. Hangi hastaların polisiklik veya persistan seyir göstereceği belirsizliğini korumaktadır.[6] Juvenil İİM'de ölüm oranı tanı ve tedavideki gelişmelerle %5'in altına düşmüştür. Ölüm nedenleri arasında masif gastrointestinal kanama veya intestinal perforasyona yol açabilecek gastrointestinal vaskülit, ilerleyici pulmoner hastalık, tedavi yanıtsız miyozit, kardiyovasküler olaylar ve enfeksiyonlar yer almaktadır.[7] İmmünosüpresif tedavinin etkisi hastalar arasında ve aynı hastadaki farklı organ belirtileri arasında farklılık gösterir. Birçok hasta, glukokortikoidle birlikte metotreksat veya azatioprin gibi bir immünosüpresif ajan ile ilk basamak tedaviye zayıf yanıt verir.[8] Tedaviler ve hastalık yönetimi son on yılda büyük ölçüde iyileşmiş olsa da, mevcut tedavilerin çoğu için kanıtlar hala eksiktir. Tanı anında hangi hastaların refrakter seyredeceği belirsizliğini koruduğu gibi, refrakter İİM'nin yönetimi de klinisyeni zorlamaya devam etmektedir. Tedaviye yanıtı, kalsinoz ve interstisyel akciğer hastalığı gibi komorbiditeleri ve hastalık seyrini tahmin etmek için doğrulanmış prognostik biyobelirteçlere ihtiyaç vardır.[2] Biyobelirteçler mevcut olana kadar, klinik uygulamada kullanılabilecek pratik belirleyicilerinin bilinmesi yararlı olacaktır. Bu çalışmanın amacı, juvenil İİM hastalarında, hastalık seyri öngörücülerini belirlemektir. Ayrıca hastalığın komplikasyonlarının hastalığın uzun dönem seyrine etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem

Hasta Seçimi

Bu retrospektif gözlemsel çalışma, 2009-2019 yılları arasında Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesi ve 2019-2022 yılları arasında Sağlık Bilimleri Üniversitesi, Ankara Bilkent Şehir Hastanesi'nde, Bohan ve Peter[9,10] kriterlerine göre İİM tanısı alan ve en az 6 ay süreyle takip edilen hastalarla yapıldı. Tanı anında İİM olarak yanlış tanı alabilecek enfeksiyonlar, maligniteler, diğer nöromusküler hastalıklar dışlandı. Hasta verileri hasta dosyalarından ve elektronik tıbbi kayıtlardan elde edildi. Verileri eksik olan, takip süresi <6 ay olan İİM'li hastalar çalışmaya dahil edilmedi.

Veri Toplama

Veriler hasta dosyalarından ve elektronik tıbbi kayıtlarından toplanmıştır. Tanı yaşı, cinsiyet, klinik bulgular, semptomların süresi, başvurudan tanıya kadar geçen süre, sistemik tutulumlar, biyokimya parametreleri, tam kan sayımı, C-reaktif protein, eritrosit sedimantasyon hızı (ESH), ferritin, miyozit spesifik antikorlar (MSA), miyozit ilişkili antikorlar, antinükleer antikor (ANA) gibi laboratuvar bulguları, görüntüleme bulguları, tedaviler [steroidler, konvansiyonel ve biyolojik hastalık modifiye edici anti-romatizmal ilaçlar [konvansiyonel hastalığı değiştiren antiromatizmal ilaçlar (cDMARD) ve biyolojik DMARD (bDMARD)], tofasitinib, intravenöz immünoglobulin (IVIG)], remisyon durumu, nüks durumu, komplikasyonlar kaydedilmiştir. MSA immünblot yöntemiyle çalışılmıştır. MSA paneli kapsamında anti-TIF1-gama, anti-NXP2, anti-MDA5, anti-Mi2, anti-SAE1, anti-SRP, anti-Jo1, anti-PL7, anti-PL12, anti-EJ, anti-OJ otoantikorları değerlendirilmiştir.

Tanımlar

Tüm olgularda İİM tanısı Bohan ve Peter [9,10] tarafından tanımlanan kriterlere dayandırılmıştır. Alt grup tanıları (ADM, İMNM) Avrupa Romatizma ile Mücadele Birliği/Amerikan Romatoloji Birliği 2017 tanı kriterleri ile doğrulanmıştır.[11] Tanı anında, tüm hastalar kas, kas dışı

ve iskelet dışı semptomları tespit etmek için klinik olarak değerlendirilmiştir. Tüm hastalara elektrokardiyografi, göğüs radyografisi, solunum fonksiyon testleri (SFT) ve akciğer karbon monoksit difüzyon kapasitesi ölçümü yapılmıştır. Fizik muayenede veya önceki tarama testlerinde şüpheli belirti ve semptomlar tespit edilirse yüksek çözünürlüklü bilgisayarlı tomografi (HRCT) ve ekokardiyografi yapılmıştır. Akciğer grafisi ve/veya HRCT taraması interstisyel fibrozis veya alveolar infiltratların varlığını gösteriyorsa; SFT anormallikleri restriktif bir paternle karakterize ise İAH olarak kabul edilmiştir. Kardiyak tutulum tanısı, aritmi, iletim defektleri, miyokardit, kardiyomiyopati ve konjestif kalp yetmezliğinin (KKY) diğer nedenlerinin dışlanmasına dayandırılmıştır.[12]

Hastalığın seyri ve tedaviye yanıt, fizik muayene ve serum kas enzimlerinin seviyelerindeki değişikliklerle değerlendirilmiştir. Kas gücünün değerlendirilmesi için Çocukluk Çağı Miyozit Değerlendirme Ölçeği (CMAS) kullanılmıştır.[13] Ölçek yaşı nedeni ile teste uyum sağlayamayan 4 (%13,3) hasta dışındaki tüm hastalara tanı anında, takiplerinin 3., 6. ve 12. aylarında uygulanmıştır. Remisyon Pediatrik Romatoloji Uluslararası Araştırmalar Organizasyonu (PRINTO) kriterlerine göre tanımlanmıştır. PRINTO kriterlerine göre remisyon aşağıdaki kriterlerin dördünden en az üçünü içerir: 1) Kreatin kinaz ≤150, 2) CMAS skoru ≥48,3) manuel kas testi skoru ≥78 ve 4) hekimin genel hastalık aktivitesine ilişkin global değerlendirmesi ≤0,2.[14]

Nüks, 6 ay veya daha uzun süren bir remisyondan sonra hastalığın yeniden aktive olması olarak tanımlanmıştır.[12] Monosiklik seyir bir hastalık dönemi ardından nüksetme olmaksızın remisyonun sürdürülmesi olarak tanımlandı. Polisiklik hastalık seyri birden fazla remisyon ve relaps atakları olarak tanımlandı. Persistan seyir hiç remisyon olmaksızın aktif hastalığın devamı olarak tanımlandı.[1]

Bu çalışma Sağlık Bilimleri Üniversitesi, Ankara Bilkent Şehir Hastanesi 2 No'lu Tıbbi Araştırmalar Bilimsel ve Etik Değerlendirme Kurulu tarafından onaylandı (karar no: TABED 2-24-314, tarih: 10.07.2024). Çalışma, kurumsal araştırma komitesinin etik standartlarına ve 1964 Helsinki Bildirgesi ve sonraki değişikliklerine uygundur.

İstatistiksel Analiz

İstatistiksel analizler SPSS yazılımı sürüm 25 kullanılarak gerçekleştirilmiştir. Değişkenlerin normal dağılıp dağılmadığı görsel (histogramlar, olasılık grafikleri) ve analitik yöntemler (Kolmogorov-Smirnov/Shapiro-Wilk testi) kullanılarak incelenmiştir. Tanımlayıcı analizler normal dağılan değişkenler için ortalama ve standart sapmalar, normal dağılmayan ve sıralı değişkenler için medyan ve çeyrekler açıklığı (ÇA) ve kategorik değişkenler için frekanslar kullanılarak sunulmuştur. Normal dağılımlı değişkenler için Student's t-testi, normal dağılımlı olmayan ve sıralı değişkenler için Mann-Whitney U testi ve kategorik değişkenler için ki-kare veya Fisher testleri kullanılmıştır. Nüks analizi için, çok değişkenli lojistik regresyon modeli tek değişkenli analizde istatistiksel olarak anlamlı bağımsız değişkenleri (p=0,05) içermiştir. P değerinin 0,05'ten küçük olması istatistiksel olarak anlamlı bir sonuç olarak kabul edilmiştir.

Bulgular

Toplam 30 İİM hastası çalışmaya dahil edilmiştir. Yirmi dört (%80) hasta juvenil DM (JDM), 5 (%16,7) hasta ADM, 1 (%3,3) hasta İMNM alt grubundaydı.

Demografik, Klinik ve Laboratuvar Bulguları

Hastaların 18'i (%60) kızdı. Ortanca tanı yaşı 118,5 (ÇA: 76,5-139,5) aydı. Semptom başlangıcından tanıya kadar geçen ortanca süre 2 (ÇA: 1-8,25) aydı. Ortanca takip süresi 25 (ÇA: 17,8-72,3) aydı.

Hastaların 26'sında (%86,7) kas güçsüzlüğü, 27'sinde (%90,0) deri bulgusu, 11'inde (%36,7) artrit, 4'ünde (%13,3) gastrointestinal sistem tutulumu, 2'sinde (%6,6) yaygın ödem, 1'inde (%3,3) akciğer tutulumu, 1'inde (%3,3) kardiyak tutulum mevcuttu. Hastaların 18'inde (%60) ANA pozitifliği saptandı. Hastaların 10'unun (%33,3) MSA sonucu bilinmiyordu. Üç (%10) hastanın MSA sonucu negatifti. On yedi (%56,7) hastada MSA pozitifliği saptandı.

Hastaların 6'sında (%20,0) anti NXP2, 4'ünde (%13,3) anti TIF1 γ, 3'ünde (%10,0) anti MDA5, 3'ünde (%10) anti Ku, 2'sinde (%6,7) anti Mi-2, 2'sinde (%6,7) anti SRP, 2'sinde (%6,7) anti Pm-Scl, 2'sinde (%6,7) anti OJ, 1'inde (%3,3) anti SAE, 1'inde (%3,3) anti PL7 MSA pozitifti.

Anti-NXP2 pozitif hastalardan 1'inde (%3,3) gastrointestinal sistem tutulumu, 1'inde (%3,3) kalsinozis ve yaygın deri alt ödemi, 1'inde (%3,3) steroide sekonder osteoporoz görüldü. Anti-TIF1-gama pozitif 1 (%3,3) hastada steroide sekonder boy kısalığı görüldü. Anti-MDA5 pozitif 1 (%3,3) hastada akciğer tutulumu ve kardiyak tutulum görüldü. Anti-SRP pozitif 1 (%3,3) hastada şiddetli kas güçsüzlüğü ve gastrointestinal sistem tutulumu görüldü. Anti-PL7 pozitif 1 (%3,3) hastada steroide sekonder osteoporoz görüldü. Anti-OJ pozitif 1 (%3,3) hastada gastrointestinal sistem tutulumu ve 1 (%3,3) hastada steroide sekonder boy kısalığı görüldü. MSA taramaları negatif olan 1 (%3,3) hastada yaygın deri altı ödemi görüldü. Hastaların demografik, klinik, laboratuvar bulguları Tablo 1'de özetlenmiştir. Ortanca CMAS skoru tanı anında 31 (ÇA: 15-

42), 3. ayda 43 (ÇA: 37-46), 6. ayda 46 (ÇA: 42-48), 12. ayda 50,5 (ÇA: 48-51) idi.

Tedavi Yönetimi

Tedaviye kontrendikasyon bulunmuyorsa kortikosteroidlerle kombine edilen metotreksat ile başlandı. Metotreksat intoleransı durumunda mikofenolat mofetil tercih edildi. Deri bulguları sebat eden hastalara hidroksiklorokin eklendi. Refrakter kas güçsüzlüğü, deri bulguları ve/veya pulmoner, kardiyak, gastrointestinal organ ve sistem tutulumu olan hastalar için siklofosfamid, ritüksimab, tofacitinib ve IVIG kullanıldı.[15] Hastaların 14'ü (%46,7) pulse metilprednizolon (PMP), 29'u (%96,7) metotreksat, 12'si (%40,0) IVIG, 7'si (%23,3) mikofenolat mofetil, 9'u (%30) hidroksiklorokin, 1'i (%3,3) siklofosfamid, 1'i (%3,3) ritüksimab tedavisi aldı (Tablo 2).

JDM tanılı 13 (%43,3) hasta steroid + cDMARD tedavisi, 11 (%36,7) hasta steroid + cDMARD + IVIG tedavisi aldı. ADM tanılı 5 (%16,7) hasta steroid + cDMARD tedavisi aldı. İmmün aracılı nekrotizan miyopati tanılı 1 (%3,3) hasta steroid + cDMARD + bDMARD + IVIG tedavisi aldı.

Hastalık Seyri ve Komplikasyonlar

Hastaların 15'inde (%50,0) monosiklik, 4'ünde (%13,3) polisiklik, 11'inde (%36,6) persistan seyir gözlendi. Dördünde (%13,3) kalsinozis, 2'sinde (%6,7) ciddi steroid yan etkisi gelişti.

Monosiklik ve polisiklik/persistan seyreden hasta grupları arasında demografik, klinik, laboratuvar bulguları açısından fark saptanmadı.

Tanı anı, 3. ay, 6. ay, 12. ay ortanca CMAS skorları monosiklik hasta grubu için sırasıyla 34 (24-46), 43 (40-48), 48 (44-50), 51 (50-51), polisiklik/persistan hasta grubu için sırasıyla 26 (15-32), 40 (30-46), 42 (40-48), 48 (42-51) idi. Altıncı ay CMAS skoru ile monosiklik hastalık seyri arasında anlamlı istatiksel ilişki mevcuttu (p=0,027).

Kalsinozis gözlenen 4 (%13,3) hastanın tamamı polisiklik/persistan seyirli hasta grubundaydı. Kalsinozis ile polisiklik/persistan hastalık seyri arasında anlamlı istatiksel ilişki mevcuttu (p=0,05).

Monosiklik seyirli hastaların 5'i (%35,7) PMP, 14'ü (%46,7) metotreksat, 4'ü (13,3) hidroksiklorokin,

2'si (%6,7) IVIG tedavisi aldı. Polisiklik/persistan seyirli hastaların 9'u (%64,3) PMP, 15'i (%50) metotreksat, 7'si (%23,3) mikofenolat mofetil (MMF), 5'i (%16,7) hidroksiklorokin, 1'i (%3,3) siklofosfamid, 1'i (%3,3) ritüksimab, 10'u (%33,3) IVIG tedavisi aldı. Monosiklik seyreden 13 (%43,3) hasta steroid + cDMARD tedavisi, 2 (%6,6) hasta steroid + cDMARD + IVIG tedavisi aldı. Polisiklik/persistan seyreden 5 (%16,7) hasta steroid + cDMARD tedavisi, 9 (%30) hasta steroid + cDMARD + IVIG tedavisi, 1 (%3,3) hasta steroid + cDMARD + bDMARD + IVIG tedavisi aldı.

Her iki hasta grubu arasında diğer tedaviler açısından anlamlı fark bulunmazken polisiklik/persistan seyirli hastalar daha fazla MMF ve IVIG tedavisi almıştı (p=0,006, p=0,008).

Monosiklik ve polisiklik/persistan seyirli hastaların demografik, klinik, laboratuvar bulguları Tablo 1'de, tedavileri, CMAS skorları ve komplikasyonları Tablo 2'de özetlenmiştir.

Tartışma

İİM kas güçsüzlüğü, deri döküntüleri, iç organ tutulumu ve vaskülopati ile karakterize, önemli morbidite ve mortaliteye yol açabilen nadir görülen multisistemik bir otoimmün hastalıktır.[2] Son yıllarda İİM yönetimindeki gelişmelere rağmen hastaların önemli bir kısmı hala polisiklik/persistan seyir göstermektedir. Hangi hastaların polisiklik/persistan seyir göstereceği belirsizliğini korumaktadır. Çalışmamızda 6. ay CMAS skoru düşük olan hastalarda ve kalsinozis gelişen hastalarda monosiklik seyir ihtimalinin daha düşük olduğu ortaya konmuştur. Monosiklik seyirli hastalara göre polisiklik/persistan seyirli hastalarda daha fazla IVIG ve mikofenolat mofetil tedavisi ihtiyacı olmuştur. Öte yandan pulmoner, kardiyak, gastrointestinal sistem tutulumları gibi hastalığın prognozunu etkileyebilecek tutulumları olan hasta sayımız az olduğundan bu tutulumların hastalık seyri üzerine olan etkisi bu çalışmada saptanamamıştır.

İİM hastalarının üçte biri bir hastalık atağı geçirir ve daha sonra nüksetmeden remisyona ulaşır. Bizim çalışmamızda hastaların %50'sinde monosiklik, %13,3'ünde polisiklik, %36,6'sında persistan seyir gözlenmiştir. Hastaların %3 ila %30'unda birden fazla remisyon ve nüks ile birlikte polisiklik bir seyir vardır. Bunun ne sıklıkta meydana geldiğine ilişkin tahminlerdeki farklılık muhtemelen farklı remisyon tanımlarından kaynaklanmaktadır. Hastaların yaklaşık %30 ila %60'ı tedaviye rağmen remisyon olmadan aktif hastalığı sürdürür.[6] Gowdie ve ark.[16] 57 JDM hastasını değerlendirdikleri çalışmalarında hastaların %46,7'sinde monosiklik, %17,7'sinde polisiklik ve %35,5'inde persistan seyir saptamışlardır. Taborda ve ark.[1] çalışmalarında hastaların %34,4'ünde monosiklik, %34,4'ünde persistan ve %31,1'inde polisiklik hastalık seyri gözlemişlerdir. Constantin ve ark.[12] 44 juvenil İİM hastasını değerlendirmiş, hastaların %59,1'inde monosiklik, %31,8'inde polisiklik ve %9,1 persistan hastalık seyri gözlemişlerdir. Hajialilo ve ark.[17] 76 erişkin İİM hastasını değerlendirdikleri çalışmalarında hastaların %52,6'sında polisiklik, %31,6'sında monosiklik ve

Tablo 1. Monosiklik ve polisiklik/persistan seyirli hastaların demografik, klinik ve laboratuvar bulgularının karşılaştırılması

	Toplam	Monosiklk	Polisiklik/persistan	p-değeri
Demografik bulgular				
Cinsiyet (n, %)				
Kadın	18 (60)	9 (30)	9 (30)	0,64
Erkek	12 (40)	6 (20)	6 (20)	
Tanı yaşı (medyan, ÇA) (ay)	118,5 (76,5-139,5)	130 (87-147)	113 (53-137)	0,43
Tanıya kadar geçen semptom süresi (medyan, ÇA) (ay)	2 (1-8,25)	2 (1-9)	2 (1-8)	0,77
Takip süresi (medyan, ÇA) (ay)	25 (17,8-72,3)	19 (18-61)	54 (17-108)	0,14
Klinik bulgular (n, %)				
Kas güçsüzlüğü	26 (86,7)	12 (40)	14 (46,7)	0,29
Deri bulgusu	27 (90)	12 (40)	15 (50)	1
Artrit	11 (36,7)	4 (13,3)	7 (23,3)	0,45
Akciğer tutulumu	1 (3,3)	0 (0)	1 (3,3)	1
Kardiyak tutulum	1 (3,3)	0 (0)	1 (3,3)	1
Gastrointestinal sistem tutulumu	4 (13,3)	1 (3,3)	3 (10)	0,59
Laboratuvar bulguları (medyan, ÇA)				
CK U/L	1281,5 (436,3-6942,5)	1504 (431-7859)	1206 (800-6637)	0,96
AST U/L	98,5 (59,5-286,3)	93 (35-202)	148 (63-314)	0,48
ALT U/L	57,5 (32,5-168,8)	57 (28-133)	72 (46-185)	0,48
LDH U/L	662,5 (413,8-878,5)	591 (363-940)	675 (565-842)	0,46
WBC x10^6/L	7465 (5477-9317)	7434 (5300-9190)	7500 (7200-9700)	0,13
ANS x10^6/L	4580 (3362,5-6530)	4050 (3250-6060)	5060 (3400-8700)	0,48
ALS x10^6/L	1610 (1195-2332)	1500 (1000-2160)	1850 (1200-2540)	0,38
Hb g/dL	12 (10,9-12,8)	11,9 (11-12,7)	12,2 (10,6-123)	0,9
Trombosit x10^6/L	287500 (230000-344750)	270000 (227000-310000)	317000 (267000-353500)	0,16
ESH mm/saat	13 (6-22)	14 (6-30)	12 (10-20)	0,93
CRP mg/L	0,55 (0,5-11,6)	0,7 (0,5-12)	0,5 (0,3-5,8)	0,21
ANA	18 (60)	10 (33,3)	8 (26,7)	0,71
Miyozit spesifik antikorlar (n,%)				
Bilinmiyor	10 (33,3)	5 (16,7)	5 (16,7)	1
Negatif	3 (10)	3 (10)	0 (0)	0,22
Anti NXP2	6 (20)	2 (6,7)	4 (13,3)	0,65
Anti SRP	2 (6,7)	1 (3,3)	1 (3,3)	1
Anti TIF1	4 (13,3)	2 (6,7)	2 (6,7)	1
Anti Mi2	2 (6,7)	1 (3,3)	1 (3,3)	1
Anti MDA5	3 (10)	1 (3,3)	2 (6,7)	0,5
Anti SAE	1 (3,3)	1 (3,3)	0 (0)	0,5
Anti Ku	3 (10)	3 (10)	0 (0)	0,22
Anti PL7	1 (3,3)	0 (0)	1 (3,3)	0,5
Anti OJ	2 (6,7)	0 (0)	2 (6,7)	0,48

ANA: Antinükleer antikor, ALS: Amyotrofik lateral skleroz, ANS: Otonom sinir sistemi, AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz, CK: Kreatin kinaz, CRP: C-reaktif protein, ÇA: Çeyrekler açıklığı, ESH: Eritrosit sedimantasyon hızı, Hb: Hemoglobin, LDH: Laktat dehidrojenaz, WBC: Beyaz kan hücresi

%5,3'ünde kronik progresif seyir izlemişlerdir. Rajarathinam ve ark.[18] çalışmalarında hastaların %74,5'unda tam klinik remisyon elde edildi. %31,9 hastada monosiklik, %12,7 hastada polisiklik ve %51,1 hastada kronik persistan seyir görüldü.

Polisiklik veya persistan seyreden hastalar uzamış steroid kullanımı ve diğer immünosüpresif tedavilerin yan etkileri riskleriyle karşı karşıyadır. Bu sebeple tanı sırasında ve hastalık seyrinin erken dönemlerinde hastalık seyrinin öngörülmesi hekimin tedavi yaklaşımlarını belirlemesine katkı sağlayacaktır. Hastalık özellikleri, zamanla iyileşme olasılığı daha düşük olan hastaların belirlenmesine yardımcı olabilir. Hastalık aktivitesindeki gelecekteki değişiklikleri öngörmeye yönelik risk puanları da hastalık seyrinde daha

Tablo 2. Monosiklik ve polisiklik/persistan seyirli hastaların tedavi, izlem ve komplikasyonlarının karşılaştırılması

	Toplam	Monosiklk	Polisiklik/persistan	p-değeri
Tedaviler (n, %)				
PMP	14 (46,7)	5 (35,7)	9 (64,3)	0,27
Metotreksat	29 (96,7)	14 (46,7)	15 (50)	1
Mikofenolat mofetil	7 (23,3)	0 (0)	7 (23,3)	**0,006**
Hidroksiklorokin	9 (30)	4 (13,3)	5 (16,7)	1
Siklofosfamid	1 (3,3)	0 (0)	1 (3,3)	1
Ritüksimab	1 (3,3)	0 (0)	1 (3,3)	1
IVIG	12 (40)	2 (6,7)	10 (33,3)	**0,008**
CMAS (medyan, ÇA)				
Tanı	31 (15-42)	34 (24-46)	26 (15-32)	0,69
3. ay	43 (37,3-46,5)	43 (40-48)	40 (30-46)	0,18
6. ay	46 (42-48,3)	48 (44-50)	42 (40-48)	**0,027**
12. ay	50,5 (48-51)	51 (50-51)	48 (42-51)	0,164
Komplikasyonlar (n, %)				
Kalsinozis	4 (13,3)	0 (0)	4 (13,3)	**0,05**
Ciddi steroid yan etkisi	3 (10)	0 (0)	3 (10)	0,36

CMAS: Çocukluk çağı miyozit değerlendirme ölçeği, ÇA: Çeyrekler arası açıklığı, PMP: Pulse metilprednizolon

agresif tedaviyi daha erken tetiklemek için kullanılabilir.[19] Literatürde İİM hastalarında hastalık seyrini öngörecek faktörlerin incelendiği az sayıda çalışma mevcuttur. Stringer ve ark.[20], üçüncü ayda sebat eden aktif döküntü, altıncı ayda tırnak yatağı kapiler damar anormallikleri ve JDM döküntüsü varlığının hastalık remisyonuna kadar geçen sürenin daha uzun olacağını öngördüğünü bulmuşlardır.Sanner ve ark.[21], tanının ilk yılında hasar varlığının, uzun süreli aktif hastalık ile ilişkili olduğunu belirtmişlerdir. Düşük tırnak yatağı kapiler damar yoğunluğu, azalmış akciğer hacmi, HRCT ile tespit edilen pulmoner hastalık nüks riski ile ilişkilendirilmiştir.[22] Kishi ve ark.[23] tam klinik yanıta kadar geçen ortalama sürenin, kortikosteroidin kesilmesine kadar geçen süre için en güçlü belirleyici olduğunu saptamışlardır. Anti-TIF 1γ antikorlarının varlığı ve tedaviye başlandıktan sonraki 12-24 ay içinde ilaç tedavisinin artırılmasını da daha uzun remisyon süresiyle ilişkilendirilmişlerdir.[23] Rajarathinam ve ark.[18] döküntünün ve artraljinin olmamasını tam klinik remisyon için olumlu faktörler olarak saptamışlardır. Hastalığın başlangıcında kas zayıflığı derecesi, yüksek laktat dehidrojenaz ve yüksek ESH, kronik seyir ile ilişkilendirilmiştir. Hastanın İİM başlangıcındaki yaşı da hastalık özelliklerini etkileyebilir. Sener ve ark.[24] Üç yaş altı ve 3 yaş üstü JDM hastalarını karşılaştırdıkları çalışmalarında erken başlangıçlı grupta nüks oranı daha yüksekti, kas biyopsisi bulguları daha ciddiydi ve bu hasta grubunun daha yoğun immünsüpresif tedavi gereksinimi mevcuttu. Çalışmamızda 6. ay CMAS skoru düşük olan hastalarda ve kalsinozis gelişen hastalarda monosiklik seyir ihtimalinin daha düşük olduğu saptanmıştır. CMAS, juvenil İİM'li hastalarda, kas kuvveti, fiziksel fonksiyon, ve dayanıklılığı derecelendirmek için geliştirilmiş performansa dayalı bir araçtır.[13] Bu mevcut çalışmada hem 6. aydaki CMAS'ın monosiklik seyrin önemli belirleyicisi olduğu hem de istatiksel olarak anlamlı farklılık saptanmasa da tanı anındaki CMAS skorunun da polisiklik/persistan seyirli hastalarda, monosiklik seyirli hastalara göre düşük olduğu gösterildi.

İİM'lerin klasik deri bulguları ve kas güçsüzlüğü dışında prezantasyonları da bulunmaktadır. İİM tanılı çocuk hastaların %22'sinde ve erişkin hastaların %10-20'sinde klinik olarak belirgin kas güçsüzlüğü olmadığı önceki çalışmalarda bildirilmiştir.[25] JDM'in karakteristik döküntülerinin bulunmadığı PM ise juvenil hastaların %2-4'ünde görülür.[26] Çalışmamızda İİM hastalarımızın %80'i JDM, %16,7'si ADM, %3,3'ü İMNM alt grubundaydı. ADM tanılı 1 hastamız kronik artriti ile birlikte persistan seyretti. Amiyopatik hastaların İAH gelişimi ile, PM hastalarının şiddetli kas güçsüzlüğü ve sekonder gastrointestinal sistem tutulumları ile persistan seyir gösterebileceği akılda tutulmalıdır.[27]

Pediatrik yaş grubunda İİM'lere ikincil organ ve sistem tutulumları erişkinlere göre nadirdir.[15] Ancak morbidite ve mortaliteyi etkileyebilecek bu tutulumların erken tanınması ve uygun tedavinin başlanması hastalığın uzun dönem prognozu açısından önemlidir. İİM'lere ikincil gelişebilecek akciğer bulguları arasında intersitisyel akciğer hastalığı, nonspesifik interstisyel pnömoni, organize pnömoni, bronşiolitis obliterans, diffüz alveoler hasar, pulmoner kapillerit ve pnömotoraks bulunmaktadır.[28] İAH, JDM olgu serilerinde %7-19 oranında bildirilmiştir.[29] Klinik olarak

belirgin kardiak tutulum ise erişkin hastalarda bile %10'dan az görülür. Miyokardit, KKY, aritmiler, kardiyomiyopati, koroner arter hastalığı ve daha az sıklıkla perikardit, perikardiyal efüzyon ve tamponad İİM hastalarında görülen önemli morbidite ve mortalite nedenleridir.[30] Faringeal ve proksimal özofagus kaslarının tutulumuna bağlı orofaringeal disfaji, İİM'lerde en sık görülen gastrointestinal semptomdur. Ağır gastrointestinal sistem tutulumları ise vaskülopatiye sekonder gastrointestinal ülserasyon ve perforasyondur.[27] Bizim hastalarımızdan da anti-MDA5 MSA pozitif olan bir hastamızda İAH ve kalp yetmezliği ve aritmi şeklinde kardiyak tutulum mevcuttu. Anti-NXP2 MSA pozitif olan 2 hastamızda, anti-SRP MSA pozitif 1 hastamızda ve MSA taramaları negatif olan 1 hastamızda disfaji ve regürjitasyon şeklinde gastrointestinal sistem tutulumu mevcuttu. Pulmoner, kardiak ve gastrointestinal sistem tutulumu olan hastalarımızın tamamı polisiklik/persistan seyirli hasta grubundaydı.

Polisiklik/persistan seyrin belirleyicilerinden birinin de kalsinozis olduğu bu çalışma ile gösterildi. Komplikasyonun patogenezinde TNF-alfa 308 polimorfizmi ile ilişkili olarak TNF-alfanın lokal üretiminin artmasının olduğu düşünülmektedir.[31] Kalsinozis hastaların %20-40'ında, özellikle tanısal gecikme, kalp tutulumu ve uzun süreli veya ciddi hastalık seyri olanlarda görülür.[26] Çoğunlukla hastalığın başlangıcından 1-3 yıl sonra başlar. Enflamasyonun yoğunluğu kalsinozis gelişimine katkıda bulunur.[32] Kalsinozis riski, hastalık başlangıcı ile tedavi arasında geçen uzun süre ve nüks ile anlamlı düzeyde ilişkilidir.[33] Anti-NXP2, tüm yaş gruplarında kalsinozis riskini artırır. Erken yaştaki çocuklar da otoantikor fenotipinden bağımsız olarak yüksek kalsinozis riskine sahiptir.[34] Kalsinozis bizim çalışmamızda olduğu gibi genel olarak persistan hastalık seyri ile ilişkilendirilse de kalsinozisin, hastalık sonucu veya hastalık seyri ile ilişkili bulunmadığını belirten yayınlar da mevcuttur.[18]

Geçtiğimiz 10 yıldaki önemli bir ilerleme, MSA profiline dayanarak hastalık fenotipinin daha iyi anlaşılmasıdır. İİM'li çocukların yaklaşık %60'ında pozitif olan MSA'lar, hastalığın gidişatı ve İAH veya kalsinozis gibi komplikasyon riski konusunda bilgi sağlamaya yardımcı olabilir. Çalışmamızda literatüre benzer şekilde %56,7 hastada MSA pozitifti.[6] En sık pozitif saptanan MSA anti-NXP2 antikoruydu. MSA pozitifliğinin hastalık seyri üzerine etkisi bu çalışmada saptanamamıştır. Ancak literatürde MSA pozitifliğinin hastalık seyri üzerine etkili olduğunu gösteren çalışmalar mevcuttur. Papadopoulou ve ark.[2] anti-sentetaz, anti-HMGCR, anti-Ro52, anti-TIF-1γ, anti SRP antikorları olan hastalarda sıklıkla kronik persistan bir hastalık seyir olduğunu ve bu hasta grubunun ek immünosüpresif tedaviye ihtiyaç duyduğunu bildirmişlerdir. McCann ve ark.[34] benzer şekilde juvenil başlangıçlı hastalıkta, TIF-1γ, anti-HMGCR, anti-SRP veya anti-sentetaz antikorlarının varlığının daha ağır, kronik veya tedaviye dirençli bir hastalık seyri riskine işaret ettiğini, anti Mi-2 otoantikorunun varlığının, düşük mortalite ile daha hafif ve daha kısa bir hastalık seyri ile ilişkili olduğunu belirtmişlerdir. Öte yandan Papadopoulou ve ark.[2] anti Mi2 antikor pozitifliğini polisiklik hastalık seyri ile ilişkilendirmişlerdir. Yamasaki ve ark.[33] anti MDA5 antikorları pozitif olan hastaların ilaçsız remisyona ulaşma olasılıklarının daha yüksek olduğunu (%29'a karşı %21) ve nüksetme risklerinin daha düşük olduğunu (%26'ya karşı %44) saptamışlardır.

İmmünosüpresif ilaçlarla tedaviye yanıt hastalar arasında büyük farklılıklar gösterir.[23] MMF'nin JDM hastalarında etkili ve iyi tolere edildiği bulunmuştur.[35] Varnier ve ark.[36] MMF tedavisiyle sırasında kas kuvveti, deri hastalığı aktivitesi ve genel hastalık aktivitesi ölçümlerinde iyileşme gördüler. İnaktif hastalığı olan hastaların sayısı MMF başlangıcında %10,3'ten son takipte %68,5'e yükseldi. MMF tedavisi ile steroid dozu 0,3 mg/kg/günden 0,1 mg/kg/güne önemli ölçüde azaltılabildi. MMF ilişkili herhangi bir yan etki bildirilmedi.[36] JDM'de IVIG tedavisinin, özellikle şiddetli veya steroidlere ve metotreksata dirençli veya baskın deri hastalığı olanlarda ikinci basamak tedavi seçeneği olarak genellikle etkili olduğu kabul edilmektedir. Steroide dirençli hastalarda daha iyi hastalık kontrolü nedeniyle dirençli deri hastalığı, şiddetli zayıflığı veya disfajisi olan hastalarda IVIG tedavisi faydalı bir seçenektir.[37] Bir diğer çalışmada, araştırmacılar, JDM'li 78 hastadan oluşan retrospektif bir kohortta IVIG'in özellikle steroide dirençli hastalığı olan hastalarda, şiddetli veya dirençli hastalığı kontrol etmede etkili olduğunu gösterdiler.[26] Çalışmamızda polisiklik/persistan seyirli hastaların daha fazla MMF ve IVIG tedavisine ihtiyaç duyduğu ortaya konulmuştur.

Çalışmanın Kısıtlılıkları

Bu çalışmanın bazı kısıtlılıkları mevcuttur. Bazı MSA pozitifliğine sahip ve ciddi sistem tutulumu olan hasta sayımızın az olması nedeniyle hastalık seyri ile ilgili daha detaylı analizler yapılamamıştır. Daha güçlü tedavilere ihtiyaç duyan hastaların belirlenmesine yönelik klinik özellikler ve biyobelirteçleri açıklığa kavuşturmak için daha fazla hasta içeren çalışmalara ihtiyaç vardır. Öte yandan hastalığın nadirliği ve bu konuda yapılmış çalışma sayısının azlığı göz önünde bulundurulduğunda çalışmamızın literatüre katkı sağlayacağını inanıyoruz.

Sonuç

Sonuç olarak İİM olgularında CMAS skoru hastalık seyri öngörüsünde önemlidir. Altıncı ay CMAS skoru

düşük olan hastalarda polisiklik/persistan seyir ihtimalinin arttığı göz önünde bulundurularak bu hasta grubu yakından izlenmelidir.

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Sensitivity and specificity of the detection of spondylodiscitis by conventional radiography

Spondilodiskit tanısının konvansiyonel radyografi ile saptanmasının duyarlılık ve özgüllüğü

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Abstract

Objective: Diagnosis of spondylodiscitis is usually possible radiographically with magnetic resonance imaging (MRI). However, the first imaging method evaluated in daily practice is conventional radiography. The aim of the study was to determine the sensitivity and specificity of detecting infectious or rheumatological spondylodiscitis in the lumbar region with conventional radiography by rheumatologists.

Methods: Among 102 patients with spondylodiscitis on lumbosacral (LS) MRI, 23 patients who also underwent simultaneous conventional LS radiography were included. TThe control group consisted of 52 outpatients with no evidence of spondylodiscitis on LS MRI. Eleven rheumatologists blindly evaluated conventional LS radiographs. Sensitivity, specificity, positive, and negative predictive values of LS conventional radiography were calculated.

Results: While the cause was infection in 8/23 (34.7%) of spondylodiscitis patients, it was spondyloarthritis in 15/23 (65.2%). According to LS MRI findings, 23 patients had spondylodiscitis in a total of 31 vertebral units. When we evaluated the detection of spondylodiscitis according to the vertebral unit level, it was mostly at one level [14 (60.8%)], primarily at the L4-5 vertebral unit [13 (56.5%)]. The sensitivity of detecting LS spondylodiscitis on conventional radiography was found to be 52% (30-65), and the specificity was 86% (59-94). While the median (minimum-maximum) sensitivity was 75.0 (50.0-87.5) in patients with infectious spondylodiscitis, it was 46.6 (13.3-76.9) in patients with spondylodiscitis due to spondyloarthritis.

Conclusion: Clinicians can miss spondylodiscitis. Although it is evaluated with conventional radiography in the first stage in the presence of appropriate clinical findings, the clinician should be careful and consider more advanced approaches.

Keywords: Spondyloarthritis, spondylitis, inflammation, sensitivity and specificity

Öz

Amaç: Spondilodiskit tanısı genellikle manyetik rezonans görüntüleme (MRG) ile radyografik olarak mümkündür. Ancak günlük pratikte ilk değerlendirilen görüntüleme yöntemi konvansiyonel radyografidir. Bu çalışmanın amacı lomber bölgedeki enfeksiyöz veya romatolojik spondilodiskitlerin romatolog tarafından konvansiyonel radyografi ile saptanmasının duyarlılığını ve özgüllüğünü belirlemektir.

Yöntem: Lumbosakral (LS) MRG'de spondilodiskit saptanan 102 hasta içerisinden eş zamanlı konvansiyonel LS grafisi çekilen 23 hasta çalışmaya dahil edildi. Kontrol grubunda LS MR'de spondilodiskit olmayan 52 hasta dahil edildi. On bir romatolog konvansiyonel LS radyografilerini değerlendirdi. LS konvansiyonel radyografinin duyarlılığı, özgüllüğü, pozitif ve negatif prediktif değeri hesaplandı.

Bulgular: Spondilodiskit hastalarının 8/23'ünde (%34,7) neden enfeksiyon iken, 15/23'ünde (%65,2) spondiloartritti. LS MR bulgularına göre 23 hastada toplam 31 vertebral ünitede spondilodiskit mevcuttu. Spondilodiskiti, vertebral ünite seviyesine göre değerlendirdiğimizde en fazla tek seviyede [14 (%60,8)], en fazla L4-5 vertebral ünitede [813 (%56,5)] görüldü. Konvansiyonel radyografide LS spondilodiskitini saptamanın duyarlılığı %52 (30-65), özgüllüğü ise %86 (59-94) olarak bulunmuştur. Enfeksiyöz spondilodiskitli hastalarda ortanca (minimum-maksimum) duyarlılık 75,0 (50,0-87,5) iken, spondiloartrite bağlı spondilodiskitli hastalarda 46,6 (13,3-76,9) idi.

Sonuç: Klinisyenler spondilodiskiti gözden kaçırabilmektedir. Uygun klinik bulguların varlığında ilk aşamada konvansiyonel radyografi ile değerlendirilse de daha ileri tetkikler açısından klinisyenin dikkatli olması gerekir.

Anahtar Kelimeler: Spondiloartrit, spondilit, enflamasyon, duyarlılık ve özgüllük

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Introduction

Spondylodiscitis is a name given to the inflammation of the intervertebral disc and adjacent vertebrae. Although its incidence has been reported to be as low as 5-6 in 100,000, the German Federal Statistics Office has reported the incidence of spondylodiscitis as high as 30 in 250,000.[1] This increase is attributed to the development of diagnostic methods. Risk factors that increase the incidence of spondylodiscitis include diabetes mellitus, immunosuppression, history of illicit drug use, and human immunodeficiency virus.[2]

Spondylodiscitis has a wide clinical spectrum. Since spondylodiscitis can mimic many clinical conditions, irreversible deformities may develop as a result of incorrect diagnosis and treatment. Therefore, it is a clinical entity that requires great attention. The heterogeneity of the disease limits the definitive diagnosis and the categorization of treatment recommendations. Spondylodiscitis can develop in relation to rheumatic, infectious, and degenerative diseases. Infection represents the prevailing factor leading to spondylodiscitis.[3] Typically, spondylodiscitis manifests as a monobacterial infection, with hematogenous dissemination being the predominant mode of transmission. *Staphylococcus aureus* is responsible for more than 50% of the cases in Europe, followed by Gram-negative pathogens such as *Escherichia coli* (11-25%). The most frequent cause of granulomatous spondylodiscitis worldwide is *Mycobacterium tuberculosis*. Brucellosis is another significant cause of spondylodiscitis in Mediterranean countries and the Middle East.[3]

One of the probable diagnoses of spondylodiscitis is rheumatic diseases. The most significant cause of spondylodiscitis in rheumatology practice is ankylosing spondylitis (AS).[4] Spondylodiscitis is a rare complication of AS. It was first identified by Andersson[4] in 1937. Its prevalence in patients with AS has been reported to be between 1% and 10%.It often has an acute onset and, unlike previously described pain characteristics, is marked by localized pain that worsens with movement and improves with rest.[5]

Spondylodiscitis is diagnosed based on radiological, laboratory, and microbiological findings in an appropriate clinical background and, if necessary, by pathological examination.[6] The most important assessment in the diagnostic process is imaging.[6] Conventional radiography plays a limited but important role in the evaluation of spondylodiscitis. Conventional radiology is a technique with low sensitivity and specificity (82% and 57%, respectively)[7], especially in the early diagnosis of spondylodiscitis, although conventional X-ray is often used for the first approach to back pain. It is generally used as a screening test and can detect early changes such as localized radiolucency in the subchondral region, often anteriorly, followed by endplate loss and narrowing of the intervertebral disc.[8,9] Once the disease is well-established, radiographic signs are specific enough for a definitive diagnosis. Erosion of two adjacent vertebral bodies extending from the narrowed intervertebral disc is quite typical of infectious spondylitis.[9] Erosion on radiography may occur days or weeks later.[10] Therefore, a negative conventional radiography does not exclude the possibility of spondylodiscitis.[7] Magnetic resonance imaging (MRI) is a preferable method for the diagnosis of spondylodiscitis. The sensitivity and specificity of MRI are 96% and 93%, respectively.[6] MRI evaluates the involvement of bone marrow, disc signal, adjacent neural structures, and paraspinal soft tissue very well. The earliest finding in MRI is bone marrow edema in the vertebral corpus. Bone marrow edema is seen as hypointense in T1A images and as hyperintense in T2A images.[6] Although MRI is the most important test for verifying a spondylodiscitis diagnosis, the imaging method first used in daily practice is the conventional lumbosacral (LS) radiography. On the other hand, we have no data on the role of conventional radiography in confirming the diagnosis of spondylodiscitis.

In this study, we aimed to determine the sensitivity and specificity of detecting infectious or rheumatological spondylodiscitis in the lumbar region, confirmed with MRI, through conventional radiography.

Materials and Methods

Patients and Study Groups

Patients who were diagnosed with spondylodiscitis on spinal MRI performed at our center between January 2010 and September 2021 were identified. Patients with spondylodiscitis were divided into two groups, infectious and AS-related, and 102 patients diagnosed with spondylodiscitis on LS MRI were included in the study. Of these 102 patients, 74 (72.5%) did not have a simultaneous conventional LS radiography in addition to MRI, 2 had low-quality LS radiographs, and 3 patients had undergone lumbar vertebra intervention. These patients were excluded from the analysis, and a total of 23 patients who had LS MRI and conventional LS radiography were included in the final analysis.

The control group was selected from patients who had LS MRI taken from the outpatient clinic due to low back pain, and no spondylodiscitis was detected according to the evaluation of the radiologist. A total of 52 patients diagnosed with spondyloarthritis, rheumatoid arthritis, and Behçet's disease were included as the control group. Conventional

radiographs of 23 spondylodiscitis patients and 52 patients in the control group were evaluated blindly by rheumatologists.

Detection of Spondylodiscitis in Conventional Radiography

Eleven rheumatologists (2 with >10 years' experience, 9 with <5 years' experience) evaluated the conventional LS radiographs. They were blind to clinical data and the presence/absence of spondylodiscitis. The region between T12-S1 was evaluated. The presence of spondylodiscitis was grouped by the doctors as "definitely absent," "suspicious," or "definitely present." The location of spondylodiscitis in the radiographs was recorded as vertebral units, and if there were findings in more than one vertebral unit, it was noted.

A vertebral unit included the lower endplate of the upper vertebra and the upper endplate of the lower vertebra. Levels were defined according to the number of vertebral units in which spondylodiscitis was detected. Moreover, patients were further categorized according to the presence of spondylodiscitis above/below the L3-4 vertebral unit. Regarding the patients who were evaluated according to the location on the lumbar vertebra, 4 patients who had spondylodiscitis both below L3-4 and above L3-4 vertebral units were not included in the localization analysis.

Our study was conducted in accordance with the 2013 amendment of the Declaration of Helsinki, ethical approval was obtained from Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision no: 2021/15-55, date: 21.09.2021) and written informed consent for participation was obtained from each participant.

Statistical Analysis

Data were analyzed using SPSS Statistics for Windows, Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Numerical variables conforming to the normal distribution were investigated by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive analyses were displayed by median and interquartile range for non-normally distributed numerical variables.

In independent groups, chi-square or Fisher's exact tests were used for analyzing categorical data and rates. The Mann-Whitney U test was utilized to compare the medians of non-normally distributed data from independent groups. A p-value of <0.05 was considered statistically significant. Positivity in MRI was accepted as the gold standard, and the sensitivity, specificity, and positive and negative predictive values of LS conventional radiography were calculated for each evaluator.

Results

Characteristics of the Patient Group and the Control Group

Twenty-three patients with spondylodiscitis were included in the study. The median [minimum-maximum (min-max)] age of spondylodiscitis patients was 53 (23-91), and 16 (69.6%) patients were male. While the proven cause was an infection in 8/23 (34.7%) of the patients with spondylodiscitis, it was spondyloarthritis in 15/23 of the patients (65.2%). The median (min-max) age of patients with infection-related spondylodiscitis was 57 (30-91), and 4 (50%) were male. The median (min-max) age of patients with spondylodiscitis due to spondyloarthritis was 48 (23-70), and 12 (80%) were male. The median (min-max) age of the 52 patients included in the control group was 58.5 (20-80). Thirty-nine (75%) of this patient group were women.

Spondylodiscitis Regions Affected in the Lumbar Vertebra According to Diseases

According to LS MRI findings, 23 patients had spondylodiscitis in a total of 31 vertebral units. Detection of spondylodiscitis in 1, 2, and 3 levels according to the number of vertebral units was as follows: 14 (60.8%), 5 (21.7%), and 4 (17.3%), respectively. The distribution of the localizations was as follows: L5-S1 4 (17.4%), L4-5 13 (56.5%), L3-4 3 (13%), L2-3 5 (21.7%), L1-L2 4 (17.4%), and L1-T12 2 (8.7%).

According to LS MRI findings of the patients who had spondyloarthritis-related spondylodiscitis, 15 patients had spondylodiscitis in a total of 22 vertebral units. Detection of spondylodiscitis in 1, 2, and 3 levels according to the number of vertebral units was as follows: 9 (60.0%), 5 (33.3%), and 1 (6.6%), respectively. The distribution of the localizations was as follows: L5-S1 4 (18.1%), L4-5 8 (36.3%), L3-4 2 (9.0%), L2-3 2 (9.0%), L1-L2 4 (18.1%), and L1-T12 2 (9.0%).

According to LS MRI findings of the patients who had infection-related spondylodiscitis, 8 patients had spondylodiscitis in a total of 12 vertebral units. Detection of spondylodiscitis in 1, 2, and 3 levels according to the number of vertebral units was as follows: 5 (62.5%), 2 (25.0%), and 1 (12.5%), respectively. The distribution of the localizations was as follows: L4-5 5 (41.6%), L3-4 4 (33.3%), L2-3 3 (25.0%).

Diagnostic Performance of Detecting Spondylodiscitis

When the results of all evaluators were analyzed, the following results were obtained: In all spondylodiscitis

patients, the median (min-max) specificity was calculated as 86.5 (58.8-94.2), sensitivity as 52.1 (30.4-65.2), positive predictive value (PPV) as 63.6 (44.7-75.0), and negative predictive value (NPV) as 79.6 (58.8-83.6). In the patients with infectious spondylodiscitis, the median (min-max) specificity was found as 86.5 (58.8-94.2), sensitivity as 75.0 (50.0-87.5), PPV as 44.4 (25.0-57.1), and NPV as 95.0 (92.1-96.7). In those with spondylodiscitis due to spondyloarthritis, the median (min-max) specificity was calculated as 86.5 (58.8-94.2), sensitivity as 46.6 (13.3-76.9), PPV as 39.1 (31.5-62.5), and NPV as 84.9 (78.6-90.9).

Specificity, sensitivity, PPV, and NPV values according to the experiences of the researchers with >10 years and <5 years of experience are presented in Table 1.

Specificity, sensitivity, PPV, and NPV values of all evaluators' detection of spondylodiscitis according to the presence of spondylodiscitis above/below the L3-4 vertebral unit and according to etiology are presented in Table 2.

Clinical information and conventional radiographs of cases diagnosed with spondylarthritis, which is recognized by rheumatologists with the highest and lowest sensitivity in direct radiography, and spondylodiscitis caused by infection, are given in Figures 1, 2 and 3.

Discussion

Spondylodiscitis is a condition that may arise from both infectious and rheumatic causes and lead to a severe clinical picture. There are no studies in the literature in which the detection of spondylodiscitis through conventional LS radiography has been demonstrated. In the present study, the sensitivity and specificity of detection of LS spondylodiscitis with conventional radiography in all patients were determined to be 52% (30-65) and 86% (59-94), respectively. Particularly, it is easier to detect infectious spondylodiscitis, probably due to the extent of the lesion. Still, lesions can go unnoticed with conventional radiography in a significant number of patients, even when an experienced rheumatologist is the assessor.

Spondylodiscitis is characterized radiographically by erosion of the vertebral endplate adjacent to the disc, its sclerosis, and sometimes narrowing of the disc space.[11-13] In the early stages of the disease in AS, it may occur without the development of ankylosis of the vertebral body, and it is reported that 13.5% of cases affect several different vertebral units of the spine simultaneously.[5,11,14-16]

In the study conducted by Langlois et al.[17] in France in 2004, which compared AS patients with and without discitis, of the 79 AS patients included in the study, 14 patients had radiological discitis, 12 of whom had discitis at one level, and 2 had discitis at two levels. It was significantly more widespread among stage III sacroiliitis cases compared to the control group (57% versus 29%, p=0.045). While Langlois et al.[17] reported predominantly thoracolumbar involvement (75%), in this study, only 38% thoracolumbar lesions and 44% lumbar lesions were reported.

In the study by Kabasakal et al.[16] with included 147 AS patients, spondylodiscitis was detected in 12 patients (8%) with a total of 32 vertebral units affected. In infection-related

Table 1. Rheumatology specialists' rates of detecting spondylodiscitis according to their experiences and spondylodiscitis etiology

	All spondylodiscitis		Spondylodiscitis due to infection		Spondylodiscitis due to spondyloarthritis	
	>10 years experience	<5 years experience	>10 years experience	<5 years experience	>10 years experience	<5 years experience
Sensitivity	63.0 (60.8-65.2)	52.1 (30.4-59.0)	75.0 (75-75)	75.0 (50.0-87.5)	56.6 (53.3- 60.0)	46.6 (13.3-76.9)
Specificity	72.0 (71.1-73.0)	88.4 (58.8-94.2)	72.0 (71.1- 73.0)	88.4 (58.8-94.2)	72.0 (71.1- 73.0)	88.4 (58.8-94.2)
PPV	49.9 (48.3- 51.7)	65.0 (44.7-75.0)	29.2 (28.5- 30.0)	46.1 (25.0-57.1)	36.9 (34.7-39.1)	50.0 (31.5-62.5)
NPV	81.5 (80.4- 82.6)	78.8 (58.8-83.6)	94.9 (94.8- 95)	95.1 (92.1-96.7)	85.1 (84.0- 86.3)	84.9 (78.6-90.9)

Data are presented as median (minimum-maximum), NPV: Negative predictive value, PPV: Positive predictive value

Table 2. Rheumatology specialists' rates of detecting spondylodiscitis according to spondylodiscitis etiology and localization

	All spondylodiscitis		Spondylodiscitis due to infection		Spondylodiscitis due to spondyloarthritis	
	L3-4 and below vertebral units	Vertebral units above L3-4	L3-4 and below vertebral units	Vertebral units above L3-4	L3-4 and below vertebral units	Vertebral units above L3-4
Sensitivity	38.4 (15.3-84.6)	33.3 (33.3-66.6)	60.0 (20-80)	50.0 (50.0-100)	37.5 (0-87.5)	25.0 (0-75.0)
Specificity	92.9 (83.8-96.5)	92.3 (81.5-98.4)	92.5 (62.5-96.2)	92.9 (80.7-100)	92.8 (80.3-98.2)	91.6 (81.6-98.3)
PPV	50.0 (28.5-71.4)	37.5 (14.2-66.6)	37.5 (16.6-50.0)	33.3 (12.5-100)	42.8 (0-75.0)	28.5 (0-90.9)
NPV	87.5 (82.8-96.6)	94.1 (92.9-96.6)	95.8 (92.4-97.7)	98.2 (97.8-100)	91.3 (83.3- 97.8)	94.8 (93.6-98.1)

Data are presented as median (minimum-maximum), NPV: Negative predictive value, PPV: Positive predictive value

spondylodiscitis, similarly, the lumbar vertebra is more frequently involved, followed by the thoracic and cervical vertebrae.[18] Tuberculosis (TB).[19] Multi-vertebral unit involvement is seen in 5-18% of patients with pyogenic infection and 20% of TB patients.[19,20]

According to the results in the literature, spondylodiscitis can be seen in both the thoracic and lumbar areas. However, it is almost impossible to detect the lesions in the thoracic region with conventional radiography. Therefore, we limited our study to the lumbar region. In the present study, according to LS MRI findings, there was spondylodiscitis at 31 vertebral units in 23 patients. When we evaluated the detection of spondylodiscitis according to the vertebral unit level, it was most frequently present at one level (60.8%), followed by two levels (21.7%) and three levels (17.3%). The distribution of the localizations was the highest at the L4-5 vertebral unit (56.5%). When we grouped the patients according to spondylodiscitis due to spondyloarthritis and infectious causes, spondylodiscitis was most frequently present at one vertebra level and the L4-5 vertebral unit.

The estimated prevalence of spondylodiscitis among AS patients varies between 1% and 10%, with an average of 4.5%.[21] Rasker et al.[5] reported a prevalence between 5-10%, Langlois et al.[17] reported a prevalence of 18%, Rosen et al.[22] reported a prevalence of 5%, and Schulitz[23] reported a prevalence of 6%.

In AS spondylodiscitis, both mechanical stress and inflammation have been identified as causes of vertebral object damage.[11,24,25] There is no consensus on whether these lesions result from the inflammation related to AS or whether mechanical factors play a role.[5] Because both patients and doctors may attribute the complaints to AS, and the lesions are asymptomatic in some cases, a diagnosis of spondylodiscitis may be missed. The clinical picture of spondylodiscitis may range from asymptomatic to severe spinal cord damage symptoms.[12,14]

Due to varying clinical symptoms and onset, it is probably more widespread than anticipated. Clinicians should suspect a diagnosis of spondylodiscitis in an AS patient when the patient has localized pain unlike typical AS pain, with an acute onset that increases with movement and decreases at rest. In the study by Rasker et al.[5] in 2009, in which sterile spondylodiscitis was detected in 6 (1.5%) of 400 AS patients, it was reported that in 5 of these 6 patients, there was a

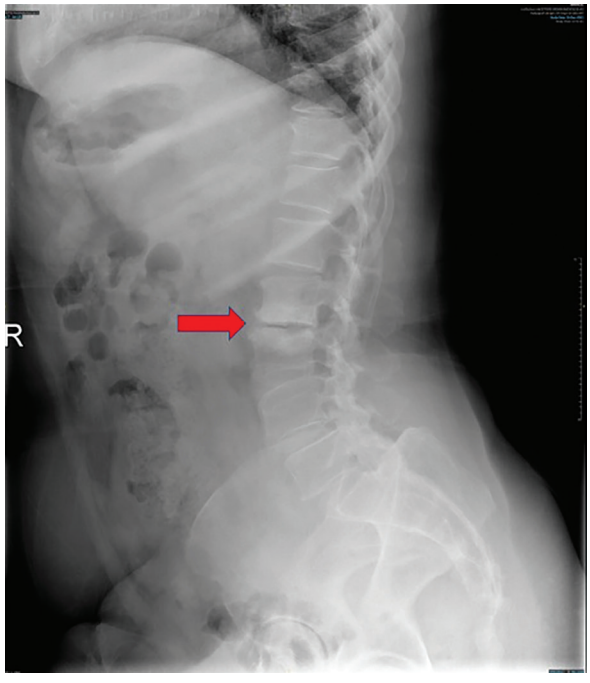

Figure 1. Lateral conventional lumbosacral radiograph. Fifty-six-year-old female patient. Complaints of back pain, night sweats, fever, weight loss. CRP: 0.88 mg/dL. Spondylodiscitis caused by infection. Lumbar MRI: Decrease in L2 and L3 vertebral body heights is evaluated as spondolidiscitis. At the L2-3 disc level, contour irregularities are observed in the palates adjacent to the disc. There is a paravertebral abscess and a right psoas abscess. *Staphylococcus aureus* growth was detected in tissue culture. All 11 of 11 rheumatologists (100%) recognized spondylodiscitis on conventional radiography

CRP: C-reactive protein, MRI: Magnetic resonance imaging

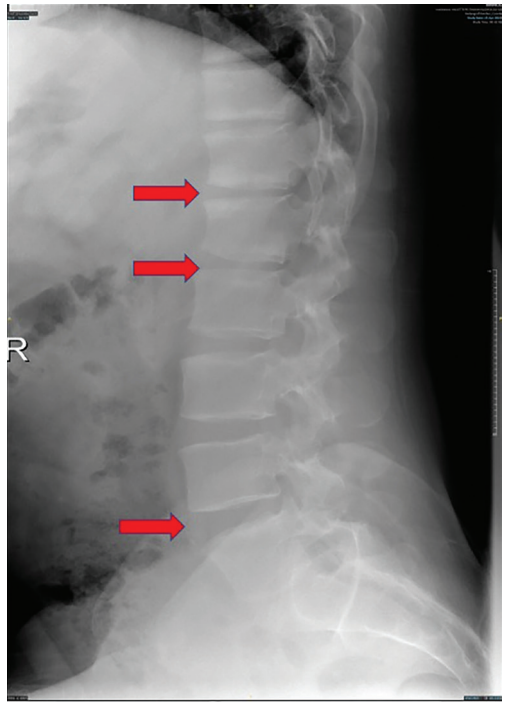

Figure 2. Lateral conventional lumbosacral radiograph. Forty-year-old male patient. Complaints of back pain that increases with movement. CRP: 2 mg/dL. Spondylodiscitis caused by spondyloarthritis. Lumbar MRI: Discal and medullary signal changes compatible with spondylodiscitis are observed in the T12-L1, L1-2, L4-5 discs and adjacent end plates. In addition, there are active corner lesions in the vertebral corners, mostly at the level of L3 and L4 vertebrae in the anterior, and signal changes thought to belong to fatty corner lesions in the posterior. Fatty corner lesions are also observed anteriorly in the L5-S1 end plates. There is no abscess. Culture was not taken. Nine of 11 rheumatologists (82%) recognized spondylodiscitis on conventional radiography

CRP: C-reactive protein, MRI: Magnetic resonance imaging

change in the characteristics of the back pain-it increased during movement instead of recovery, and it decreased after resting instead of exacerbating.

In such situations, clinicians typically begin evaluation with conventional radiography. According to our results, AS-related spondylodiscitis can be detected with conventional radiography with a sensitivity of 46.6%. In other words, spondylodiscitis cannot be detected in more than half of these patients with conventional radiography. Hence, it might be appropriate for clinicians to prioritize MRI instead of conventional radiography in spondyloarthritis patients with changes in pain characteristics where spondylodiscitis is suspected.

Infectious spondylodiscitis constitutes another significant group. In the presence of infectious spondylodiscitis, in addition to the disc area and endplate, surrounding tissues are frequently affected. These lesions can be more widespread.[26] Therefore, the detection of these lesions with conventional radiography can be easier compared to AS. In our study, the sensitivity in detecting infectious sacroiliitis can reach up to 75%.

In other words, with conventional LS radiography, spondylodiscitis can be detected in 3/4 of the patients. More importantly, the negative predictive value in infectious spondylodiscitis is as high as 95%. Accordingly, in the presence of severe pain and fever that disrupts sleep, unresponsiveness to rest and non-steroidal anti-inflammatory drugs, neutrophilic leukocytosis, and elevated acute phase reactants, conventional radiography can be used to exclude spondylodiscitis in the LS region.

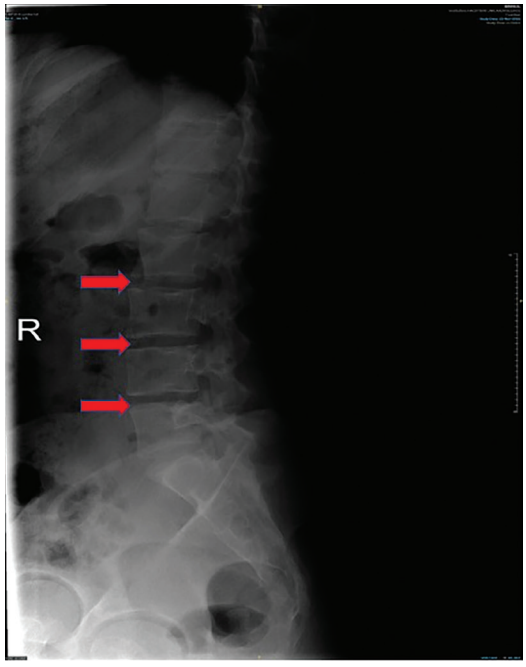

Figure 3. Lateral conventional lumbosacral radiograph. Twenty-four-year-old female patient. Complaints of back pain that increases with movement. CRP: 0.3 mg/dL. Spondylodiscitis caused by spondyloarthritis. Lumbar MRI: There are erosive changes compatible with Anderson lesions in the end plates adjacent to the L2-3, L3-4 and L4-5 discs. There is no abscess. Culture was not taken. Eleven of 11 rheumatologists (100%) could not recognize spondylodiscitis on conventional radiography

CRP: C-reactive protein, MRI: Magnetic resonance imaging

Evaluating these graphs requires minimal experience. No significant differences have been observed between doctors with more than 10 years of experience and those newly specializing in rheumatology. However, it should not be overlooked that infectious spondylodiscitis can develop in the thoracic region as well. If the clinical suspicion is prominent, it is advisable to use advanced imaging techniques such as spinal MRI.

While it should be remembered that while conventional radiography images were investigated in the evaluation of spondylodiscitis lesions, the lumbar region was specifically targeted.

Study Limitations

One limitation of the study is that the thoracic region, which could be affected, was not considered in the present study. The limitations of our study include its retrospective design and the small sample size, as only 23 of 102 patients with spondylodiscitis detected on MRI had conventional radiography. Another limitation is the lack of grouping based on the experience of the rheumatologists who evaluated the radiological images..

The strength of this study is that the opinion of a rheumatologist was used in the evaluation of conventional radiography. Since no second doctor (radiologist) evaluated the images, this study directly relates to clinical practice. The reason why the sensitivity of direct radiography in the literature is higher than in our study is that radiologists evaluated the radiographs.

Conclusion

In conclusion, spondylodiscitis is a disease with variable clinical presentations and onset, and it is more common than expected. Clinicians may miss spondylodiscitis, especially in AS, with direct radiographic assessment. It should be remembered that clinical experience does not make much difference in interpreting conventional radiographs in spondylodiscitis evaluation. It should also be kept in mind that spondylodiscitis can be observed in the thoracic vertebrae, and this lesion cannot be detected by conventional radiography.

Although it is possible to detect lumbar spondylodiscitis in some patients using lumbar spine radiography, the rate of undetected patients is quite high. While conventional

radiography can be used primarily in the presence of consistent clinical symptoms, clinicians should be aware of the need for more advanced approaches when suspicion arises.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision no: 2021/15-55, date: 21.09.2021).

Informed Consent: Written informed consent for participation was obtained from each participant.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.Ö., E.C., G.A., G.S.U., M.E., E.Ü., B.F., G.S.B.K., B.B., L.K., Concept: Z.Ö., E.C., G.A., G.S.U., M.E., E.Ü., B.F., G.S.B.K., B.B., L.K., Design: Z.Ö., E.C., G.A., G.S.U., M.E., E.Ü., B.F., G.S.B.K., B.B., L.K., Data Collection or Processing: Z.Ö., E.C., G.A., G.S.U., M.E., E.Ü., B.F., G.S.B.K., B.B., L.K., Analysis or Interpretation: Z.Ö., E.C., G.A., G.S.U., M.E., E.Ü., B.F., G.S.B.K., B.B., L.K., Literature Search: Z.Ö., E.C., G.A., G.S.U., M.E., E.Ü., B.F., G.S.B.K., B.B., L.K., Writing: Z.Ö., E.C., G.A., G.S.U., M.E., E.Ü., B.F., G.S.B.K., B.B., L.K.

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Improvement in rheumatoid sarcopenia with biological therapy; muscle ultrasound study

Biyolojik terapi ile romatoid sarkopenide iyileşme; kas ultrason çalışması

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Abstract

Objective: The present research evaluated the use of muscle ultrasonography in individuals with rheumatoid arthritis (RAs) who were starting therapy with biologic disease-modifying antirheumatic drugs (b-DMARDs).

Methods: A total of 56 individuals diagnosed with RAs, who had not yet received b-DMARDs, were included in the current prospective study. The control and baseline muscular strength, physical performance tests, ultrasonographic muscle parameters, and disease activity scores were analyzed in a group of 40 patients under controlled conditions.

Results: Rectus abdominis muscle's thickness, rectus femoris (RF) muscle's cross-sectional area (RFCSA), external oblique muscle's thickness, and transverse abdominis muscle's thickness all showed substantial improvements. Additionally, Clinical Disease Activity Index scores showed significant associations with the percentage variations in RF muscle thickness, RFCSA, and gastrocnemius medialis muscle thickness in those who had achieved remission or had low disease activity.

Conclusion: Ultrasonographic muscle imaging can assist clinicians in monitoring both patients and disease activity scores during the treatment of RA.

Keywords: Rheumatoid arthritis, b-DMARDs, muscle, ultrasonography

Öz

Amaç: Bu çalışmada, biyolojik hastalığı modifiye eden antiromatizmal ilaçlar (b-DMARD) tedavisine başlayan romatoid artritli (RA) bireylerde kas ultrasonografisinin kullanımını araştırılmıştır.

Yöntem: RA tanısı almış ve henüz b-DMARD almamış toplam 56 kişi mevcut prospektif çalışmaya dahil edildi. Kontrol ve başlangıç kas gücü, fiziksel performans testleri, ultrasonografik kas parametreleri ve 40 hastadan oluşan bir grupta kontrollü koşullar altında hastalık aktivite skorları analiz edildi.

Bulgular: Rektus abdominis kasının kalınlığının, rektus femoris (RF) kasının kesit alanı (RFCSA), dış oblik kasının kalınlığı ve transvers abdominis kasının kalınlığı önemli iyileşmeler gösterdiği saptandı. Ek olarak, Klinik Hastalık Aktivitesi Indeksi puanları, remisyona ulaşan veya düşük hastalık aktivitesine sahip olanlarda RF kas kalınlığı, RFCSA ve gastrokinemius medialis kas kalınlığındaki yüzdelik değişimlerle istatiksel anlamlılık saptanmıştır.

Sonuç: Ultrasonografik kas görüntülemesi, RA hastalarının tedavisi sırasında klinisyene hastalık aktivite skorlarını izlemede yardımcı olabilir.

Anahtar Kelimeler: Romatoid artrit, b-DMARDs, kas, ultrasonografi

Introduction

Rheumatoid arthritis (RA) is a progressive inflammatory disease that often leads to severe joint deterioration and dysfunction. Despite the efficacy of disease-modifying antirheumatic drugs and biological therapies, there is no curative treatment for RA.[1] Its average occurrence is reported to be 0.5%.[2] Patients with RA are more likely to experience a decline in muscle strength compared to the

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general population of the same age group. "Rheumatoid cachexia" is a well-known symptom of the disease, characterized by a decrease in muscle mass and an increase in intramuscular adipose mass. Tumor necrosis factor alpha (TNF-α) and several other cytokines, which are crucial in RA pathogenesis, catabolize muscle, which is the reason behind it. In this patient group, the loss of muscle mass is accompanied by a reduction in muscle strength and an increase in age-related sarcopenia.[3]

When the general literature was reviewed, it was discovered that there was considerable variation regarding the occurrence of sarcopenia, a condition marked by a reduction in athletic performance, muscle mass, and strength among RA patients. The frequency of sarcopenia, among RA patients, ranged widely from 1 to 56%, according to a review of the general literature.[4–7] It appears that the use of varying diagnostic techniques to identify sarcopenia and the incapacity to establish common diagnostic criteria are the reasons for the inconsistent prevalence results. In researchs investigating the impact of biologic disease-modifying anti-rheumatic drugs (b-DMARDs) on muscle mass in rheumatic diseases, conflicting results have been observed. Sarcopenia in inflammatory illnesses can be diagnosed using ultrasonography (USG) among other methods.[8,9]

The aim of this study was to evaluate the alterations in muscle strength and quantity, physical performance, in RA patients who were receiving b-DMARDs during the initial stages of treatment, as measured by USG.

Materials and Method

Investigation Design

A prospective investigation was carried out at a university hospital. Patients were evaluated at their first examination before starting biological treatment and at their 3rd or 6th-month follow-up examinations.

Study Population

The study comprised 56 patients who had never used b-DMARDs. Patients under 18 years old and over 80 years old were not included in our study. Patients with previous rheumatoid cachexia, active malignancy, and active infection, patients with disability, and patients with prosthesis were also not included in the study. Patients with active RA [Disease Activity Score 28 (DAS28) >5.1 or expert judgment)] were administered b-DMARDs. There were forty patients at the third or sixth-month follow-up. The clinical assessment included information on previous therapies, current b-DMARDs, and demographic data.

Disease Activity Assessments

The data were obtained from the TReasure database. The TReasure database was previously described concisely as the collection of data at the start of therapy and during the initial follow-up session.[10] The Clinical Disease Activity Index (CDAI)[11], Simplified Disease Activity Index (SDAI)[1]. DAS-28[12], visual analog scale (VAS) global-physician assessment[13], VAS global-patient assessment[13], VAS for global pain[13], VAS fatigue[13], Health Assessment Questionnaire-Disability Index (HAQ-DI)[14], and EuroQol Group (EQ5D)[15] prior to treatment initiation and at the initial visit were noted.

Anthropometric Parameters

Anthropometric characteristics such as body mass index (BMI), hip, and waist circumference were assessed. In our study, all muscle ultrasound measurements at baseline and in the controls were performed by a single experienced physician for the reliability and standardization of the evaluations. The anterior superior iliac spine was used to measure the hip circumference, while the umbilicus was used to measure the waist circumference.

Assessment of Muscle Strength and Physical Performance

To evaluate muscle strength, the sit-stand test (SST) and the handgrip strength test (HGST) were executed. To evaluate physical performance, the timed up and go test (TUG), gait speed, and the 4-meter walking test were used. The presence of sarcopenia was assessed using the SARC-F test. HGST was applied while the elbow was at a 90-degree angle using a hand dynamometer.[9] The SST is conducted with the patient's arms crossed in front of their torso. They are required to sit and stand at a rate of five times their maximum capacity.[9] By measuring the average walking speed of four meters, the gait speed was computed.[9] The TUG test was assessed by observing the individual's performance of standing up, walking a distance of 3 meters, turning around, and sitting back down.[16] The patient was asked to complete the SARC-F exam, indicating that they had trouble walking around the room, getting out of a chair, climbing ten flights of stairs, and having experienced a fall during the previous year, in addition to having trouble carrying a weight of five kilograms. Each response was assigned a score between 0 and 2 (0=none, 2=a lot, use aides, or be unable). Scores of 4 or higher were deemed positive for sarcopenia screening.[17,18]

Ultrasonographic Measurements

Rectus abdominis (RA) muscle thickness, transverse abdominis (TA) muscle thickness, internal oblique (IO)

muscle thickness, external oblique (EO) muscle thickness, gastrocnemius medialis (GM) muscle thickness, GM pennation angle, GM fascicle length, rectus femoris (RF) muscle thickness, and RF cross-sectional area (RFCSA) were all evaluated using USG. A linear instrument with a 5 cm width and an operating frequency of 8-10 MHz was employed (LOG IQ 200 PRO, General Electric's Medical Systems). Transversal images were obtained to measure the thickness of the muscle at the broadest distance between the superficial and deep fascia. For both GM in the prone position and the RF thickness in the supine position, the largest region of the medial head is located midway between the anterior superior iliac spine and the upper edge of the patella. Longitudinal images were used to determine the pennation angle (PA) of the GM muscle, which is the angle between the muscle fibers and the deep fascia of the muscle. The distance between the superficial and deep aponeuroses was quantified to determine fascicle length (FL). The RFCSA was defined as the cross-sectional area of the RF muscle that is perpendicular to its longitudinal axis. While the patient was in a supine position, the images of the abdominal muscles were obtained at the conclusion of a typical expiration. The RA is located 2 cm lateral to the umbilicus, while the EO, IO, and TA are located at the midpoint between the iliac crest and the 12th costal cartilage. [19-21] Intraclass correlation coefficients (ICC) were evaluated using two images taken at 15-minute intervals of 10 healthy participants to evaluate interobserver reliability. The ICCs for muscle thickness of the GM, RF, and RA were 0.94, 0.92, and 0.96, respectively, and 0.94 for RFCSA.

Statistical Analysis

A statistical analysis was conducted using SPSS software version 25. Analysis of histograms, probability graphs, and analytical procedures was conducted to assess the normality of the variables. Descriptive information was presented as the mean ± standard deviation for normally distributed data and the median (Inter Quartile Range) for non-normally distributed variables. A comparison was made between variables using the Wilcoxon test and the paired sample Student's t-test. The variations between baseline and control data were used to illustrate the changes in muscular strength, physical performance assessments, and USG measurements. To assess the variations between disease activity scores, physical performance assessments, and muscle measurements, percent changes were shown. To explore the relationships between baseline disease activity ratings and physical parameters, muscular strength, and physical performance tests, partial correlation analyses were adjusted based on baseline BMI. A comparison of therapy responses based on CDAI scores, percent improvements in muscular strength and physical performance test assessments, and ultrasonographic measurements was made. The statistical significance was inferred at a 5% type-1 error level. Using G-power analysis, the sample size was determined to be 55 when the effect size was accepted as 0.45 with a 0.05 (alpha) margin of error and a 95% power.

The study was approved by the Hacettepe University Clinical Research Ethics Committee [decision no: 2022/20-08 (KA-21151), date: 22.11.2022] and Turkish Medicines and Medical Devices Agency. Informed consent form was obtained from all participants in the study.

Patient Characteristics

Control visits were conducted for 40 (71.4%) of the 56 patients who were incorporated into the research. The median disease duration was 5.1 years, with a range of 1 to 8. The duration of observation at the midpoint of the study was 4.2 months (range, 3-6). 46 (82.1%) of the study population were female, and the median age was 52 (19-76) years. The demographic parameters and disease activity scores of the patients were reported in Table 1. The control visit was attended by a greater number of seropositive RA patients [31 (81.6%) compared to 7 (46.7%), p=0.01].

Variations in Disease Activity and Laboratory Parameters Pre and Post b-DMARDs Treatment

At the follow-up visit, there were substantial modifications in the comprehensive evaluation of disease activity and functional status in comparison to the patients' baseline values: Median [minimum-maximum (min-max) CDAI 24 (12; 66) vs. 8 (0; 2.5), p<0.001; SDAI 27 (12.3; 73.6) vs. 10 (0.19; 60.4), p<0.001; DAS-28 5.1 (2; 7.7) vs. 2.5 (0; 7.9), p<0.001; VAS global physician 60 (30; 100) vs. 30 (0; 100), p<0.001; VAS global patient 70 (40; 100) vs. 40 (0; 100), p<0.001; VAS pain 70 (30; 100) vs. 45 (0; 100), p<0.001; VAS fatigue 70 (10; 100) vs. 40 (0; 100), p<0.001; HAQ-DI 0.95 (0.1; 4.6) vs. 0.35 (0 ;7.9), p<0.001; EQ5D 11 (5; 13) vs. 6 (0; 15), p<0.001]. Erythrocyte sedimentation rate (ESR) [median (min-max)] [20 (4-72) mm/h vs. 12.5 (3-98) mm/h, p=0.002] was significantly different. The C-reactive protein levels [median (min-max)] were not statistically different [0.67(0.14-9.96) mg/dL vs. 0.88 (0.11-14.5) mg/dL, p=0.11].

Anthropometric Measurements Prior to and Following b-DMARDs Treatment

The baseline BMI of 40 patients was 26.9 kg/m² [median (min-max)], with a waist circumference of 96 cm (70-126) and a hip circumference of 101.5 cm (78-135). The only significant increase observed during the control visits was in BMI, with a median value of [cm] (p=0.008).

Table 1. Baseline characteristics of participants

Characteristics	All participants (n=56)	Patients with control visits (n=40)	Patients without control visits (n=16)	p
Age [median (minimum-maximum)]	52 (19;76)	54 (19;76)	50 (32;68)	0.97
Female gender [n (%)]	46 (82.1)	33 (82.5)	13 (81.3)	0.91
Disease duration [median (minimum-maximum)]	5 (1-38)	6 (1-38)	3 (2-31)	0.36
Seropositive rheumatoid arthritis [n (%)]	38 (71.7)	31 (81.6)	7 (46.7)	0.01
Previous or current cs-DMARDs treatments [n (%)]				
Sulfasalazine	19 (33.9)	16 (40)	3 (18)	0.12
Methotrexate	45 (80.4)	33 (82.5)	12 (75)	0.52
Leflunomide	41 (73.2)	28 (70)	13 (81.3)	0.39
Plaquenil	45 (80.4)	33 (82.5)	12 (75)	0.52
Steroıds	55 (98.2)	39 (97.59)	16 (100)	1.00
b-DMARDs treatments [n (%)]				
Anti-TNF				
Adalimumab	18 (32.1)	13 (32.5)	5 (31.3)	0.92
Certolizumab	5 (8.9)	3 (7.5)	2 (12.5)	0.61
Etanercept	1 (1.8)	0	1 (6.3)	0.28
Infliximab	1 (1.8)	1 (2.5)	0	1.00
Janus kinase inhibitors				
Baricitinib	10 (17.9)	6 (15)	4 (25)	0.37
Tofacitinib	14 (25.0)	10 (25)	4 (25)	1.00
Anti CD20 monoclonal antibody				
Rituximab	10 (17.9)	9 (22.5)	1 (6.3)	0.15
T-cell inhibitor				
Abatacept	4 (7.1)	4 (10)	0 (0)	0.31
Disease activity parameters [median (minimum-maximum)]				
CDAI	22 (8; 66)	24 (12; 66)	18 (8; 65)	0.08
SDAI	24.4 (9; 73.6)	26.9 (12.3; 73.6)	18.3 (9; 68.5)	0.08
DAS-28	5.1 (1.9; 8.2)	5.1 (2; 7.7)	4.2 (1.9; 8.2)	0.36
VAS global physician	60 (10; 100)	60 (30; 100)	50 (10; 90)	0.33
VAS global patient	70 (20; 100)	70 (40; 100)	70 (20; 100)	0.81
VAS pain	70 (30; 100)	70 (30; 100)	80 (30; 100)	0.93
VAS fatigue	70 (10; 100)	70 (10; 100)	65 (10; 100)	0.95
HAQ-DI	1 (0.1; 4.6)	0.9 (0.1; 4.6)	1.3 (0.2; 3)	0.14
EQ5D	11 (5; 14)	11 (5; 13)	11 (7; 14)	0.52

b-DMARDs: Biologic disease-modifying antirheumatic drugs, CDAI: Clinical disease activity ındex, cs-DMARDs: Conventional synthetic disease-modifying antirheumatic drugs, DAS-28: Disease activity score 28, EQ5D: EuroQol group EQ-5D-3L, HAQ-DI: Health assessment questionnaire-disability ındex, SDAI: Simple disease activity ındex, TNF: Tumor necrosis factor, VAS: Visual analog scale

Evaluation of Muscular Strength, Physical Performance Tests, and Muscle Alterations Before and After Therapy with b-DMARDs

The SARC-F test, locomotor speed, and 4-m walking test exhibited no statistically significant differences (p=0.87, p=0.76, and p=0.22, respectively). The scores of the HGST, TUG, and SST differed significantly (p=0.008, p=0.087, and p=0.012, respectively). Significant differences were observed in the thickness of the RA muscle, the TA muscle, the EO muscle, and the RFCSA (Table 2).

Associations Between Initial Disease Activity Scores, Physical Parameters, Physical Performance Tests, and Muscular Strength

The scores of CDAI (r=0.338), SDAI (r=0.326), DAS-28 (r=0.329), VAS global patient (r=0.314), VAS pain (r=0.378), HAQ-DI scores (r=0.641), and EQ5D (r=0.426) were all correlated with the SARC-F score. The SST score had a correlation with the following variables: DAS-28 (r=0.303), VAS global patient (r=0.311), VAS fatigue (r=0.419), HAQ-DI scores (r=0.47), and EQ5D (r=0.311). The TUG score was correlated with the following variables: CDAI (r=0.372), SDAI (r=0.367), DAS-28 (r=0.357), VAS global physician (r=0.322), VAS global patient (r=0.342), VAS pain (r=0.325), VAS fatigue (r=0.346), HAQ-DI scores (r=0.523), and EQ5D (r=0.451). The DAS-28 (r=-0.358) and HAQ-DI

Table 2. Baseline and control muscle strength and physical performance tests and ultrasonographic parameters in patients with control visit

	Baseline	Control	p
Muscle strength and physical performance tests [median (minimum-maximum)]			
HGST (kg)	15.4 (5; 51.2)	20.1 (5; 0.6)	0.008
4-m walking test (sec)	3.8 (2.5; 6.1)	4 (2.2; 9.9)	0.87
Gait speed (m/sec)	1 (0.6; 1.5)	1 (0.4; 1.8)	0.76
TUG (sec)	8.5 (5.7; 13.6)	7.5 (3; 18.7)	0.087
SST (sec)	14.1 (5.8; 24.3)	11.9 (7; 33.5)	0.012
SARC-F	4 (0; 8)	4 (0; 7)	0.22
Ultrasonographic parameters [median (minimum-maximum)]			
GM MT (mm)	16 (8.3; 42.2)	16 (9.2; 54.3)	0.34
GM FL (mm)	29.9 (6.3; 38)	29.7 (8.6; 53.8)	0.19
GM PA (°)	24.5 (13; 37)	24.5 (16; 45.3)	0.14
RF MT (mm)	15.7 (9.4; 23.1)	15.8 (3.8; 22.7)	0.68
RFCSA (mm^2)	5.6 (2.5; 12.5)	6.8 (3.8; 12)	0.025
RA MT (mm)	7.5 (3.9; 14.1)	8.2 (4.5; 11.7)	0.038
TA MT (mm)	2.9 (1.6; 8.8)	3.5 (1.7; 6.7)	0.01
IO MT (mm)	6.3 (3.3; 9.4)	6.7 (1.9; 10.6)	0.72
EO MT (mm)	3.1 (1.6; 7)	4 (2; 12.2)	0.021

EO MT: External oblique muscle thickness, GM MT: Gastrocnemius medialis muscle thickness, GM FL: Gastrocnemius medialis fascicle length, GM PA: Gastrocnemius medialis pennation angle, HGST: Hand Grip Strength test, IO MT: Internal oblique muscle thickness, RA MT: Rectus abdominis muscle thickness, RF MT: Rectus femoris muscle thickness, RFCSA: Rectus femoris cross sectional area, SST:Sit-to-stand test, TA MT: Transverse abdominis muscle thickness, TUG: Time up and go

scores (r=-0.431) were correlated with the gait speed score. EQ5D (r=0.351), CDAI (r=0.346), SDAI (r=0.339), DAS-28 (r=0.44), and HAQ-DI scores (r=0.523) were all correlated with the 4-m walking test score. The CDAI (r=-0.296), SDAI (r=-0.296), and DAS-28 (r=-0.321) were all correlated with the TUG score.

Comparison of Percentage Changes and Discrepancies in Muscular Strength and Physical Performance Test Evaluations, Ultrasonographic Measures, and Treatment Responses Based on CDAI Scores

When patients were categorized according to their control CDAI scores as remission or low disease activity and moderate or high disease activity, no distinction was observed, with the exception of the TUG percent change in assessments of muscular strength and physical performance. In the remission or low disease activity group, the percentage changes in GM MT, RFCSA, and RF MT were significantly higher in ultrasonographic measurements (Table 3).

Discussion

In this observational study, we found that the thickness of the RA muscle, RFCSA, TA muscle, and EO muscle all

Table 3. Comparison of percent changes of muscle strength and physical performance tests assessments, ultrasonographic measurements and treatment responses according to CDAI scores

	Disease activity regarding to CDAI score					
	Remission and/or low disease activity regarding to CDAI score (<10.1) (n=26)		Moderate and/or high disease activity regarding to CDAI score (>10) (n=14)			
	Percent changes of muscle strength and physical performance tests assessments [median (minimum-maximum)]	Muscle strength and physical performance tests differences [median (minimum-maximum)]	Percent changes of muscle strength and physical performance tests assessments [median (minimum-maximum)]	Muscle strength and physical performance tests differences [median (minimum-maximum)]	p1	p2
HGST (kg)	20.9 (-46.3; 132.4)	5.1 (-9.6; 15.1)	7.6 (-52.2; 135.2)	1.5 (-8.3; 11.7)	0.34	0.36
4-m walking test (sec)	-0.4 (-31.2; 85.9)	-0.01 (-1.4; 4)	7.5 (-34.4; 102.4)	0.2 (-2.1; 5)	0.63	0.63
Gait Speed (m/sec)	0.94 (-47; 44.9)	0.01 (-0.6; 0.5)	2.2 (-50.6; 53.8)	0.01 (-0.5; 0.3)	0.77	0.70
TUG (sec)	-100 (-100; -89.1)	-0.4 (-6.6; 9.4)	-100 (-100; 19.9)	-1.1 (-4; 5.1)	0.02	0.67
SST (sec)	-15.2 (-47.8; 94.1)	-1.8 (-8.9; 16.2)	-11.6 (-38.4; 35.7)	-1.9 (-7.4; 5)	0.91	0.82
SARC-f	0 (-100; 300)	0 (-4; 3)	-31.2 (-100; 100)	-1 (-4; 3)	0.69	0.64
	Percent changes of muscle measurements [median (minimum-maximum)]	Muscle measurements differences (median [median (minimum-maximum)]	Percent changes of muscle measurements [median (minimum-maximum)]	Muscle measurements differences [median (minimum-maximum)]		
GM MT (mm)	10.9 (-24.8; 229.1)	1.6 (-5.5; 37.1)	-6.1 (-50.7; 57)	-1 (-21.4; 9.7)	0.02	0.01
GM FL (mm)	3.9 (-76.8; 433.3)	1.2 (-28.8; 27.3)	0 (-18.1; 94)	0 (-6.4; 14.1)	0.75	0.60
GM PA (°)	4.6 (-35; 126)	1 (-12; 25.5)	18.8 (-29; 87.9)	3.5 (-9; 11.7)	0.44	0.53
RF MT (mm)	4.5 (-67.8; 57.6)	0.6 (-8.1; 8.3)	-6.1 (-52.8; 39)	-1 (-12.2; 5)	0.03	0.04
RFCSA (mm^2)	29.5 (-43.5; 122.1)	1.3 (-4.9; 6.2)	-6.3 (-62.2; 90.4)	-0.3 (-7.8; 3.9)	0.02	0.01
RA MT (mm)	5.7 (-38.1; 51.2)	0.4 (-3.7; 2.8)	11.5 (-45.7; 53.5)	0.8 (-3.8; 3)	0.81	0.80
TA MT (mm)	19.1 (-49.1; 235)	0.5 (-4.1; 4.7)	23.6 (-60.5; 121)	0.7 (-4.6; 2.3)	0.60	0.45
IO MT (mm)	2.5 (-39.7; 49.1)	0.1 (-3.3; 3)	2.3 (-59.5; 121.2)	0.1 (-3.4; 5.8)	0.85	0.85
EO MT (mm)	11.7 (-57.1; 351.8)	0.4 (-4; 9.5)	20.3 (-24.2; 68.7)	0.6 (-0.8; 1.8)	0.78	1.0

P1: Comparison of percent changes of muscle strength and physical performance tests and muscle measurements

P2: Comparison of muscle strength and physical performance tests and muscle measurements differences

CDAI: Clinical disease activity ındex, EO MT: External oblique muscle thickness, IO MT: Internal oblique muscle thickness, HGST: Hand grip strength test, GM MT: Gastrocnemius medialis muscle thickness, GM FL: Gastrocnemius medialis fascicle length, GM PA: Gastrocnemius medialis pennation angle, RF MT: Rectus femoris muscle thickness, RA MT: Rectus abdominis muscle thickness, RFCSA: Rectus femoris cross sectional area, SST:Sit-to-stand test, TUG: Time up and go, TA MT: Transverse abdominis muscle thickness

increased substantially during the initial stages of treatment. Furthermore, the disease activity scores, HGST, SST, and TUG scores improved significantly during treatment. The correlation between the change in VAS global physician, EQ5D scores and the change in SST scores, as well as the correlation between the change in VAS pain scores and the change in HGST scores, was identified. We found that the treatment-responsive group exhibited superior percentage changes in RF muscle thickness, RFCSA, and GM muscle thickness when the treatment response was assessed using the CDAI scores.

Sarcopenia is defined as a condition characterized by low muscle mass, low skeletal muscle strength, and/or poor physical performance, as per the criteria of the European Working Group on Sarcopenia in Older People.[9] It has been demonstrated that sarcopenia is not exclusively associated with age; it can also be the result of inflammation and is linked to an undesirable prognosis and an elevated risk of mortality.[22] In a straightforward regression analysis, Ange Ngeuleu et al. demonstrated that sarcopenia was associated with DAS 28, ESR, waist circumference, and HAQ.[23] In accordance with this, Wanruchada et al.[24] demonstrated that sarcopenia was correlated with elevated disease activity.

Previous research has demonstrated that appendicular lean mass in the limbs is a more accurate indicator of skeletal muscle than total lean mass, as the extremities contain over half of the total muscle mass.[25] A more rational approach may involve assessing total muscle mass through regional measurements administered with USG.

The most valuable imaging methods for evaluating muscle mass are magnetic resonance, computed tomography, bioelectrical impedance analysis, and dual energy X-ray absorptiometry (DXA). However, these methods require experienced personnel, are costly, lack portability, depend on the patient's hydration level, and the presence of metallic devices. There is also the possibility that the results of various DXA devices may differ.[26-28] USG is preferable to other methods of muscle evaluation due to its lack of radiation exposure.[29] Muscle USG can offer objective and consistent quantitative and qualitative measurements of the muscle and can also be employed at the bedside.

In RA, sarcopenia may be caused by a variety of factors. The total muscle mass and stamina may be adversely affected by the increased production of cytokines, including TNFα, interleukin (IL)-1β, and IL-6, which inhibit muscle metabolism. Also, the risk of muscle atrophy is elevated in RA patients due to the prevalence of physical inactivity, which is caused by functional impairment.[30,31] It has been demonstrated that b-DMARDs can result in an increase in muscle mass in approximately 50% of RA patients.[32] In a single study, RA patients who were administered anti-TNF showed a substantial increase in their HGST and 6-minute walk test scores.[33] During therapy, no notable enhancement was reported in HGST, gait speed, or SST in RA patients in another study.[34] In a study conducted on RA patients who were taking b-DMARDs, no significant change was observed in HGST.[35] Significant improvements were observed in the HGST, TUG, and SST assays in our investigation. The gait speed, SARC-F, and 4-minute walk test did not exhibit any significant differences. Despite the improvements in HGST and SST tests detected after treatment, no improvement was detected in SARC-F, gait speed, 4-m walking tests, which have similar results to the literature. It can be explained by suggesting that a longer treatment and follow-up period may be required to make a more definitive interpretation of the improvement in these tests.

The majority of the literature on this topic pertains to muscle quantity measurement. The increase in appendicular skeletal mass and fat-free mass index in RA patients with minimal disease activity was enhanced by b-DMARDs, as demonstrated by a study.[35] Lemmey et al.[36], in contrast, reported that RA patients with minimal disease activity have a higher total fat mass and a lower TLM compared to healthy controls. The relationship between sarcopenia results and disease activity after treatment in RA patients was not investigated, as demonstrated by a meta-analysis.[32] Also, skeletal mass index and muscle strength were not examined. Our research demonstrated a negative correlation between the change in VAS global physician, EQ5D scores, and SST scores. Significant increases in the percentage changes of GM muscle thickness, RFCSA, and RF muscle thickness were observed in patients in the remission or reduced activity group when evaluated according to CDAI responses. The study's assets are the concurrent evaluation of three sarcopenia-related metrics, namely muscle mass, muscle strength, and physical performance, as well as the examination of the correlation between these values and disease activity scores. To date, no studies in the literature have demonstrated the use of ultrasound to measure muscle size in RA patients undergoing treatment with b-DMARDs.

Study Limitations

Lack of a control group is the study's primary limitation. Additionally, due to the ongoing coronavirus disease 2019 pandemic at the time of our investigation, certain patients were unable to attend for control visit. Although the c-DMARD treatments used by the patients before biological treatment are given in detail in Table 1, the fact that we do not have records of their characteristics such as basic and

daily physical activity level and nutritional status is one of the limitations of our study. The fact that the proportion of female patients is higher than that of male patients in our study is not a limitation of our study but rather due to the fact that RA is a disease more common in women. Another limitation of our study is that sarcopenia could not be evaluated comprehensively due to the lack of data on muscle quality of the patients in our study.

Conclusion

In inflammatory disorders such as RA, muscle assessment is essential for guiding patient management and contributing disease activity scores to the evaluation of treatment efficacy. It also provides prognostic insights for diseases. This could be accomplished using a non-invasive technique such as USG, similar to our investigation. A larger patient population and extended follow-up periods are still necessary for the investigation of this topic.

Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Clinical Research Ethics Committee [decision no: 2022/20-08 (KA-21151), date: 22.11.2022] and Turkish Medicines and Medical Devices Agency.

Informed Consent: Informed consent form was obtained from all participants in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practies: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Concept: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Design: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Data Collection or Processing: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Analysis or Interpretation: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Literature Search: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H., Writing: Z.Ö., M.H., Z.Öz., Z.Ş., D.K., G.S.U., E.Ü., Y.T., M.G.H.

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The frequency of Celiac disease in primary Sjögren's syndrome

Primer Sjögren sendromunda Çölyak hastalığının sıklığı

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Abstract

Objective: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, affecting many organs. Celiac disease (CD), which causes inflammatory damage to the small intestine, develops as a result of the immunological response to gluten. The incidence of CD has increased in pSS. This research aims to investigate the frequency of CD in pSS.

Methods: This is a cross-sectional study conducted in a single-center between 2019 and 2020. A total of 90 patients diagnosed with pSS were questioned regarding CD symptoms. Laboratory tests and small bowel biopsies were requested from patients with suspected CD. Anti-gliadin immunoglobulin (Ig)A and IgG, anti-tissue transglutaminase (anti-TTG) IgA and IgG antibodies from celiac antibodies were evaluated using the ELISA method, and anti-endomysium IgA and IgG were evaluated by indirect immunofluorescence. Upper gastrointestinal endoscopy was performed in patients with CD symptoms and autoantibody positivity. The diagnosis of CD was made according to endoscopic biopsy results.

Results: The pSS patients comprised 98% females, with a mean age of 51.6±11.5 years. The rates of CD symptoms were as follows: 10% loss of appetite, 13.3% abdominal pain, 11.1% diarrhea, 18.9% constipation, 37.8% flatulence, and 2.2% weight loss. Anti-gliadin IgA positivity was determined in 6.7%, anti-gliadin IgG in 6.7%, anti-endomysium IgA in 2.2%, anti-endomysium IgG in 15.6%, and IgA in 1.1%. Gastroscopy was planned for 43 patients with suspected CD based on clinical and laboratory findings. CD was diagnosed in two patients before this study; subsequently, four more patients were diagnosed with CD.

Conclusion: The findings of this investigation revealed a 6.7% prevalence of CD in pSS. The diagnosis of CD in pSS was supported by histopathology. According to these findings, CD is more prevalent in pSS patients, and the risk of developing CD is higher than that in the general population.

Keywords: Sjögren's syndrome, Celiac disease, gluten

Öz

Amaç: Primer Sjögren sendromu (pSS), ekzokrin bezlerin lenfositik infiltrasyonu ile karakterize, birçok organı etkileyen sistemik, otoimmün bir hastalıktır. Glutene karşı gelişen immünolojik yanıt sonucu ortaya çıkan Çölyak hastalığı (ÇH), ince bağırsakta enflamatuvar hasara neden olur. ÇH'nin pSS'de insidansı artmıştır. Bu araştırmanın amacı, pSS'de ÇH sıklığını incelemektir.

Yöntem: Bu çalışma, 2019-2020 yılları arasında tek merkezde yürütülen kesitsel bir çalışmadır. pSS tanısı alan toplam 90 hasta, ÇH semptomları açısından sorgulandı. ÇH şüphesi olan hastalardan laboratuvar testleri ve ince bağırsak biyopsisi istendi. Çölyak antikorlarından anti-gliadin immünoglobulin (IgG), anti-doku transglutaminaz (TTG) (IgG) antikorları ELISA yöntemi ile ve anti-endomisyum IgA-IgG ise indirekt immünofloresan yöntemi ile değerlendirildi. ÇH semptomları ve otoantikor pozitifliği olan hastalara üst gastrointestinal sistem endoskopisi yapıldı. ÇH tanısı, endoskopik biyopsi sonuçlarına göre kondu.

Bulgular: pSS hastalarının %98'i kadın olup, ortalama yaşları 51,6±11,5 yıl idi. ÇH semptom oranları şu şekildedir; %10 iştah kaybı, %13,3 karın ağrısı, %11,1 ishal, %18,9 kabızlık, %37,8 gaz ve %2,2 kilo kaybı. Anti-gliadin IgA pozitifliği %6,7, anti-gliadin IgG %6,7, anti-endomisyum IgA %2,2, anti-endomisyum IgG %15,6 ve anti-TTG IgA %1,1 olarak saptandı. Klinik ve laboratuvar bulgularına göre ÇH şüphesi olan 43 hastaya gastroskopi planlandı. Bu çalışmadan önce iki hastada ÇH tanısı konmuştu, çalışmadan sonra ise 4 hastaya daha ÇH tanısı kondu.

Sonuç: Bu araştırmanın bulguları, pSS hastalarında %6,7 oranında ÇH prevalansı olduğunu ortaya koydu. pSS'te ÇH tanısı, histopatolojik bulgularla desteklendi. Bu bulgulara göre, ÇH pSS hastalarında daha yaygın olup, ÇH gelişme riski genel popülasyona göre daha yüksektir.

Anahtar Kelimeler: Sjögren sendromu, Çölyak hastalığı, gluten

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphoplasmacytic infiltration of exocrine glands.[1] The disease affects many organs and systems.[2] In addition to gastrointestinal system findings such as dysphagia, pancreatic dysfunction, antral inflammation in the stomach, and autoimmune liver disease,[1] the frequency of Celiac disease (CD) has increased in pSS patients.[3,4]

An immune reaction to gluten and related proteins causes CD to manifest with inflammatory damage to the small intestine. Adult CD clinical symptoms can vary greatly. Gastrointestinal findings in patients may range from asymptomatic to malabsorption-related findings. Abdominal pain, diarrhea, dyspepsia, osteoporosis, dermatitis herpetiformis, infertility, and persistent anemia (due to iron, folic acid, or vitamin B12 deficiency) are common findings.[5] CD is categorized into three clinical forms -classical, atypical, or asymptomatic- depending on the presence of symptoms and/or extraintestinal findings. The classic form of CD presents with symptoms and signs of malabsorption. In approximately 50% of adult CD patients, gastrointestinal symptoms are non-specific.[6] Patients with atypical forms may have extraintestinal or gastrointestinal symptoms, such as stomach discomfort, constipation, vomiting, and distension. Hematological, endocrine, renal, rheumatological, and dermatological symptoms may also occur, which can result in a delayed CD diagnosis.[6]

Most autoimmune diseases, including type 1 diabetes mellitus, autoimmune thyroid disease, and Sjögren's syndrome (SS), are more common in celiac sufferers compared to the general population.[6] Data on the incidence and prevalence of autoimmune diseases are limited. A population-based study[7] conducted in the UK observed a 22% increase in new diagnoses of autoimmune diseases between 2000 and 2019. A significant portion of this increase was attributed to patients who initially had one autoimmune disease and were subsequently diagnosed with a second. Notably, there was an increase in diagnoses of CD, Graves' disease, and SS.

Since the first study by Pittman and Holub,[8] several studies have explored the relationship between these two diseases.[3,4,9,10] These studies emphasize the increased frequency of CD in SS. The British Society for Rheumatology guidelines for managing adult and juvenile-onset SS[11] highlight the importance of the anti-tissue transglutaminase (anti-TTG) test used in the diagnosis of CD, citing data from some population-based studies,[12] including the findings of two studies.[3,4] Anti-TTG has also been recommended as a screening test after SS diagnosis to identify comorbidities and related autoimmune diseases in SS patients.

In light of all these data, considering that adult patients may be asymptomatic concerning CD, SS patients were included in this study. This study's objective was to investigate the frequency of CD in pSS patients monitored in our outpatient clinic.

Materials and Methods

This study is a cross-sectional study conducted in a single center between 2019 and 2020. Ninety pSS patients who fulfilled the classification criteria of the European-American Consensus Group[13] and were admitted to the rheumatology outpatient clinic between 2004 and 2020 were screened for CD symptoms, including abdominal pain, appetite loss, nausea, diarrhea, constipation, flatulence, and weight loss. The laboratory tests included anemia panel examinations, vitamin D levels, anti-TTG immunoglobulin (Ig)A and IgG, anti-endomysium IgA and IgG, and anti-gliadin IgA and IgG antibodies. Deamidated gliadin peptide antibodies (DGP) were not studied because they are not routine tests. Anti-gliadin IgA and IgG, and anti-TTG IgA and IgG antibodies were evaluated using the ELISA method (anti-TTG IgA cut-off >20 U/mL, anti-TTG IgG cut-off >1 U/mL, anti-gliadin IgA and IgG cut-off >25 U/mL). Anti-endomysium IgA and IgG were evaluated using indirect immunofluorescence, and the outcomes were reported as positive or negative. Upper gastrointestinal endoscopy was conducted in patients with pronounced CD symptoms, persistent anemia, and especially those with positive celiac antibodies. A small intestinal biopsy was taken to confirm the diagnosis of CD. All patients gave written informed consent to participate in the study. The characteristic histological changes linked to CD include crypt hyperplasia, flattening or deletion of villi (villus atrophy), and an increase in intraepithelial lymphocytes.[14] Patients were evaluated according to the diagnostic CD algorithms recommended by the American College of Gastroenterology.[15] The Kocaeli University Ethics Committee approved the study protocol (date: 19.04.2021, approval number: 2021/151).

Statistical Analysis

IBM SPSS software version 20.0 (IBM Corp., Armonk, NY, USA) was used to statistically analyze the study's data. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine if the data adhered to a normal distribution. Numerical variables were presented as mean ± standard deviation and median ± IR (min-max) values, and categorical variables as number (n) and percentage

(%). For numerical variables with a normal distribution, the Independent Samples t-test was used to compare group differences; for variables without a normal distribution, the Kruskal-Wallis and Mann-Whitney U tests were used. Factors impacting the relevant variable were identified using logistic regression analysis. Relationships between categorical variables were assessed using chi-square analysis. A p-value <0.05 was considered statistically significant for two-sided hypothesis testing.

Results

The laboratory, clinical, and demographic characteristics of individuals with pSS are presented in Table 1. The pSS patients comprised 98% females and 2% males, with a mean age of 51.6±11.5 years and mean disease duration of 7.3±4.1 years. The rheumatoid factor test was positive in 60% of patients, while antinuclear antibody, SS-A, and SS-B positivity rates were 90%, 61.1%, and 47.8%, respectively. Salivary gland biopsy was conducted in 81.1% of the participants, and 76.7% of these supported the diagnosis of pSS. In salivary gland scintigraphy, decreased uptake and excretion were detected in 70% of the patients. The clinical and demographic characteristics of pSS patients are presented in Table 1.

The patients were primarily questioned about CD symptoms. The clinical and laboratory findings related to CD are presented in Table 2. The presenting symptoms were as follows: Loss of appetite in 10%, nausea in 7.8%, abdominal pain in 13.3%, diarrhea in 11.1%, constipation in 18.9%, flatulence in 37.8%, and weight loss in 2.2% of the patients. Despite being affected by many parameters, 31.1% of patients had iron deficiency, 22.2% had folate deficiency, 36.7% had vitamin B12 deficiency, 88.8% had vitamin D deficiency, and 52.2% had osteoporosis. Leukopenia was determined in 25.6% of patients, and no patient had thrombocytopenia. The C3 level was low in 11.1% of patients, the C4 level was low in 3.3%, and 21.1% had hypergammaglobulinemia. IgA levels were normal in all patients. When CD antibodies were examined, anti-gliadin IgA positivity was found in 6.7% of patients, anti-gliadin IgG in 6.7%, anti-endomysium IgA in 2.2%, anti-endomysium IgG in 15.6%, and TTG IgA in 1.1%. Anti-TTG IgG was negative in all patients (Table 2).

Gastroscopy was performed for cases with suspected CD based on clinical and laboratory findings. Thus, gastroscopy data for 43 patients were obtained. According to gastroscopy, reflux was observed in 9.3% of patients, pangastritis in 16.3%, erythematous gastroduodenitis in 30.2%, erythematous antral gastritis in 37.2%, duodenitis in 4.7%, and atrophic gastritis in 2.3%. In the duodenal biopsy, intraepithelial lymphocytosis was detected in 41.9% of patients, blunting of villi in 16.3%, and crypt hyperplasia in 16.3%. *Helicobacter pylori* was detected in biopsy samples from 23.3% of patients. The gastric biopsy results showed chronic inflammation in 27.9% of patients, intestinal metaplasia in 9.3%, antral gastritis in 37.2%, and dysplastic changes in the stomach in 2.3%.

Following this stage, the clinical, laboratory, gastroscopy, and biopsy results of the patients were re-evaluated by

Table 1. Clinical and demographic features of patients with primary Sjögren's syndrome

Feature	n (%)
Gender	
Female	88 (97.8)
Male	2 (2.2)
Dry mouth	76 (84.4)
Dry eye	79 (87.8)
Arthritis	31 (34.4)
Parotitis	17 (18.9)
Vasculitis	4 (4.4)
Raynaud phenomenon	22 (24.4)
Neuropathy	6 (6.7)
Myositis	2 (2.2)
Lymphadenopathy	28 (31.1)
Interstitial lung disease	7 (7.8)
Nephrological involvement	6 (6.7)
Rheumatoid factor positivity	54 (60)
Antinuclear antibody positivity	81 (90)
Anti-SSA positivity	55 (61.1)
Anti-SSB positivity	43 (47.8)
Salivary gland biopsy positivity	56/73 (76.7)

Table 2. Clinical and laboratory findings of patients in terms of Celiac disease

Finding	n (%)
Loss of appetite	9 (10)
Nausea	7 (7.8)
Abdominal pain	12 (13.3)
Diarrhea	10 (11.1)
Constipation	17 (18.9)
Flatulence	34 (37.8)
Iron deficiency	28 (31.1)
Vitamin B12 deficiency	33 (36.7)
Folate deficiency	20 (22.2)
Vitamin D deficiency	80 (88.8)
Anti-gliadin IgA	6 (6.7)
Anti-gliadin IgG	6 (6.7)
Anti-endomysium IgA	2 (2.2)
Anti-endomysium IgG	14 (16)
Anti-TTG IgA	1 (1.1)
Anti-TTG IgG	-

Ig: Immunoglobulin, TTG: Anti-tissue transglutaminase

the gastroenterology department. Two patients had been diagnosed with CD before this study and had followed a gluten-free diet for many years. Based on the data obtained in the study, four more patients were diagnosed with CD. These patients have been following a gluten-free diet for approximately two years. A significant reduction in symptoms was observed in patients after starting a gluten-free diet.

When pSS patients with and without CD were compared, a statistically significant difference was observed regarding loss of appetite, flatulence, and arthritis. These results are presented in Table 3.

In the laboratory findings, statistically significant differences were observed in terms of iron deficiency and the presence of anti-endomysium IgG and anti-gliadin IgG. When gastroscopy and pathology biopsy results were evaluated, the presence of duodenitis, intraepithelial lymphocytosis, villus atrophy, and crypt hyperplasia were found to be significantly different between the groups (Table 4).

A significant correlation was also observed in the regression analysis of laboratory and clinical findings. In multivariate analysis, only loss of appetite and the presence of atrophic villi in duodenal biopsy were linked to the

Table 3. Comparison of clinical features of primary Sjögren's syndrome patients with and without Celiac disease

Feature	With CD (n=6)	Without CD (n=84)	p
Gender			
Female	6 (100)	82 (97.6)	1
Male	-	2 (2.4)	
Age* (mean ± SD)	49.7±5.6	51.7±11.9	0.457
Disease duration* (mean ± SD)	7.5 (5.3-11.5)	7 (4-9.9)	0.593
Disease onset age* (mean ± SD)	41.2±6.1	44.5±11.5	0.267
Dry mouth	6 (100)	70 (83.3)	0.585
Dry eye	6 (100)	73 (86.9)	1
Arthritis	5 (83.3)	26 (31)	0.017
Parotitis	1 (16.7)	16 (19)	1.000
Vasculitis	-	4 (4.8)	-
Neuropathy	-	6 (7.1)	-
Loss of appetite	4 (66.7)	5 (6)	0.001
Nausea	1 (16.7)	6 (7.1)	0.394
Diarrhea	2 (33.3)	8 (9.5)	0.131
Abdominal pain	2 (33.3)	10 (11.9)	0.189
Constipation	2 (33.3)	15 (17.9)	0.316
Flatulence	5 (83.3)	29 (34.5)	0.027
Weight loss	1 (16.7)	2 (2.4)	0.218

**CD: Celiac disease, years, SD: Standard deviation*

Table 4. Comparison of laboratory and gastroscopic histopathology results of primary Sjögren's syndrome patients with and without Celiac disease

Finding	With CD (n=6)	Without CD (n=84)	p
Anti-gliadin IgA	1 (16.7)	5 (6)	0.361
Anti-gliadin IgG	3 (50)	3 (3.6)	0.004
Anti-endomysium IgA	2 (33)	-	-
Anti-endomysium IgG	6 (100)	8 (9.5)	0.000
Anti-TTG IgA	1 (16.7)	0	-
Iron deficiency	5 (83.3)	23 (27.4)	0.010
Folate deficiency	3 (50)	17 (20.2)	0.121
Vitamin B12 deficiency	4 (66.7)	29 (34.5)	0.187
Vitamin D deficiency	6 (100)	74 (88.1)	1.000
Histopathological findings			
Duodenitis	7 (100)	13 (15.5)	0.000
Intraepithelial lymphocytosis	5 (83.3)	14 (16.7)	0.001
Atrophic villi	4 (66.7)	4 (4.8)	0.000
Crypt hyperplasia	3 (50)	4 (4.8)	0.005

CD: Celiac disease, Ig: Immunoglobulin, TTG: Anti-tissue transglutaminase

presence of CD in pSS patients. The regression analysis of the relationship between the presence of CD and clinical, laboratory, and pathological findings in pSS patients is presented in Table 5.

Discussion

SS affects many organs and systems,[2] and CD frequency is known to increase in SS. This study investigated CD frequency in pSS patients and demonstrated an increased incidence of CD in SS patients compared to healthy individuals.

In this study, the most prevalent gastrointestinal symptoms in pSS patients with CD were flatulence and loss of appetite. Although the frequency of bloating was observed at different rates (46-73%) in various studies,[16,17] it was a prominent symptom in most CD patients in this study (83.3%). Loss of appetite has low sensitivity in diagnosing CD;[18] however, a significant correlation was observed between CD diagnosis and loss of appetite in this study. Abdominal pain, nausea, and diarrhea were less common symptoms. Anemia, the most frequent extraintestinal finding in CD, is seen in 20% of cases.[19] It can be due to iron, B12, or folate deficiency. The prevalence of iron deficiency anemia in CD varies between 3% and 5%. In this study, this rate was found to be quite high, possibly because the patient group primarily comprised females, and iron loss could be due to the menstrual cycle. Anemia and iron deficiency have been shown to improve with a gluten-free diet. Iron and folate deficiencies were higher in CD participants compared to non-CD participants. Anemia parameters improved in 85% of participants on a gluten-free diet, and iron therapy was also given to patients with poly-hypermenorrhea.

CD is an enteropathy triggered by gluten and associated with various autoantibodies. Both humoral and cellular immune responses play a role in CD. CD-specific antibodies include endomysial antibodies (EMA), DGP, and autoantibodies against transglutaminase 2.[20-22]

In CD diagnosis, both TTG and EMA tests have high specificity and sensitivity.[23] In this study, anti-TTG IgA and endomysium IgA were not detected in any pSS patients without CD. Anti-TTG IgA positivity was low in CD patients in this study; however, anti-endomysium IgG was positive in all CD patients. Although anti-gliadin antibodies have low specificity and sensitivity and are not used in diagnosis, anti-gliadin IgG was observed at a high rate in individuals with CD. DGP were not studied because this is not a routinely performed test.

The gold standard for diagnosing CD remains a small intestinal biopsy. Typical findings in endoscopic distal duodenal biopsies in CD include increased intraepithelial lymphocytes, crypt hyperplasia, and flattening or deletion of villi (villus atrophy).[14] Histopathological classifications, such as the Marsh-Oberhuber classification,[6,14] are used to grade intestinal mucosal lesions in CD. However, none of the histopathological findings listed above are pathognomonic for CD. Therefore, histopathological findings may need to be evaluated alongside serological and clinical findings, and genetic testing may be required for confirmation when necessary. In this study, all pSS patients with CD exhibited duodenitis, and CD-specific histopathological findings were identified in the biopsies. Regression analysis in this study revealed a significant correlation between these histopathological findings and CD diagnosis.

Previous studies show that CD frequency in pSS patients varies between 4.5% and 15%.[3,4,9,10] In a study by Iltanen et al.,[9] although the sample size was small, CD prevalence was found to be quite high in pSS patients. Histopathological data and positive celiac antibodies (anti-gliadin IgA and anti-endomysium IgA) were high in these patients.[9] Szodoray et al.[3] reported CD prevalence in pSS patients as 4.5%, with diagnosis confirmed by serology and histopathology. According to that study, SS patients with CD were younger than those without CD. In another study, the prevalence of CD in pSS patients was 7.06%, with the majority (24 out of 25) diagnosed with CD before the study, confirmed with an intestinal biopsy. It was also noted that pSS patients with CD were younger than those without CD and that CD was diagnosed at a younger age.[10] However, no significant age

Table 5. Regression analysis of the relationship between the presence of CD and clinical, laboratory, and pathological findings in pSS patients

	Univariate			Multivariate		
	p	OR	95% CI	p	OR	95% CI
Flatulence	0.044	9.48	1.06-85.04			
Iron deficiency	0.021	13.26	1.47-119.67			
Arthritis	0.031	11.15	1.24-100.29			
Loss of appetite	0.000	31.6	4.62-216.2	0.009	28.3	2.4-347.5
Intraepithelial lymphocytosis	0.005	25	2.70-230.73			
Atrophic villi	0.000	26.3	5.56-287.45	0.005	35.9	2.9-441.5
Crypt hyperplasia	0.002	20	3.02-132.29			

CD: Celiac disease, CI: Confidence interval, OR: Odds ratio, pSS: Primary Sjögren's syndrome

difference between the groups was observed in the present study.

The current study found the CD prevalence in pSS patients to be 6.7%. CD diagnosis in pSS patients was confirmed by histopathology. According to 2018 Ministry of Health public health data, CD prevalence in Türkiye is 1%.[24] Thus, the study suggests that CD prevalence in pSS patients is high, with an increased risk for CD compared to the general population.

Arthralgia and arthritis can be observed in CD patients. CD-associated arthritis was once thought to be rare, with a reported frequency between 0-26%. Non-erosive oligoarticular involvement occurs in peripheral large joints and is not associated with spondyloarthropathy or sacroiliitis.[25] Intermittent, non-erosive symmetrical inflammatory polyarthritis occurs in 30% of SS patients, particularly affecting the fingers, wrists, and ankles.[26] In this study, arthritis incidence in patients with CD was significantly higher than in the non-Celiac group. The arthritis pattern in CD patients in this study was symmetrical polyarthritis (60%) and an oligoarticular pattern (40%). None of the patients had a diagnosis of spondylitis.

Advanced complications of CD, such as collagenous sprue, ulcerative jejunoileitis, and enteropathy-associated T-cell intestinal lymphoma (EITCL), can occur at advanced stages of CD. EITCL is the most serious CD complication, with a poor prognosis.[27] Thus, it is crucial for patients to maintain a gluten-free diet and receive regular follow-ups after diagnosis.

Study Limitations

Study limitations include the small sample size and the low rate of anti-TTG antibodies, which have high sensitivity and specificity in diagnosis. The lack of both a patient control group and a healthy control group is another limitation. The use of anti-gliadin antibodies, which have low specificity, is also a limitation. A study strength is that patients were evaluated through detailed anamnesis, laboratory testing, gastroscopy, and histopathological examination for CD diagnosis.

Conclusion

The results of this study showed that CD prevalence is increased in patients with pSS. Therefore, CD should especially be considered in patients with treatment-resistant anemia, and a thorough gastrointestinal investigation with antibody screening and endoscopic examination is recommended. Patients should be monitored for malabsorption syndromes, anemia, and potential lymphoma development and managed with an appropriate diet.

Ethics

Ethics Committee Approval: The Kocaeli University Ethics Committee approved the study protocol (date: 19.04.2021, approval number: 2021/151).

Informed Consent: All patients gave written informed consent to participate in the study.

*Preliminary results of this study was presented as an oral presentation at the XX. National Rheumatology Congress (16-20 October 2019, Antalya SS-18).

Footnotes

Authorship Contributions

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

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Düşük doz metotreksat kullanımına bağlı nötropenik hastaların retrospektif analizi

Retrospective analysis of cases with low dose methotrexate-induced neutropenia

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Öz

Amaç: Düşük doz metotreksat (MTX) romatolojide en sık kullanılan ilaçların başında gelip, nadir olarak yanlış kullanım sonucunda veya toksisite için risk faktörleri bulunan hastalarda nötropeniye sebep olabilmektedir. Çalışmamızın amacı düşük doz MTX tedavisiyle ilişkili nötropeni ile hastanemiz romatoloji kliniğine başvuran hastaların klinik özelliklerini ve kısa dönem takip sonuçlarını göstermektir.

Yöntem: Ekim 2022 ve Nisan 2024 tarihleri arasında kliniğimize düşük doz MTX tedavisiyle ilişkili nötropeni (nötrofil <1500/mm³) nedeniyle yönlendirilen 18 yaş ve üzeri hastalar retrospektif olarak incelendi. Hastaların demografik özellikleri, MTX kullanım dozu ve süreleri, MTX toksikasyonu açısından risk faktörleri, başvurudaki laboratuvar ve klinik bulguları, aldıkları tedavi ve nötropeniden çıkma süreleri, mortalite oranı incelendi.

Bulgular: Düşük doz MTX ilişkili nötropeni nedeniyle takip ettiğimiz 9 hastanın 6'sı kadındı ve hastaların ortalama yaşı 71 idi. 7/9 hastada pansitopeni mevcuttu. 7/9 hastada yanlış yüksek doz (7,5-15 mg/gün) kullanım tespit edildi. 8/9 hasta acile mukozit ile başvurmuştu, hastaların 3'ünde febril nötropeni mevcuttu. Başvuruda ortalama lökosit 1520/mm³, nötrofil 600/mm³, hemoglobin 8,7 g/dL, trombosit 66000/mm³ saptandı. Tüm hastalara intravenöz lökovorin tedavisi başlandı. Hiçbir hastaya granülosit koloni-stimüle edici faktör uygulanmadı. Nötropeni ve lökopeninin ortalama düzelme süresi sırasıyla ortalama 8 ve 8,6 gün olarak saptandı. Mortalite gelişen olgu saptanmadı.

Sonuç: Hastalarımızın çoğunda MTX ile ilişkili nötropeninin uygunsuz kullanımdan kaynaklandığı görülmüştür. Lökovorin tedavisi ve enfeksiyon kontrolü ile ortalama 8 günde nötropeni düzelmiştir.

Anahtar Kelimeler: Metotreksat, nötropeni, pansitopeni, toksisite, lökovorin

Abstract

Objective: Low dose methotrexate (MTX) is among the most commonly used drugs in rheumatology and rarely associated with neutropenia. It is generally observed as a result of improper use or in patients with risk factors for toxicity. This study aimed to demonstrate the clinical characteristics and short-term follow-up outcomes of patients who presented with neutropenia related to low-dose MTX therapy.

Methods: Patients (>18 years) who were referred to our clinic due to neutropenia (neutrophil <1500/mm³) associated with low-dose MTX use between October 2022 and April 2024 were retrospectively analyzed. We recorded patients' demographics, MTX dosage, risks for toxicity, laboratory and clinical findings at the time of presentation, the treatments, duration of recovery from neutropenia and mortality rates.

Results: There were 9 patients followed for low-dose MTX-associated neutropenia; 6 were female, and the mean age was 71. Seven patients had pancytopenia. Improper high-dose (7.5-15 mg/d) usage was detected in 7 patients. Eight patients presented with mucositis, and 3 had febrile neutropenia. At presentation, mean leukocyte count was 1520/mm³, neutrophil count was 600/mm³, hemoglobin was 8.7 g/dL, and platelet count was 66000/mm³. All patients were started on intravenous leucovorin without granulocyte-colony stimulating factor treatment, and the mean time to improvement for neutropenia and leukopenia was 8 and 8.6 days, respectively. No cases of mortality were detected.

Conclusions: In most of our cases MTX-associated neutropenia resulted from improper use. With leucovorin monotherapy and infection control, neutropenia improved within 8 days.

Keywords: Methotrexate, neutropenia, pancytopenia, toxicity, leucovorin

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Giriş

Folat antimetaboliti olan metotreksat (MTX) dihidrofolat redüktaz enzimini yarışmalı olarak inhibe ederek DNA sentezini bozan, aktif olarak prolifere olan hücreleri etkileyen ve ayrıca enflamasyonu birçok farklı yolaktan baskılayan hastalık modifiye edici bir ilaçtır. Romatoloji pratiğinde romatoid artrit (RA) başta olmak üzere psöriatik artrit, sistemik vaskülitler, bağ dokusu hastalıkları ve enflamatuvar miyozitlerde en sık kullanılan ilaçların başında gelmektedir. Düşük doz (<25 mg/hafta) MTX sıklıkla geçici gastrointestinal, hafif konstitüsyonel, nörolojik veya mukokütanöz yan etkiler ve hafif transaminaz yüksekliğine neden olabilmektedir. Sık görülen bu yan etkilerin çoğunlukla haftalık folik asit desteği ile önlenebildiği gösterilmiştir.[1] Literatürde düşük doz MTX kullanımıyla sitopeni gibi hematolojik yan etki gelişme oranı %5,5, lökopeni/nötropeni %1-3,4, pansitopeni ise %0,3-1,4 olarak bildirilmiştir.[2-4]

Hematolojik yan etkiler çoğunlukla ilacın yanlış yüksek doz kullanımı ve/veya toksisite için risk faktörleri bulunan hastalarda kullanımı ile görülmektedir. Romatolojik hastalıklarda düşük doz MTX kullanımına bağlı myelosupresyon için bu risk faktörleri; folik asit desteği kullanılmaması, hipoalbüminemi varlığı, eş zamanlı kullanılan non-steroid anti-enflamatuvar ilaçlar ve proton pompa inhibitörleri (PPİ) gibi ilaç etkileşimleri ve renal fonksiyonlarda düşüş olarak bilinmektedir.[5,6]

Özellikle yanlış yüksek doz MTX kullanımında myelosupresyon riskinin arttığı bilinmektedir. Bunun nedeni; yanlış günlük alımlarda her dozun tamamen emilmesi ve birikime (yüksek toplam maruziyete) neden olmasıdır.[7] Ciddi nötropeni veya pansitopeni gelişen hastalarda tedavide folinik asit (kalsiyum folinat/lökovorin) tedavisi önerilse de literatürde dozu ve süresi ile ilgili veya diğer destek tedaviler için net öneriler bulunmamaktadır. Litaratürde çoğunlukla düşük doz MTX toksikasyonunun takibi ve tedavisini içeren olgu sunumları mevcut olup tek merkezli geniş seride bildiri çok az sayıdadır.

Çalışmamızın amacı düşük doz MTX ilişkili nötropeni ile hastanemiz romatoloji kliniğine başvuran hastaların klinik özelliklerini, aldıkları tedavi ve takip sonuçlarını göstererek MTX intoksikasyonu ile karşılaşıldığında klinisyenlere pratik bilgiler sağlamaktır.

Gereç ve Yöntem

Ekim 2022 ve Nisan 2024 tarihleri arasında Göztepe Prof. Dr. Süleyman Yalçın Şehir Hastanesi'ne başvuran ve düşük doz MTX kullanımına bağlı nötropeni nedeniyle romatoloji kliniğine danışılan 18 yaş üzeri hastalar retrospektif olarak incelendi. Nötropeni <1500/mm^3; pansitopeni beyaz kan hücresi (WBC) <4000/mm^3 hemoglobin (Hb) <12 g/dL trombosit (Plt) <150.000/mm^3 olarak tanımlandı. Çalışmaya, MTX ilişkili nötropeni saptanan hastalar dahil edildi. Nötropeni sebebi olabilecek hematolojik malignite, başka sitotoksik/immünosupresif ilaç kullanımı, B12 ve folat vitamin eksikliği, veya yeni gelişen kanıtlanmış akut viral (HIV) enfeksiyon gibi başka etiyoloji saptanan hastalar dışlandı. Hastaların yaş, cinsiyet, MTX kullanım endikasyonu, MTX dozu, kullanım şekli ve süresi (yanlış kullanım varsa MTX reçete bilgileri), ek hastalıkları, eş zamanlı kullanılan ilaçlar, folik asit desteği, öncesinde hipoalbüminemi (<3,5 g/dL) varlığı, başvuruda anındaki hemogram, karaciğer ve böbrek fonksiyon testleri, periferik yayma, serum MTX düzeyi kaydedildi. Ayrıca hastaların başvurusu sırasındaki şikayetleri ve bulguları, hastane yatış durumu, yatış esnasında kan transfüzyonu gereksinimi, lökovorin destek tedavi dozu ve süresi, Granülosit koloni-stimüle edici faktör (G-CSF) uygulanma durumu, eşlik eden enfeksiyon varlığı ve antimikrobiyal tedavi gereksinimleri, lökopeni ve nötropeniden çıkma süreleri, mortalite durumu incelenmiştir. İstanbul Medipol Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu 18.09.2024 tarihli E-10840098-202.3.02-5682 etik kurul onayı mevcuttur. Hastalardan aydınlatılmış onam alındı.

İstatistiksel Analiz

Sürekli veriler ortalama (maksimum-minimum) olarak, kategorik veriler sayısal olarak gösterildi.

Bulgular

Ekim 2022 ve Nisan 2024 tarihleri arasında hastanemize başvuran ve düşük doz MTX kullanımına bağlı nötropeni saptanan 9 hasta (6 kadın, 3 erkek) olup, hastaların ortalama yaşı 71,4 (60-87) idi. Demografik ve klinik özellikler tabloda verilmiştir (Tablo 1). Sekiz hastada komorbid hastalık mevcuttu ve 6 hastada ≥2 komorbid hastalık bulunuyordu. Eşlik eden risk faktörleri açısından 2 hastada kronik böbrek hastalığı (KBH), 8 hastada eş zamanlı PPİ kullanımı saptandı. Hipoalbüminemi başvuru öncesi 1 hastada (olgu 1, mide kanseri tanılı) mevcuttu, 3 hastada ise yoktu. Beş hastanın ise başvuru öncesi albümin değerine ulaşılamadı, ancak başvuru anında hipoalbüminemi mevcuttu.

Tüm hastalara başka bir merkezde (8 hastada RA, olgu 3 ise psöriazis tanısıyla) MTX tedavisi başlanmıştı. Sadece 1 hastanın mevcut MTX dozu 2,5 mg/hf'den 7,5 mg/hf'ye olacak şekilde romatoloji polikliniğimizde artırılmıştı. Hastalarının hepsinin reçetesi E-reçete sisteminde doğru yazılmıştı. Ancak 7 hastada yanlış dozda MTX kullanımı, 2 hastada folat desteği ile birlikte doğru kullanım mevcuttu.

Tablo 1. Hastaların demografik ve klinik özellikleri, tedavileri

	Olgu 1	Olgu 2	Olgu 3	Olgu 4	Olgu 5*	Olgu 6	Olgu 7	Olgu 8	Olgu 9
Yaş	79	68	75	66	87	60	63	68	77
Cinsiyet	Kadın	Erkek	Erkek	Erkek	Kadın	Kadın	Kadın	Kadın	Kadın
Hemogram	Pansitopeni	Pansitopeni	Pansitopeni	Lökopeni anemi	Pansitopeni	Pansitopeni	Pansitopeni	Pansitopeni	Pansitopeni
Başvuru şikayeti	Mukozit, umblikus ve makatta ülsere lezyonlar	Mukozit, ateş	Mukozit, ateş, ishal	Mukozit	-	Mukozit, ishal	Mukozit, öksürük	Mukozit, ishal, melena, ateş	Mukozit, ishal
MTX kullanım süresi	8 yıl	10 gün	3,5 yıl	10 gün	10 yıl	7 gün	11 gün	6 ay	3 gün
Aldığı doz	15 mg/hf	15 mg/gün	15 mg/hf	15 mg/gün	10 mg/hf	12,5 mg/gün	15 mg/gün	2,5 mg/gün	7,5 mg/gün
Yanlış kullanım	-	+	+	+	-	+	+	+	+
Folik asit desteği	2/7	1/7	-	2/7	1/7	1/7	1/7	1/7	1/7
Komorbid hastalık	DM, KBH, HT, mide Ca	KOAH, BPH	HT, KOAH, BPH, Parkinson	HT, DM	KAH, KBH	HT	-	KKY, HT	DM, SVO
Lökovorin 4x15 mg	4 gün	3 gün	6 gün	3 gün	Folik asit tablet	6 gün	5 gün	5 gün	8 gün
Lökopeniden çıkış	5 gün	Veri yok	6 gün	4 gün	23 gün*	7 gün	6 gün	9 gün	13 gün
Nötropeniden çıkış	5 gün	16 gün	6 gün	2 gün	23 gün*	7 gün	8 gün	8 gün	12 gün
Transfüzyon	-	-	1 Ü ES	-	-	-	-	1 Ü TS, 1Ü ES	1 Ü TS

**: Ayaktan poliklinikten takip edilen hasta (hemogram kontrolünde gecikme yaşanmıştır)*

BPH: Benign prostat hiperplazisi, DM: Diabetes mellitus, ES: Eritrosit süspansiyonu, Hf: Hafta, HT: Hipertansiyon, KAH: Koroner arter hastalığı, KBH: Kronik böbrek hastalığı, KOAH: Kronik obstrüktif akciğer hastalığı, KKY: Konjestif kalp yetmezliği, SVO: Serebrovasküler olay, TS: Trombosit süspansiyonu

Yanlış kullananlar arasında; 1 hastada folat desteği almadan doğru dozda (15 mg/hf) MTX kullanımı; 1 hastada ise folat desteği almadan 2,5 mg/gün şeklinde yanlış kullanım mevcuttu. Diğer yanlış kullanan 5 hastada ise MTX dozu ortalama 8,2 (3-11) gün boyunca 7,5-15 mg/gün şeklindeydi.

MTX 10 mg/hf şeklinde doğru kullanımı olan 87 yaşındaki hastada kreatinin 0,68 mg/dL idi ancak glomerüler filtrasyon hızı (eGFR): 54 mL/dk olup evre 3 KBH saptandı. Pansitopeni dışında bulgu olmaması ve şikayeti veya fizik muayenesinde anormal bulgu olmaması nedeniyle oral folik asit tedavisi ile ayaktan takip edildi. Doğru kullanımı olan diğer hastada (olgu 1) ise risk faktörü olarak tanılı ancak takipsiz evre 4 KBH mevcuttu.

Sekiz hasta acil servis başvurusu sonrası hastaneye yatırılarak tedavi edildi. Hepsinde mukozit mevcuttu, 4 hastada ishal (2'si febril nötropeni), toplam 3 hastada febril nötropeni mevcuttu. Yedi hastada pansitopeni, 1 hastada bisitopeni (lökopeni ve anemi) mevcuttu. Başvuruda ortalama WBC: 1520 (400-2900)/mm^3, ortalama nötrofil: 600 (200-1330)/mm^3, ortalama Hb: 8,7 (4,3-11,2) g/dL, ortalama Plt: 66000 (3000-204000)/mm^3 olarak saptandı. Tüm hastalarda periferik yayma değerlendirildi, atipik hücre veya hematolojik malignite yönünden şüpheli bulgu saptanmadı.

Yatırılarak tedavi edilen tüm hastalara intravenöz (İV) 6 saatte bir 15 mg folinik asit ortalama 5 (3-8) gün boyunca verildi. Sadece 1 hastada (olgu 8) servisimize alınmadan önce yapılmış olan tek doz G-CSF uygulaması dışında, hiçbir hasta G-CSF desteği almadı. Mukozit nedeniyle tüm hastalara oral nistatin ve semptomatik topikal tedavi verildi.

Hastaların hiçbirinde başvuruda transaminaz yüksekliği yoktu. Akut böbrek hasarı ise 2 hastada mevcuttu. Bunlardan birinde KBH zemininde gelişmiş olup ve bazal kreatinin değerine 6 günde geriledi. Diğer hastada ise yeni akut böbrek hasarı tablosu (kreatinin: 1,37 mg/dL, üre: 89 mg/dL) 18 günde düzeldi.

Serviste takip edilen 6/8 hastanın başvuruda bakılan serum MTX düzeyi ortalama 0,08 (0,04-0,13) mikromol/L ölçüldü. Serum MTX düzeyi ile pansitopeni ağırlığı arasında ilişki görülmedi.

Nötropeni düzelme (nötrofil >1500/mm^3) süresi ortalama 8 (2-16) gün; lökopeni düzelme (WBC >4000/mm^3) süresi ortalama 8,6 (4-19) gün olarak izlendi. 1 hastada eritrosit süspansiyonu, 1 hastada trombosit süspansiyonu, 1 hastada ise hem eritrosit hem trombosit süspansiyon transfüzyon ihtiyacı oldu. Tek doz G-CSF alan 1 hastanın nötropeniden çıkış süresi 8, lökopeniden çıkış süresi 9 gün idi.

Yatırılarak tedavi edilen 2 hasta pnömoni, 1 hasta yüzeyel yumuşak doku enfeksiyonu, 3 hasta febril nötropeni (2 hastada kültürlerde üreme) nedeniyle uygun antibiyoterapi aldı. Başvuruda ortalama C-reaktif protein: 109 (64-181) mg/dL idi. Yalnızca 2 hasta ateş olmaması veya enfeksiyon odağı olmaması nedeniyle antibiyotiksiz takip edildi. Yoğun bakım ihtiyacı ya da mortalite gelişen hasta olmadı.

Tartışma

Düşük doz MTX tedavisi alan hastalarda yanlış günlük yüksek doz MTX kullanımına bağlı nötropeni nadir ama hayatı tehdit edebilen ciddi bir komplikasyon olup literatürde görülme oranı yaklaşık %1 olarak bildirilmiştir.[2-4] Tek merkezli retrospektif değerlendirmemizde 19 ayı içeren süreçte 9 hastada düşük doz MTX tedavisine bağlı gelişen nötropeni saptanmış olup hiçbir hastada mortalite gözlenmemiştir. Çalışmamızdaki hastaların hepsine başka merkezlerde MTX başlanmış ve hepsinin reçetesinde MTX kullanımı doğru yazılmıştı ancak 7/9 hastada yanlış kullanım öyküsü mevcuttu. Sadece yeni tedavi başlanan hastalarda değil; biri hastanemizde diğeri başka bir romatoloji polikliniğinde olmak üzere önceden doğru şekilde kullandığı MTX dozu (yine düşük doz sınırlarında kalacak şekilde) artırılan 2 hastada yanlış kullanımın sonradan da olabileceği görüldü. Fransız Zehir Danışma ve Farmakovijilans Merkezi'nden 7 yıllık tarama ile yapılan bir çalışmada yanlış yüksek doz kullanımı bildirilen 74 hastada %23 yanlış reçetelenme, %56 hasta veya evde bakan kişi kaynaklı yanlış kullanım, %20 ise sağlık çalışanı tarafından ilacın yanlış verildiği saptanmıştır.[8] Çalışmamızda yanlış yüksek doz kullanımının hepsi hasta kaynaklıydı. Bunu önlemek amacıyla doğru reçetelemenin yanı sıra hastaya sözlü ve gerekirse ayrıntılı yazılı ek açıklama ve uyarıda bulunmanın önemi ortaya çıkmaktadır.

Hem onkolojik tedavide kullanılan yüksek doz MTX hem de haftalık düşük doz MTX'in etki ve yan etkilerinin bir kısmı folik asidin aktif formu olan folinik aside dönüşmesinin engellenmesi ile açıklanmaktadır. Yüksek doz MTX tedavi protokolünde toksisite yönetiminde İV lökovorin kurtarma tedavisi kullanılmaktadır. Lökoverin tedavisinin myelosupresyon, gastrointestinal toksisite ve nörotoksisite açısından etkinliği kanıtlanmıştır.[9] Düşük doz MTX yan etkisini azaltmak için ise haftalık (≤7 mg/hf) hem folik asit hem de folinik asit desteğinin etkinliği bilinmektedir ve aralarında fark gösterilmemiştir. Shea ve ark.'nın[1] yaptıkları metaanalizde bu desteği alanlar ve almayanlar arasında gastrointestinal ve hepatik yan etkiler açısından anlamlı fark bulunsa da; hematolojik yan etkilerin nadir görülmesi nedeniyle myelosupresyon riskinin istatistiksel olarak anlamlı derecede azaldığı gösterilememiştir, ancak myelosupresyonun azalma eğiliminde olduğu görülmüştür. Bu açıdan haftalık 5-10 mg oral folik asit kullanımı önerilmekte olup maliyet etkinliği nedeniyle oral folinik asit tercih edilmemektedir.

Akut yüksek doz MTX kullanımı ile bizim hasta serimizde olduğu gibi yanlışlıkla yüksek günlük MTX alımına bağlı arasındaki toksisite arasında fark vardır. Bunun nedeni MTX'in oral emiliminin doygun hale gelebilmesidir. Günlük 25 mg'den fazla dozlarda biyoyararlanım belirgin şekilde azalır ve serum konsantrasyonları 24 saat sonra hızla tespit edilemez hale gelir. Bunun nedeni, metotreksatın hızlı bir dağılım yarı ömrü (2 saat) ve eliminasyon yarı ömrü (6 ila 8 saat) olmasıdır. MTX'in hücreye alımı da doyurulabilir, bu nedenle akut yüksek doz durumunda, dozun çoğu emilmez ve sadece küçük bir kısmı hücreler tarafından alınır. Ancak hastalarımızdaki tekrarlanan yanlış günlük alımlarda, her doz tamamen emilir ve hücreye tamamen alınır, bu da birikime ve çok daha yüksek toplam maruziyete neden olur.[7,10] MTX'in hedef bölgesi olan hücrelere yavaş alımı ve eliminasyonu, serum MTX konsantrasyonlarının toksisite şiddetini yansıtmadığı anlamına gelir. Serum MTX düzeyi tespit edilemezken, hücre içi konsantrasyonlar çok daha yüksek olacaktır. Bu hasta grubunda rutin serum MTX düzeyi bakılması önerilmemektedir; çünkü nötropeni derecesi veya mortalite ile korelasyon gösterilmemiştir.[6,7]

Literatürde düşük doz MTX ilişkili pansitopeni/nötropeni olgularında İV lökovorin kurtarma tedavisi konusunda standart veya kanıtlanmış bir tedavi dozu veya süresi bulunmamakla birlikte genel uygulama 3 gün boyunca 4x15 mg/gün şeklindedir. Ayrıca nötropenik hastalarda G-CSF kullanımı açısından da net öneri bulunmamaktadır. Düşük doz MTX ilişkili pansitopeni olgularında 3 gün boyunca 4x15 mg/gün lökovorin kurtarma tedavisinin etkinliğinin araştırıldığı çalışmada; lökovorin kurtarma tedavisi tek başına veya G-CSF ile birlikte verildiğinde, tek başına G-CSF tedavisi veya diğer tedavilere göre hematolojik tabloyu daha kısa sürede düzelttiği gösterilmiştir.[11] Lökovorin kurtarma tedavisi alanlarda pansitopeniden çıkış süresi G-CSF'den bağımsız olarak ortalama 5,4 (±2,9) gün iken, lökovorin kurtarma tedavisi almayanlarda ortalama 10 (±3,7) gün bulunmuştur.[11] Çalışmamızdaki hastalara (1 hastada tek doz dışında) G-CSF tedavisi verilmedi, nötropeni

ve lökopeni tablosunun ortalama 8 günde düzeldiği saptandı. Literatürde G-CSF eklenmesiyle de bu süre açısından ve mortalite açısından benzer sonuçlar bildirilmiştir.[7,12]

Dokuz hastalık olgu serimizde mortalite izlenmedi ancak MTX ilişkili pansitopeni olgu serilerinde mortalite %10-28 olarak raporlanmıştır.[4,11,13,14] Mortalitenin sepsis nedenli olduğu ve bunun gelişmesinde en önemli risk faktörünün nötropeni olduğu düşünüldüğünde; nötropeniden çıkış süresini lökovorin tedavisiyle kısaltmanın sepsis yönetimine ve mortaliteye katkısı olacağı düşünülmektedir. Ancak bu konuda kontrollü çalışmalar bulunmamaktadır. Çalışmamızda 5 hastada şiddetli (<500), 1 hastada orta derecede (500-1000), 3 hastada hafif nötropeni (1000-1500) mevcuttu. Ortalama yaşın 71 olduğu hasta serimizde mortalite veya yoğun bakım ihtiyacı görülmemesinin sebeplerinden biri enfeksiyon bulgusu olan tüm hastalarda (7/9 hasta) erken antibiyoterapi ve lökovorin başlanması olarak gösterilebilir. Ayrıca stabil seyreden komorbid hastalıkları olsa da 1 hasta (kronik üzerine akut böbrek hasarı) dışında ek organ yetmezliği olan hastamız yoktu.

Çalışmanın Kısıtlılıkları

Çalışmamızın kısıtlılıkları az sayıda hasta içermesi, retrospektif karakterde olması, lökoverin tedavi süresinin hastalar arasında değişiklik göstermesi ve sınırlı popülasyon nedeniyle farklı tedavi süreleri ve yanıt oranları ile ilgili karşılaştırma yapılamaması olarak sayılabilir. Literatürde düşük doz MTX ilişkili nötropeni/lökopeni; 11 yılda 15 hasta; 10 yılda 40 hasta; 8 yılda 10 hasta; 5 yılda 25 hasta sayıları ile raporlanan olgu serileri düşünüldüğünde 1,5 yılda saptanan 9 hastalık serimizde daha düşük oranda değildir.[3,5,11,13]

Hastaların klinik özellikleri, mevcut riskleri, takip ve yönetim süreçleri ayrıntılı olarak belirtilip sonuçlarımızın klinik pratikte MTX intoksikasyonu yönetimine ışık tutacağını düşünmekteyiz. Ayrıca bu açıdan riskli hastalarda, bulgularımızın tedavi başlangıcında ilaç seçimine katkısı olabilir. Örneğin serimizde doğru kullanmasına rağmen toksisite gelişen 2 hastada da KBH mevcuttu. Literatürde kreatinin klirensi 50 mL/dk altında olanlarda doz azaltılması önerilmiştir.[15] Buna dikkat edilmeden ve/veya böbrek fonksiyonlarının stabil seyretmeyeceği 2 hastada başlandığında gelişen toksisiteyi vurguladık.

Sonuç

Sonuç olarak çalışmamızdaki hastaların çoğunun nötropeni sebebi MTX yanlış yüksek günlük doz kullanımı, doğru kullanımda ise KBH risk faktörü varlığı (eGFR <55 mL/dk) olarak saptandı. Yanlış kullanma riski olan özellikle yaşlı hastalarda tedavi başında ve doz değişikliğinde yazılı ve sözlü olarak ayrıntılı açıklama önemlidir. Bu tabloda gelen hastalarda erken dönemde İV lökovorin tedavisi ve enfeksiyon kontrolü mortalite ve morbidite yönetiminde etkilidir.

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Dipnotlar

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Evaluation of ACR/EULAR 2022 ANCA associated vasculitis classification criteria: The impact of reclassification in a large cohort with long-term follow-up

ACR/EULAR 2022 ANCA ilişkili vaskülit sınıflandırma kriterlerinin değerlendirilmesi ve mevcut kriterler ile karşılaştırılması

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Abstract

Objective: To compare the performance of the EMA (European Medicines Agency) algorithm for classification of necrotizing vasculitis and the new American College of Rheumatology (ACR)/European League of Rheumatology (EULAR) 2022 classification criteria in our single center long-term anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) cohort.

Methods: Patients classified as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) according to EMA algorithm were included into the study. ACR/EULAR 2022 classification criteria were implemented retrospectively. Antibody-based classification (ABC) was performed as a third model, which classify patients either GPA or MPA if anti-proteinase 3 (PR3) or myeloperoxidase (MPO) is positive, respectively. Kappa analysis was used to explore the agreement between criteria sets.

Results: Data of 221 patients classified as GPA (85.6%) and MPA (14.5%) according to EMA algorithm were included. PR3-ANCA and MPO-ANCA was positive in 124 (56.1%) and 79 (35.7%) patients. ACR/EULAR 2022 classified 137 (62%) and 84 (38%) patients as GPA and MPA, respectively. Nine (4%) patients were classified as both GPA and MPA, nine (4%) patients were unclassifiable. The new criteria set was in weak agreement with EMA algorithm (kappa=0.28 for GPA and 0.24 for MPA). On the other hand, strong agreement with ABC was observed (kappa=0.88 for GPA and 0.89 for MPA).

Conclusion: A significant number of patients who classified as GPA could be classified as MPA with the ACR/EULAR 2022 criteria and agreement with EMA algorithm was weak. The new criteria set was indecisive for some AAV patients. Strong agreement with ABC indicated the significant influence of serology in the ACR/EULAR 2022 criteria.

Keywords: ANCA associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis, classification criteria

Öz

Amaç: Çalışmamızda tek merkezden uzun dönem takipli antinötrofil sitoplazmik otoantikor (ANCA) ilişkili vaskülit hastalarında nekrotizan vaskülitler için geliştilen Avrupa İlaç Kurumu (EMA) algoritması ve ACR/EULAR 2022 küçük damar vasküliti sınıflandırma kritlerlerinin performasını karşılaştırmayı amaçladık.

Yöntem: Çalışmamıza EMA algoritmasına göre granülomlu polianjiitis (GPA) ve mikroskopik polianjiitis (MPA) olarak sınıflandırılan hastalar dahil edildi. Amerikan Romatoloji Cemiyeti (ACR)/Avrupa Romatizma Birliği (EULAR) 2022 sınıflandırma kriterleri retrospektif olarak uygulandı. Üçüncü model olarak, antikora bağlı sınıflandırma uygulandı ve anti-proteinaz-3 (PR3) pozitif hastalar GPA, anti-myeloperoksidaz (MPO) pozitif hastalar MPA olarak sınıflandırıldı. Kriterler arasındaki uyum Kappa analizi ile değerlendirildi.

Bulgular: Çalışmaya EMA algoritmasına göre GPA (%85,6) ve MPA (%14,5) olarak sınıflandırılan toplam 221 hasta dahil edildi. PR3-ANCA 124 (%56,1) and MPO-ANCA 79 (%35,7) hastada pozitifti. ACR/EULAR 2022 sınıflandırma kriterleriyle 137 (%62) hasta GPA, 84 (%38) hasta MPA olarak sınıflandırıldı. Dokuz (%4) hasta hem GPA hem MPA olarak sınıflandırılırken, dokuz (%4) hasta sınıflandırılamadı. Yeni kriterler ve EMA algoritması arasında zayıf uyum gözlendi (GPA için kappa=0,28 ve MPA için kappa=0,24). Ek olarak, ACR/EULAR 2022 kriterleri ve antikora bağlı sınıflandırma metodu arasında yüksek uyum mevcuttu (GPA için kappa=0,88 ve MPA için kappa=0,89).

Sonuç: Önemli sayıda ANCA asosiye vaskülitler (AAV) hastasının dahil edildiği çalışmamızda daha önce GPA olarak sınıflandırılan yüksek sayıda hastanın MPA olarak sınıflandırıldığı gözlendi. ACR/EULAR 2022 ve EMA algoritması arasındaki uyum düşüktü. Yeni kriterlerle daha önce AAV olarak sınıflandırılan hastaların bir bölümü sınıflandırılamadı. Antikora bağlı sınıflandırma ve yeni kriterler arasındaki yüksek uyum yeni kriterlerde antikorların ciddi oranda etkili olduğu şeklinde yorumlanabilir.

Anahtar Kelimeler: ANCA ilişkili vaskülit, mikroskopik polianjiitis, granülomlu polianjiitis, sınıflandırma kriterleri

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises an important subset of small vessel vasculitis and includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic microscopic polyangiitis (EGPA).[1] ANCAs raise against the myeloperoxidase (MPO) and proteinase-3 (PR3) antigens in neutrophil and monocyte cytoplasm. Clinical phenotypes of GPA and MPA are highly correlated with anti-PR3 and anti-MPO antibodies. Granulomatous inflammation is the hallmark of GPA and ear, nose, throat and orbital involvement in addition to pulmonary nodules are characteristic clinical features.[2] These involvements are seldom observed in MPA, and patients often present with pulmonary-renal syndrome, defined by concurrent presence of glomerulonephritis and alveolar bleeding.[3,4]

The first classification criteria for systemic vasculitis were published by American College of Rheumatology (ACR) in 1990 and included seven different types of vasculitis including Wegener's granulomatosis (GPA) and Churg-Strauss syndrome (EGPA).[5,6] MPA was defined as a separate disease entity and AAV subgroup in 1994 and revised 2012 Chapel Hill Consensus Conference (CHCC) definitions. The substantial role of ANCAs in the pathogenesis and emergent clinical features of AAV was also highlighted.[7] To overcome the high rate of overlapping and unclassifiable cases in ACR 1990 and CHCC, Watts et al. developed a classification algorithm [European Medicine Association (EMA) classification] with a step-by-step approach in 2007 using ANCA serotype, histopathologic features and surrogate markers for Wegener's granulomatosis which previously described by Sorensen et al.[8,9] It has been extensively used in recent years for epidemiological studies on AAV.

In 2022, a new criteria set was established by ACR and European League of Rheumatology (EULAR) through Diagnostic and Classification Criteria in Vasculitis (DCVAS) project for systemic vasculitis.[10,11] These criteria set is a product of a multinational collaboration and includes the analysis of approximately 7000 patients with clinical, laboratory, histopathologic and imaging findings. The most noticeable change for the classification AAV in these criteria is the significant weight of ANCA-serotype. Emphasizing the crucial importance of serology is a novelty consistent with current knowledge, however, this approach also has raised questions about the need to classification into two different clinical phenotypes due to presence of shared clinical characteristics and treatment options.[12]

In this study, we aim to evaluate the performance of different criteria in our single centre long-term cohort of AAV patients.

Materials and Methods

Patients diagnosed with AAV in a single tertiary referral center between 1998 and 2021 were evaluated and patients classified as GPA and MPA according to EMA classification were included in this study. Patient data were collected using a predefined protocol consisted of demographic information, clinical features, laboratory, histopathologic and imaging findings. Four researchers (Bİ, NK, MB and DA) collected the data from all available patient records. In cases where there was uncertainty about the data, the researchers who followed up the patients (LO, MI, AG, YY) were contacted. Clinical diagnoses determined by clinicians who followed up the patients were obtained from patient records. Borderline cases were re-evaluated by BI and final classification of these cases was performed by senior researcher (MI). ANCA testing was performed with indirect immunofluorescence (IIF) and enzyme linked immunosorbent assay (ELISA), ELISA results were considered as true positivity in case of discrepancy.[13]

For classification purposes, ACR/EULAR 2022 classification criteria for GPA and MPA were implemented retrospectively. A final classification was performed according to ANCA-serotype, anti-PR3 and anti-MPO patients were classified GPA and MPA, respectively. The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (decision no: 75926, date: 06.07.2020).

Statistical Analysis

IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA), was used for statistical analyses. For descriptive analysis categorical variables were presented as a number and percentage, whereas the continuous variables were presented as the mean (standard deviation) or median (inter quantile range). For categorical comparisons, the chi-square test and logistic regression analysis were used. Kappa analysis was used to explore the agreement between criteria sets. A p-value less than 0.05 was accepted as statistically significant.

Results

In this study, data of 241 patients were evaluated and 221 patients were classified as GPA and MPA according to EMA algorithm. Mean age at diagnosis was 54.6±14.2 and 117 (52.9%) patients were female. PR3-ANCA and MPO-

ANCA was positive in 124 (56.1%) and 79 (35.7%) patients, respectively. Only 18 (8.1%) patients were ANCA negative. Clinical diagnosis was GPA in 165 (74.7%) patients and MPA in 56 (25.3%) patients. Table 1 provides a summary of clinical features of patients with AAV.

According to EMA algorithm, 189 (85.6%) patients were classified as GPA and 32 (14.5%) patients were classified as MPA. Classification flowchart for EMA algorithm was shown in Figure 1. One hundred twenty seven (57.5%) patients were classified as GPA (formerly Wegener's granulomatosis) according to ACR 1990 classification criteria and fulfilled the EMA algorithm step 2a. Surrogate markers for GPA were present in 185 (83.7%) patients. A total of 60 (27.1%) patients who did not meet the ACR 1990 criteria were classified as having GPA using the EMA algorithm steps 2c and 2d, based on surrogate markers.

Implementation of ACR/EULAR 2022 Classification Criteria

After implementation of ACR/EULAR 2022 criteria to our cohort, 137 (62%) and 84 (38%) patients met the criteria for GPA and MPA, respectively. Nine (4%) patients met both GPA and MPA criteria. Nine (4%) patients were unclassifiable with the new criteria. A total of 58 patients switched to other AAV subgroup with the new criteria (Figure 2).

Of the 189 patients classified as GPA with the former criteria, 130 (68.8%) fulfilled the new criteria for GPA. Eight (4.2%) of these patients met both GPA and MPA criteria. Fifty-two of 189 (27.5%) patients classified as GPA only met the new criteria for MPA.

Twenty-four of 32 patients (75%) classified as MPA with the former criteria met the ACR/EULAR 2022 criteria for MPA and one of these patients met both GPA and MPA criteria. Six of 32 (18.8%) patients classified as MPA only met the new GPA criteria (Figure 2). Three patients with histopathological examination that revealed granulomatous inflammation only met the MPA criteria. All of these patients were anti-MPO positive and had pauci-immune glomerulonephritis, one had pulmonary nodules and mononeuritis multiplex, two had pulmonary infiltrations revealed granulomatous inflammation. Interstitial lung disease (ILD) was present in 42 patients, and 28 (66%) of these patients were classified as MPA.

In eighteen patients with negative ANCA, seven and three patients met the criteria for GPA and MPA, respectively. Eight patients were unclassifiable.

The Features of Unclassifiable Patients

There was a total of nine (4%) patients who did not meet ACR/EULAR 2022 criteria. Five patients were ANCA negative patients with surrogate markers and were classified

Table 1. Selected features of patients with AAV (n=221)

	n	%		n	%
Ear nose throat involvement			Kidney involvement		
Nasal crusting	77	34.8	Asymptomatic hematuria	23	10.4
Septal perforation	29	13.1	Proteinuria	50	22.6
Saddle nose deformity	3	1.4	Nephritic syndrome	145	65.6
Tracheal stenosis	6	2.7	Glomerulonephritis in renal biopsy	133	60.2
Otitis	50	22.6	Skin involvement		
Conductive hearing loss	19	8.6	Palpable purpura	41	18.6
Sensorineural hearing loss	25	11.3	Skin ulcer	9	4
Sinusitis	94	42.5	Gangrene/infarction	1	0.5
Lung involvement			Peripheral nerve involvement		
Hemoptysis	67	30.3	Polyneuropathy	30	13.6
Nodules	104	47.1	Mononeuritis multiplex	22	10
Cavitations	44	14.9	Central nervous system involvement	14	6.3
Infiltration	74	33.5	Cardiac involvement	16	7.2
Interstitial lung disease	42	19	Urogenital involvement	6	2.7
Diffuse alveolar bleeding	30	13.6	Granulomatous inflammation in biopsy	18	8.1
Pleurisy	12	5.4	Giant cells in biopsy	2	0.9
Mucosal and eye involvement					
Oral ulcer	21	9.5			
Scleritis	37	16.7			

AAV: Associated vasculitis

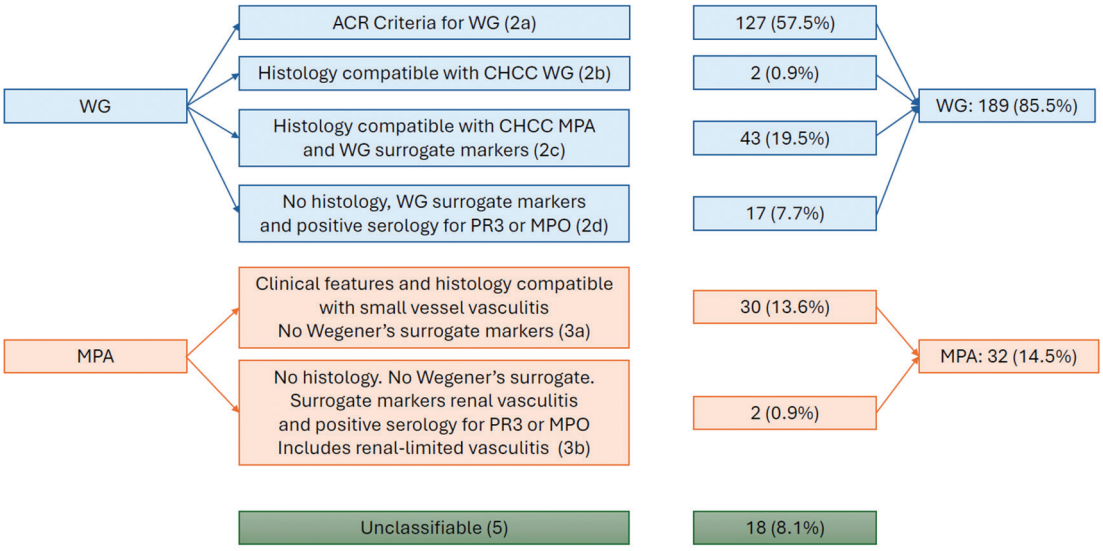

Figure 1. Classification of AAV patients with EMA algorithm
ACR: American College of Rheumatology, AAV: Associated vasculitis, CHCC: Chapel Hill Consensus Conference, EMA: European Medicine Agency, MPA: Microscopic polyangiitis, MPO: Myeloperoxidase, PR3: Proteinase-3, WG: Wegener's granulomatosis

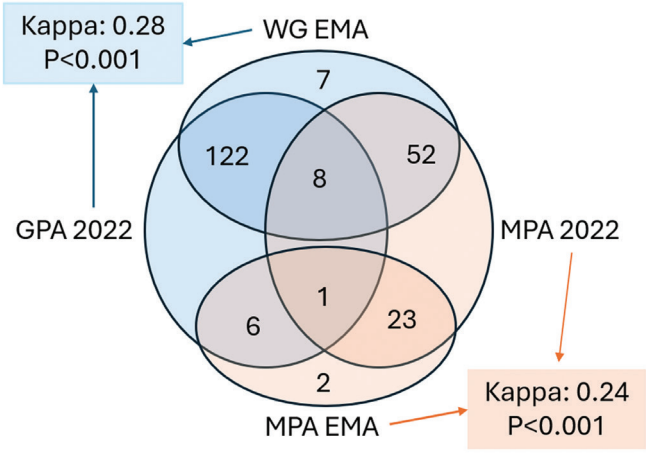

Figure 2. Venn of diagram of distribution of patients with AAV with the EMA algorithm and ACR/EULAR 2022 criteria. Significant inter-class change from WG to MPA with the new criteria could be observed. New criteria also caused overlap in 4% of patients in contrast to EMA algorithm. There was statistically significant but low level of agreement between EMA algorithm and ACR/EULAR 2022 criteria
GPA 2022: ACR/EULAR 2022 classification criteria for granulomatosis with polyangiitis, MPA 2022: ACR/EULAR 2022 classification criteria for microscopic polyangiitis
AAV: Associated vasculitis, ACR: American College of Rheumatology, EULAR: European League of Rheumatology, EMA: European Medicine Agency, GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis, WG: Wegener's granulomatosis

as GPA according to EMA algorithm. A single patient was MPO-ANCA positive with nasal involvement and sinusitis. Remaining three patients were ANCA negative renal limited vasculitis. Detailed features of unclassified patients are provided in Table 2. None of the patients had a history of asthma, nasal polyposis, eosinophilia, eosinophilic inflammation in biopsy or mononeuritis multiplex, therefore none of them could be classified as EGPA.

Kappa analysis between the EMA algorithm and ACR/EULAR 2022 criteria for GPA and MPA were both significant (p<0.001), but agreement was low (kappa=0.28 for GPA and 0.24 for MPA) (Figure 2).

Implementation of Antibody-Based Classification to the Cohort

Patients with anti-PR3 and anti-MPO positivity were classified as GPA and MPA according to antibody-based classification (ABC), respectively. A total of 124 (56.1%) patients with anti-PR3 and 79 (35.7%) patients with anti-MPO positivity were classified according to this method. Eighteen (8%) patients were unclassified. The ABC was in perfect agreement with ACR/EULAR 2022 criteria [kappa=0.89 (p<0.001)] for MPA 2022 criteria, 0.88 (p<0.001) GPA 2022 criteria. After the exclusion of double-classified patients with the ACR/EULAR 2022 criteria, two patients classified as GPA with ACR/EULAR 2022 criteria were MPO-ANCA positive, and none of the patients classified as MPA were anti-PR3 positive.

When clinical diagnosis is accepted as reference in our cohort composed of GPA and MPA patients, sensitivity and specificity of EMA algorithm for GPA is 95.2% and 42.9%, ACR/EULAR 2022 criteria for GPA is 82.5% and 100% and ABC for GPA is 75.2% and 100%, respectively. Sensitivity and specificity of EMA algorithm for MPA is 42.9% and 95.2%, ACR/EULAR 2022 criteria for MPA is 98.2% vs. 82.4%, ABC for MPA is 96.4% and 84.8%, respectively.

Table 2. Scoring of ACR/EULAR 2022 classification criteria in unclassified patients

	Nasal involvement or septal perforation (+3)	Sinusitis and mastoiditis (+1)	Hearing loss (+1)	Pulmonary nodules and cavitations (+2)	Pauci-immune GN (+1 for GPA, +3 for MPA)	Granuloma or giant cells in biopsy (+2)	ANCA	GPA criteria points	MPA criteria points
Patient 1	+	+					MPO-ANCA	3	3
Patient 2	+	+					Negative	4	-3
Patient 3				+		+	Negative	4	0
Patient 4			+	+	+		Negative	4	3
Patient 5	+						Negative	3	-3
Patient 6	+	+					Negative	4	-3
Patient 7					+		Negative	1	3
Patient 8					+		Negative	1	3
Patient 9					+		Negative	1	3

ACR: American College of Rheumatology, ANCA: Anti-neutrophil cytoplasmic antibody, EULAR: European League of Rheumatology, GN: Glomerulonephritis, GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis

Discussion

In this study, we applied the new ACR/EULAR 2022 classification criteria to patients previously classified as GPA and MPA with the EMA algorithm and observed acceptable agreement between criteria sets. High agreement between ABC and new ACR/EULAR 2022 criteria was remarkable. Another important finding was significant inter-class change between subgroups, especially from GPA to MPA.

Most rheumatological disorders, including AAV, have a multifactorial pathogenesis which is considered to be associated with the interaction of genetic and environmental factors and does not have a "gold standard" clinical, laboratory, histopathological or radiological feature for a consensus diagnosis. Therefore, development of criteria for use in clinical care and research is an important issue. Main objective of disease classification criteria is to provide a standard method to include homogenous groups of patients in clinical and epidemiological studies.[14] We included only the patients classified as AAV according to EMA algorithm to ensure the homogeneity of analysis in our cohort. In a previous study from our group, it was reported that only 1% of cases diagnosed as necrotizing vasculitis were unclassified according to EMA algorithm, which demonstrated the strength and practicality of this method.[15]

GPA and MPA are two clinical subphenotypes of AAV with significant differences in geographical distribution, genetic background, clinical features, and prognostic outcomes. In epidemiological studies, a higher prevalence of GPA and MPA was reported in Caucasian and Asian populations, respectively. This finding can be largely explained by diverse genetic background of these two subsets which lead to either anti-PR3 or anti-MPO positivity.[16,17] Therefore, the dichotomous classification of these clinical subgroups against each other has significant importance for such studies. In our cohort, 85% and 62% of cases were classified as GPA according to EMA algorithm and ACR/EULAR Classification criteria, respectively. These results were similar to the previous studies from Germany, France, and the United Kingdom, which reported a doubling prevalence of GPA compared to MPA.[18-20] As surrogate markers were detected in over 80% of patients, a greater number of patients were categorized as GPA based on the EMA algorithm in our study.

Implementation of the updated criteria led to a reclassification of 27.5% of patients initially labelled as GPA into the MPA subgroup in our cohort. 56 of 189 (29.6%) patients with anti-MPO positivity classified as GPA with former criteria due to presence of surrogate markers and this relatively high anti-MPO positivity in GPA might explain this finding. Similarly, a South Korean study that included 65 patients with GPA, 28 of whom tested positive for anti-MPO, reported 16 (24.5%) patients to be reclassified as MPA.[21] This change was thought to result from higher sensitivity of EMA algorithm for GPA, which may have contributed to the low agreement between the criteria sets. Upper airway involvement, which is the main component of surrogate markers, is not an exclusive finding to GPA. It was reported as high as 25.8% in 325 patients with MPA in a study from DCVAS group.[22] In this regard, we believe that including antibodies in the criteria is a significant improvement.

Another reason for the low agreement may be the underemphasis of specific clinical findings in the new criteria. Three patients with granulomatous inflammation on biopsy were classified as MPA in our cohort. This subgroup of patients is contradictory to 2012 Chapel-Hill consensus criteria which underlined the importance of granulomatous pathology in GPA and should be approached with caution.[7] Additionally, one third of patients with ILD could not

be classified as MPA in our cohort, due to PR3-ANCA positivity. With regard to pathogenesis, we believe that these specific histopathological and radiological findings should be adequately emphasized in the new criteria, regardless of antibody status.

Nine patients (4%) did not meet the new criteria in our cohort. Among these patients, one MPO-ANCA positive and three ANCA-negative patients with limited upper airway disease and sinusitis couldn't be classified as AAV. Granulomatous involvement in the upper airway is recognized as a significant predictor of treatment resistance.[23] Therefore, we suggest that more inclusive enrolment of patients with upper airway vasculitis in clinical trials may be necessary, particularly those with positive ANCA. Additional 3 unclassifiable patients had ANCA-negative renal limited disease. More than 20% of patients with AAV and glomerulonephritis were reported to have negative ANCA in cohort studies.[20] Due to the high rate of end-stage kidney disease and death in these patients, careful application of treatment recommendations are important.[24] We believe that the failure to categorize these patients, diagnosed with small vessel vasculitis and classifiable under previous criteria, is an important drawback.

Our attempt to explore ABC in our cohort disclosed strong agreement with the new criteria, along with close sensitivity and specificity. When the two methods were compared, the new criteria classified only 4% more patients than ABC and a change from GPA to MPA was observed in three patients. Therefore, ABC might have similar sensitivity for inclusion in both epidemiological studies and clinical trials. The authors of the criteria also concluded that this criteria set is only useful for the discrimination between AAV subgroups rather than making differential diagnoses or discrimination from potential mimickers.[10] This warning should be considered cautiously in the routine clinical practice as the excessive weight of ANCA in the criteria might be misleading due to non-vasculitic conditions that can cause ANCA positivity, such as inflammatory bowel disease, infective endocarditis, and malignancies.[25-27] Rathmann et al.[28] reported a concordance of 98% for GPA and 84% for MPA between ACR/EULAR 2022 criteria and ABC in a study from Sweden similar to our study, showing that our results are applicable to diverse patient cohorts as well.

Study Limitation

The main limitation of our study is the collection of the data retrospectively, in a large patient group extending to 25 years in some patients. The inclusion of patients in the study over a long time period may have led to missing information in the patient data and patient selection bias. To overcome these issues, we used predefined protocol to collect the patient data and included the patients only classifiable according to the EMA algorithm in our study. We believe that exclusion of patients who are unclassifiable according to EMA algorithm ensured consistency on the results. Additionally, the exclusion of EGPA patients could be considered a limitation and caused a decrease in patient count. The rationale for the exclusion was the distinct clinical features and relatively low ANCA positivity of EGPA patients. Unclassifiable patients in our cohort also did not meet ACR/EULAR 2022 EGPA criteria. A final important concern is the possible usage of IIF for ANCA testing in the early years of our cohort. However, we think that long-term follow-up in a single-center cohort with the same investigators ensured homogenization in data collection.

Conclusion

In conclusion, our findings suggest that while the new criteria introduce novelty regarding the cohorts eligible for inclusion in clinical research but may fail to change the approach in drug trials due to collective enrolment in these studies. Also, the fact that ANCA positivity can manifest in mimicking conditions such as chronic infections, drug reactions, and malignancies might pose challenges in clinical practice and patient selection for trials. Adequate differentiation also may not be reached in the presence of disease-specific findings such as granulomatous inflammation in histopathology and interstitial lung disease. Further studies on the validation of the criteria and review of scoring in diverse patient groups may be needed.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (decision no: 75926, date: 06.07.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.İ., N.K., M.B., D.A., Y.Y., A.G., M.L.Ö., M.İ., Concept: B.İ., M.B., Design: B.İ., N.K., M.B., Data Collection or Processing: B.İ., N.K., M.B., D.A., Analysis or Interpretation: B.İ., N.K., M.B., Y.Y., A.G., M.L.Ö., M.İ., Literature Search: B.İ., D.A., Writing: B.İ., M.B., Y.Y., A.G., M.L.Ö., M.İ.

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Letter to the Editor / Editöre Mektup

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Case that could be misleading in the diagnostic process: Differentiating between DISH and AS

Tanı sürecinde yanıltıcı olabilecek bir olgu: DISH ve AS arasındaki ayrım

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Keywords: DISH, axSpA, spinal hyperostosis, sacroiliac joint
Anahtar Kelimeler: DISH, axSpA, omurga hiperostozu, sakroiliak eklem

Dear Editor,

Although its etiology is largely unknown, the prevalence of diffuse idiopathic skeletal hyperostosis (DISH), which has been closely associated with obesity, diabetes, cardiovascular diseases, and metabolic syndrome, ranges from 2.9% to 27%. The differential diagnosis of DISH and spondyloarthropathy should be made carefully because of enthesal new bone formation in the spinal and peripheral regions, frequent involvement of the lower part of the thoracic spine and the upper part of the lumbar spine, and similar radiographic findings.[1]

The confusion between DISH and ankylosing spondylitis (AS) stems from overlapping clinical symptoms and radiologic findings. Both conditions predominantly affect the axial skeleton, causing spinal stiffness, reduced mobility, and postural abnormalities. In addition, they can present with similar symptoms such as chronic back pain, and morning stiffness, which can lead to confusion in the diagnostic process.

Moreover, the radiographic features of DISH, such as ossifications running along the anterior aspect of the vertebral bodies, sacroiliac joint involvement, and ligamentous ossification, can closely mimic the characteristic findings observed in AS, such as syndesmophytes, sacroiliitis and bamboo spine appearance. This radiologic similarity may lead to misinterpretation or misdiagnosis, especially when patients exhibit atypical clinical features.[2]

The aim of this paper is to underline the difficulty in the differential diagnosis process between DISH and AS due to common clinical features and radiologic findings. Clinical suspicion combined with advanced imaging techniques and a thorough understanding of the unique features of each condition is essential to ensure accurate diagnosis and appropriate management strategies.

Case

A 62-year-old male patient presented to our outpatient clinic with complaints of persistent hip, back, and lower back pain, which started one year ago. He reported morning stiffness lasting slightly more than 30 minutes and worsening with physical activity. He stated that his complaints partially decreased with the use of non-steroidal anti-inflammatory drugs. There is no description of pain that wakes him up from sleep at night. He also did not report a history of trauma. His medical history included hypertension, diabetes mellitus, dyslipidemia, and obstructive sleep apnea syndrome.

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The patient stated that he had been on anti-tumor necrosis factor (TNF) therapy for the past 6 months, but there had been no improvement in symptoms.

During the physical examination, active movements of the lumbar and thoracic spine were painful and limited at the end of the range of motion. The modified Schober test was negative, and chest expansion was normal. The patient did not report pain in the sacroiliac joint region during bilateral Gaenslen and Patrick-FABER tests. No neurological deficits or pathological reflexes were detected.

Serum C-reactive protein, tumor markers, thyroid, liver and kidney function tests, erythrocyte sedimentation rate and complete blood count were among the laboratory tests showing results within normal ranges.

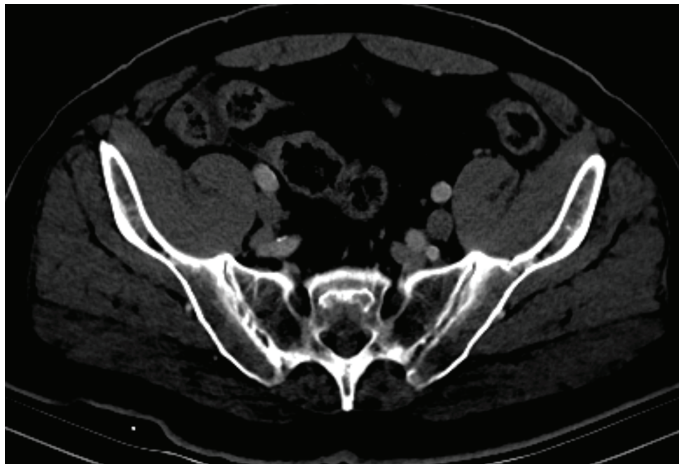

Figure 1. Bridging ossification is seen at the anterior and superior aspects of the sacroiliac joints in this CT scan
CT: Computed tomography

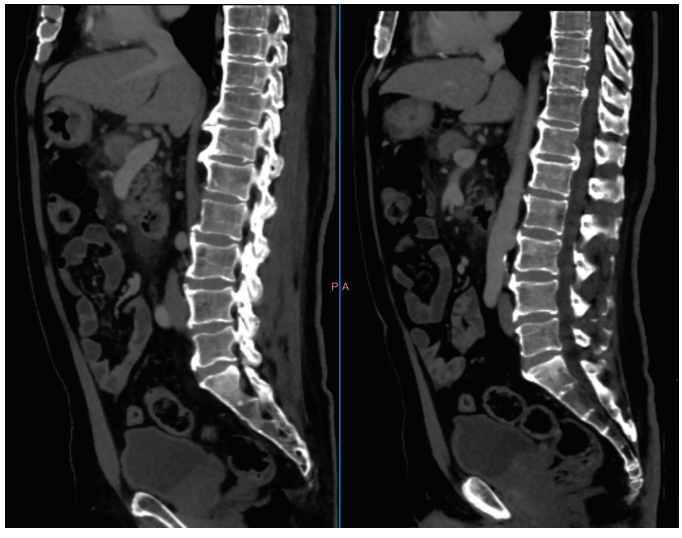

Figure 2. A) Ossification along the anterior longitudinal ligament of the thoracolumbar vertebrae with relatively preserved disc spaces. B) Ossification along the posterior longitudinal ligament of the thoracolumbar vertebrae with relatively preserved disc spaces

Review of the thoracolumbar two-way spine X-ray and computed tomography previously taken at an external center revealed osteophytes forming a bridge anterior to the sacroiliac joint (Figure 1) and bony protrusions associated with mild to moderate degenerative changes at the vertebral level (Figure 2).

Following our request, lumbar vertebra and sacroiliac joint magnetic resonance imaging (MRI) examinations were performed. MRI of the sacroiliac joints did not show signs of active sacroiliitis in both sacroiliac joints and on the iliac and sacral surfaces forming the joint. Bilateral sacroiliac joint distance was reduced, particularly in the anterior aspect, with a mild appearance of fusion in the anterior aspect (Figure 3). The lumbar vertebra MRI did not reveal any inflammatory findings but showed osteophytic protrusions at multiple levels of the anterior vertebral bodies.

As a result of the evaluations, the patient was diagnosed with DISH. The anti-TNF therapy was discontinued, and the patient was included in a physical therapy program at our clinic.

Research indicates that DISH is characterized by enthesopathy of the sacroiliac joint capsule and anterior and posterior ligaments, as well as bridging and fusing enthesophytes inside the joints, which imitate the joint ankylosis of AS.[3] As in our patient, sacroiliac joint changes accompanying changes at the vertebral level were observed on tomography. MRI was needed to support our diagnosis radiologically.

For the clinical examination of symptomatic, painful, or post-traumatized DISH patients, MRI is now the suggested imaging modality. When other imaging modalities are

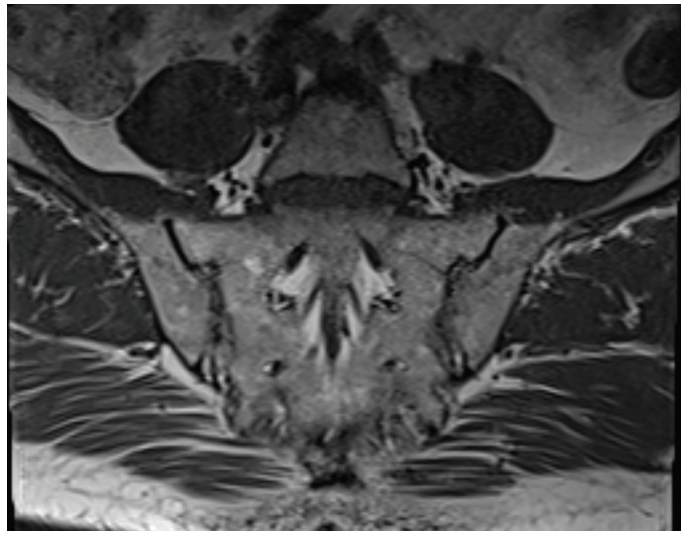

Figure 3. Bridging ossification is seen at the anterior and superior aspects of the sacroiliac joints in this MRI
MRI: Magnetic resonance imaging

ineffective, MRI can aid in the distinction between DISH and AS. Determining a relationship between DISH imaging characteristics and clinical findings could help in the early diagnosis of DISH.[4]

Conclusion

In conclusion, we believe that a careful evaluation of clinical, laboratory, and imaging findings, as demonstrated in our case, will shed light on the differential diagnosis process.

Footnotes

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

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Letter to the Editor / Editöre Mektup

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Mimicking inflammatory sacroiliitis: Bertolotti syndrome

Enflamatuvar sakroiliiti taklit etme: Bertolotti sendromu

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Keywords: Bertolotti syndrome, low back pain, inflammatory sacroiliitis, pseudoarthrosis, differential diagnosis
Anahtar Kelimeler: Bertolotti sendromu, bel ağrısı, enflamatuvar sakroiliit, psödoartroz, ayırıcı tanı

Dear Editor,

Bertolotti syndrome is a variation in the lumbosacral transition articulating with the sacrum or ilium, characterized by the presence of a transverse mega-apophysis, which leads to a change in the biomechanics of the axial skeleton.[1] Although the prevalence in the general population is uncertain due to underdiagnosis, it is estimated to range from 4% to 30%. Among patients with complaints of low back pain, 4-8% may be diagnosed with Bertolotti syndrome. Most patients are asymptomatic, but the likelihood of developing clinical symptoms is higher when it is asymmetric. Typically, it presents with low back pain after the second decade of life.[2,3]

The purpose of this case presentation is to highlight that Bertolotti syndrome can mimic inflammatory sacroiliitis, emphasizing its rarity and clinical significance in the young population.

Case: A 37-year-old male patient presented to us with complaints of pain radiating to the lower back and right gluteal region for the past three months. The patient reported morning stiffness lasting more than 30 minutes and noted that his symptoms were provoked by physical activity. He reported that his complaints were reduced with the use of non-steroidal anti-inflammatory drugs. However, there was no description of pain waking him from sleep at night. Despite elevated sedimentation levels, rheumatological examination revealed no significant findings, and the patient had no comorbidities. He also had a family history of colon cancer.

On physical examination, inguinal tenderness was detected. The range of motion of the spine and bilateral hip joints was normal. The patient experienced pain in the sacroiliac joint region on the right side during the Gaenslen and Patrick-FABER tests. The modified Schober test yielded normal results. The straight leg raise test was negative. No neurological deficits or pathological reflexes were observed.

Pelvic radiograph revealed a transverse mega-apophysis of the L5 vertebra, articulating with the sacral ala (Figure 1). Magnetic resonance imaging examination revealed a hyperintense change in the T2A sequence and a hypointense large intensity change in the T1A sequence in the right wing of the sacrum at the right sacroiliac level (Figure 2).

The history, examination findings, and imaging results were evaluated, leading to the conclusion that the cause of the underlying inflammatory changes might be pseudoarthrosis between the right transverse process of L5 and the right sacral ala.

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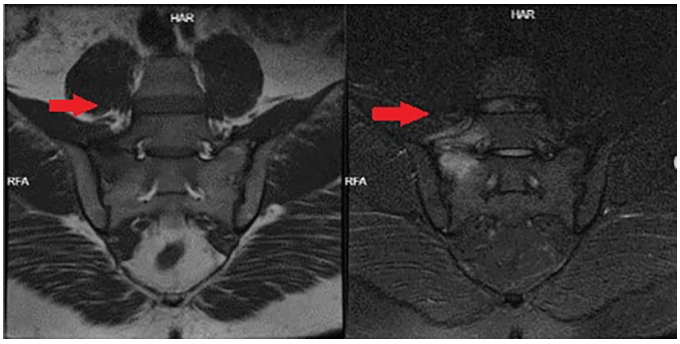

Figure 1. MRI examination revealed a hyperintense change in the T2A sequence and a hypointense large intensity change in the T1A sequence in the right wing of the sacrum at the right sacroiliac level
MRI: Magnetic resonance imaging

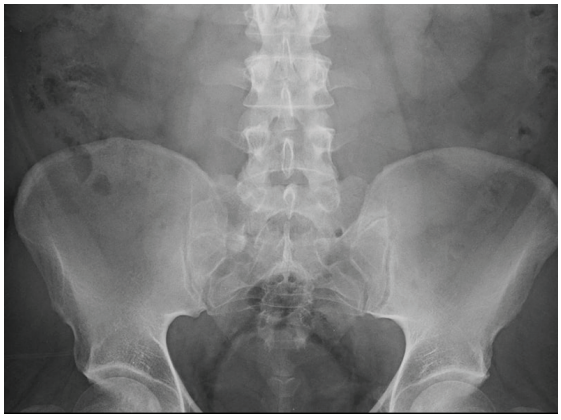

Figure 2. Pelvic radiograph, transverse mega-apophysis view of the L5 vertebra articulating with the bilateral sacral ala

A conservative treatment approach was chosen for the patient, including a physical therapy program and the prescription of analgesics. The treatment approaches for Bertolotti syndrome vary depending on the severity of the symptoms. Conservative management typically includes physical therapy and the use of analgesics. However, in resistant cases, interventional procedures such as steroid injections or surgical resection of the pseudoarthrosis may be necessary. With appropriate treatment, the long-term prognosis is generally positive, although some patients may continue to experience chronic pain.[4]

In diagnosing Bertolotti syndrome, it is important to differentiate it from other causes of lower back pain, such as degenerative disc disease, facet joint arthritis, and spondyloarthritis. While each of these conditions has its unique clinical and radiological features, they can present with similar clinical pictures. Additionally, it is crucial to keep in mind the possible coexistence of Bertolotti syndrome and spondyloarthritis,

This case is one of the rare examples that clearly demonstrate that Bertolotti syndrome can mimic inflammatory sacroiliitis and emphasizes the importance of thorough evaluation in the differential diagnosis of low back pain. Careful correlation of clinical, laboratory, and imaging findings provides valuable insights into the diagnostic challenges and management of Bertolotti syndrome.

Note: The patient was informed about the publication of the case report and written consent was obtained.

Footnotes

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