

Rheumatic diseases detected in patients presenting with uveitis

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ABSTRACT

OBJECTIVE: Uveitis may occur in the course of systemic inflammatory rheumatic diseases (IRD), or it may be the first clinical manifestation of these diseases. The aim of this study was to determine the incidence of IRD in patients whose initial clinical manifestation was non-infectious uveitis.

METHODS: The study included adult patients diagnosed as having noninfectious uveitis in the department of ophthalmology and referred to rheumatology for further investigation of potential rheumatic diseases as underlying etiology of uveitis. The patients' demographic and clinical features, laboratory, and imaging findings were examined.

RESULTS: One hundred six patients who were diagnosed as having uveitis (42.4% anterior, 2.8% intermediate, 19.8% posterior, and 34.9% panuveitis) were included. Just over half (52.8%) of the patients were male and the mean age was 40.1±14.8 years. The mean age at the uveitis attack was 38.7±15 years. One-third (33%) of the patients were diagnosed as having rheumatologic disease (spondyloarthritis (SpA) n=10, Behcet disease (BD) n=17, vasculitides n=2, sarcoidosis n=2, undifferentiated connective tissue diseases n=3, rheumatoid arthritis n=1). SpA was diagnosed in 20% of patients presenting with anterior uveitis. BD was detected in 27% of patients referred with panuveitis and in 33.3% of patients whose first clinical finding was posterior segment involvement. Bilateral uveitis was detected in two-thirds of patients with posterior uveitis and tended to recur more frequently (p=0.014).

CONCLUSION: Rheumatic diseases have been identified in approximately one-third of patients presenting with different types of uveitis. Investigations addressing systemic rheumatic diseases are of paramount importance in patients with uveitis because they may change diagnosis and treatment processes.

Keywords: Behcet disease; spondyloarthritis; uveitis.

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Uveitis is an inflammatory disorder of the part of the eye known as the uvea, which consists of the iris, ciliary body, and choroid [1, 2]. Uveitis, which accounts for 9–15% of blindness cases in Western countries [3], is one of the most important ocular findings detected in rheumatology clinics. Uveitis is among the causes of

preventable blindness; therefore, it requires immediate treatment once diagnosed [4]. In a study conducted in the United States, the prevalence of non-infectious uveitis in adults was 121 cases per 100,000 [5]. In a recent study evaluating 6191 patients with uveitis, sarcoidosis (n=348) was the most common IRD in etiology,

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followed by AS (n=158) and BD (n=158) [6]. The difference of our study is that it investigates which IRDs are at the forefront in Turkish patients whose first clinical symptom is uveitis.

Any damage to the blood-retinal barrier that limits access to the micro-environment of the eye may play an essential role in the development of uveitis. The main factors contributing to the pathophysiology of uveitis include genetic factors associated with susceptibility to endothelial damage, and inflammatory cell recruitment, mainly including T-helper 1 (Th1), T-helper 17 (Th17), macrophages, and inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) [7].

Patients most often present with symptoms such as blurred vision, eye pain, and sensitivity to light. The underlying causes of uveitis include infectious diseases, trauma, masquerade syndromes, systemic immune-mediated diseases, medication reactions, and conditions limited to the eye. Ocular inflammation may be a signal for the onset or severity of immune reactivation in systemic rheumatic diseases [8]. This single-center study aimed to determine the incidence of systemic IRD in patients presenting with noninfectious uveitis and demographic and clinical characteristics in patients with confirmed rheumatic diseases.

MATERIALS AND METHODS

This study included 106 adult patients who were diagnosed as having noninfectious uveitis in the Ophthalmology Clinic and further evaluated at rheumatology between October 2018 and March 2021. Patients with infectious uveitis or diagnoses of rheumatic disease before the uveitis attack were excluded from the study. Of 203 patients with uveitis, 25 patients aged younger than 18 years, and 25 patients who were not referred for rheumatologic evaluation were excluded from the study. In addition, 23 patients with missing data, nine patients with Vogt-Koyanagi-Harada syndrome, and 15 patients with a rheumatic disorder before the uveitis attack were excluded.

Data on sociodemographic characteristics (age, gender), habits (tobacco use, current medications), family history of rheumatic diseases, time to diagnosis, type of involvement in uveitis (unilateral or bilateral), localization (anterior, intermediate, posterior, panuveitis) of uveitis, number of uveitis attacks, laboratory parameters, and radiologic findings were evaluated.

Highlight key points

- Rheumatic diseases were found in about one-third of patients who presented with different types of uveitis.
- SpA was diagnosed in 20% of patients presenting with anterior uveitis.
- Behcet Disease was detected in 27% of patients referred with panuveitis and in 33.3% of patients whose first clinical finding was posterior segment involvement.
- Bilateral uveitis was detected in two-thirds of patients with posterior uveitis and tended to recur more frequently.

The patients were questioned about the signs and symptoms of all systemic IRDs. Physical examination of each referred patient was performed by an experienced rheumatologist. The patients' baseline acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate), complete blood count, human leukocyte antigen (HLA)-B27 subtype, angiotensin-converting enzyme (ACE), anti-nuclear antibody (ANA), extractable nuclear antibody (ENA), anti-neutrophilic cytoplasmic antibody (ANCA), and pathergy test results were analyzed. Pelvis radiographs were assessed according to the modified New York criteria [9]. If available, inflammatory changes on sacroiliac magnetic resonance imaging (MRI) were recorded [10]. Lung radiographs and, if present, chest tomography were evaluated in terms of pulmonary nodules, cavitation, ground glass appearance, fibrosis, and hilar adenopathy. Those who met the recent classification or diagnostic criteria were considered to have rheumatological disease.

Ethics

The study was conducted with the permission of Dokuz Eylul University Faculty of Medicine, Non-invasive Clinical Ethics Committee (No: 2021/15-23; Date: 21.05.2021). All participants gave written informed consent to participate in the study. All procedures were performed according to the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

Data obtained in the study were evaluated using the IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA) program. The Kolmogorov–Smirnov normality test was used to determine the distribution pattern of the variables. Continuous variables were presented as mean \pm standard deviation (SD) and nominal and ordinal data were ex-

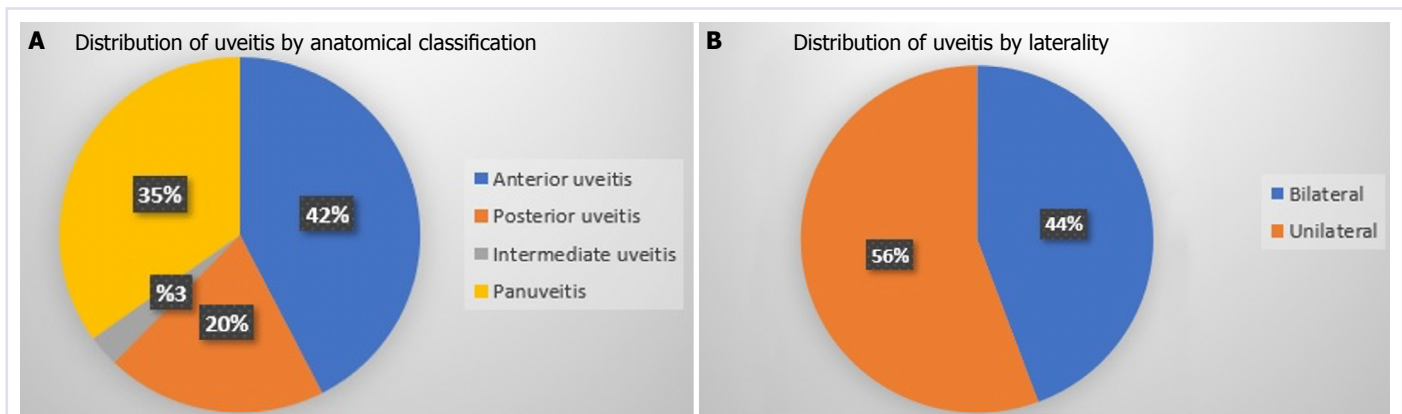


FIGURE 1. (A) Distribution of uveitis by anatomical classification. (B) Distribution of uveitis by laterality.

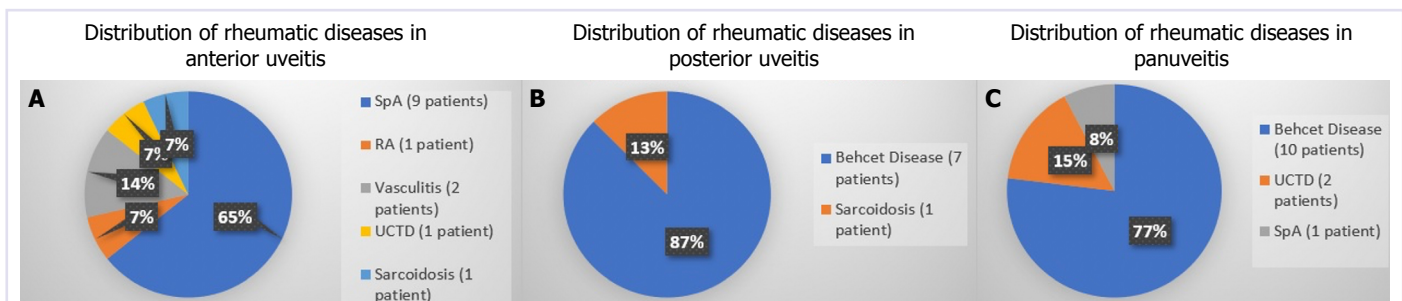


FIGURE 2. Distribution of rheumatic diseases according to the affected eye segment.

pressed as percentages. Mann-Whitney U test and χ^2 test were used to compare quantitative and qualitative data, respectively. The significance level was set at $p < 0.05$.

RESULTS

This study included 106 patients who were referred to the Department of Rheumatology due to noninfectious uveitis as a presenting manifestation. Overall, 52.8% of the patients were males ($n=56$), and the mean age was 40.19 ± 14.82 years. The mean age at the time of the uveitis attack was 38.7 ± 15.02 years. Forty-five (42.4%) patients had anterior uveitis, 2.8% ($n=3$) had intermediate uveitis, 19.8% ($n=21$) had posterior uveitis, and 34.9% ($n=37$) had panuveitis (Fig. 1A). Although the rates of unilateral and bilateral uveitis were comparable, unilateral uveitis was more common (Fig. 1B). Around one-quarter (26.4%) of the patients were smokers. Thirty-eight (35.8%) of the patients had increased acute-phase reactants. IRD was detected in 44.7% ($n=17$) of the patients with acute-phase reactant elevation. A diagnosis of IRD was made in 33% ($n=35$) of patients. None of these patients had been diagnosed as having a rheumatic disorder

before presenting with uveitis. The demographic and clinical characteristics of the patients are summarized in Table 1.

Bilateral uveitis was present in 44.3% ($n=47$) of patients in this cohort, whereas 51.4% ($n=18$) of patients with IRD had bilateral involvement. Bilateral uveitis was most common in BD ($n=11$), followed by SpA ($n=3$), sarcoidosis ($n=2$), vasculitis ($n=1$), and UDCTD ($n=1$). Some of the patients (37.7%) experienced a single uveitis attack and the others had recurrent uveitis. Almost half (47.2%) of patients presented to rheumatology clinics during the first uveitis attack and 52.8% of patients were referred in the presence of recurrent uveitis. When compared according to localization, non-anterior uveitis was associated with a higher rate of bilateral involvement ($p=0.023$). A tendency towards unilateral involvement was more prominent in cases of anterior uveitis compared with other types of uveitis. The age at the time of the uveitis attack was significantly higher in patients with anterior uveitis than those with other uveitis types (43.1 ± 16.31 and 35.4 ± 13.21 , respectively) ($p=0.09$). The characteristics of anterior uveitis and other uveitis types are compared in Table 2.

TABLE 1. Demographic and clinical findings of patients (n=106)

Age, years*	40.1±14.8
Gender (male), (%)	52.8
Smoker, (%)	26.4
Uveitis attack age, years*	38.7±15
Uveitis type, (%)	
Anterior	42.5
Intermediate	2.8
Posterior	19.8
Panuveitis	34.9
Unilateral uveitis, (%)	55.7
Bilateral uveitis, (%)	44.3
Number of uveitis attacks in rheumatology admission, (%)	
First attack	47.2
Recurrent attack	52.8
Diagnoses rheumatologic diseases, n (%)	35 (33)
Spondyloarthritis	10 (9.4)
Behcet disease	17 (16.0)
Sarcoidosis	2 (1.9)
Rheumatoid arthritis	1 (0.9)
UDCTD	3 (2.8)
Vasculitis	2 (1.9)
Elevated acute phase reactant	38 (35.8)
CRP level during uveitis attack mg/L*	7.6±16.6
ESR level during uveitis attack, mm/hr*	19.3±17.3
Treatment for uveitis, n (%)	
Steroid (oral)	33 (31.1)
Azathioprine	33 (31.1)
Cyclosporine	5 (4.7)
Adalimumab	11 (10.4)
Infliximab	3 (2.8)
Interferon-alpha	5 (4.7)

UDCTD: Undifferentiated connective tissue disease; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; *: Mean±Standard deviation.

The diagnosis of a systemic IRD was made in 31% of patients who presented with anterior uveitis, 38% of patients with posterior uveitis, and 35% of patients who presented with panuveitis. In this study, the incidence of IRD was 33% in the group of patients in whom non-infectious uveitis was the initial manifestation. IRDs detected in these patients and their distribution was as follows: BD (n=17), SpA (n=10), UDCTD (n=3), vasculitis (n=2), sarcoidosis (n=2), and rheumatoid arthritis (RA) (n=1). IRDs were more common in patients with recurrent uveitis attacks compared with those who

had a single attack (p=0.015). Anterior uveitis tended to be unilateral (p=0.023). Ninety percent of patients diagnosed as having SpA had anterior uveitis. In patients with BD, 41.2% had posterior uveitis and 58.8% had panuveitis. In patients with panuveitis, uveitis tended to recur (p=0.01). The distribution of IRDs by localization of uveitis is shown in Figures 2A, 2B, and 2C.

The review of clinical signs and symptoms of patients revealed that aphthous ulcerations of the oral mucosa, acneiform eruptions, and arthralgia were the most common findings, while constitutional symptoms were not observed. One-third of patients experienced back pain and 45.7% of these patients' pain had inflammatory characteristics. Uveitis affected the anterior chamber in 85.2% of patients who were experiencing morning stiffness exceeding 30 minutes (p=0.04). SpA was detected in 20% of patients presenting with anterior uveitis in the entire cohort. The sex distribution of the patients diagnosed with SpA was similar and the mean age was 39±15.33 years. Most patients (70%) had unilateral uveitis. Two-thirds of HLA-B27-positive patients (n=12) were diagnosed as having SpA. The other two patients with SpA were HLA-B27 negative. The review of available X-rays revealed syndesmophytes in two out of 25 cervical X-rays, bamboo spine in one out of 59 thoracolumbar radiographs, sacroiliitis in five out of 79 pelvic X-rays, and enthesitis in five out of 29-foot radiographs. All patients with syndesmophytes, bamboo spine, or sacroiliitis and two patients with enthesitis were diagnosed as having SpA. HLA-B27 positivity, sacroiliitis on pelvic X-ray, morning stiffness for >30 minutes, inflammatory back pain (IBP), and heel pain were significantly more common in patients diagnosed as having SpA (p<0.001, p<0.001, p=0.018, p=0.014, and p=0.007, respectively).

BD was detected in 27% of patients referred with panuveitis and in 33.3% of patients whose first clinical presentation was posterior uveitis. The mean age was 30±9.0 years in 17 patients with BD, 76.5% of these patients were male, and two out of these 17 patients had incomplete BD. In patients diagnosed with BD, oral aphtha (n=17), genital ulcer (n=9), and acneiform rash (n=8) were most frequently observed, followed by erythema nodosum-like lesions (ENLL) (n=4), DVT (n=4) and pathergy positivity (n=2). Forty percent of HLA-B51-positive patients (n=5) were diagnosed as having BD. Panuveitis was present in 58.8% of the patients diagnosed with BD, and posterior uveitis was present in the remainder. Posterior chamber involvement,

TABLE 2. Comparison of the features of anterior uveitis and other types of uveitis

	Anterior uveitis (%)	Other uveitis (%)	p
Gender (male)	40	62.3	0.023
Uveitis attack age*	43.1 (±16.3)	35.4 (±13.2)	0.009
Uveitis diagnosis duration*	5.46 (±4.6)	5.56 (±6.0)	0.931
Uveitis side			0.023
Unilateral	66.7	47.5	
Bilateral	33.3	52.5	
Number of uveitis attacks			0.221
1	44.4	32.8	
≥2	56.6	67.2	
Uveitis attack status at the time of admission to rheumatology			0.616
First attack	51.1	44.3	
Recurring attack	48.9	55.7	
HLA-B27 positivity, n (%)	9 (20)	3 (4.9)	0.039
SpA diagnosis, n (%)	9 (20)	1 (1.6)	0.002
Inflammatory back pain, n (%)	10 (22.2)	6 (9.8)	0.174
Morning stiffness >30 minutes, n (%)	6 (13.1)	1 (1.6)	0.04

HLA: Human leukocyte antigen; SpA: Spondyloarthritis; *: Years, Mean±Standard deviation.

recurrent uveitis attacks, aphthous lesions in the oral mucosa, genital ulcerations, acneiform eruptions, ENLL, and HLA-B51, and pathergy test positivity were significantly more common in patients with BD ($p=0.002$, $p=0.033$, $p<0.001$, $p<0.001$, $p=0.001$, $p=0.012$, $p=0.03$, and $p=0.04$, respectively).

In our study, both patients diagnosed with vasculitis were male and had hematuria, proteinuria, decreased glomerular filtration rate, *c*-ANCA and PR3 positivity, and elevated acute phase reactants. There were ground glass areas and nodules on lung imaging of a patient with hemoptysis. The diagnosis of granulomatosis with polyangiitis (GPA) was confirmed through kidney biopsies showing crescentic glomerulonephritis in both patients.

Both patients with sarcoidosis had granulomatous uveitis; one patient had anterior and the other had posterior uveitis. Computed tomography of the lung revealed enlarged hilar and mediastinal lymph nodes in both patients and the diagnosis was confirmed through endobronchial lymph node biopsy in one patient and skin biopsy from an erythema nodosum lesion in the other patient. Potential differential diagnoses were excluded based on clinical and laboratory findings and in terms of mycobacterium tuberculosis; no acid-fast bacillus was

observed in cultures of biopsy materials. ACE levels were elevated in 13.2% of all patients and only one was diagnosed with sarcoidosis.

Thirty-seven (34.9%) of all patients had ANA positivity, the nucleolar pattern was the most frequent. Three female patients were diagnosed with UDCTD. The mean age of these patients was 43 ± 10.6 years, and all patients had ANA positivity in the nucleolar pattern.

In this study, the only patient diagnosed as having RA was a 20-year-old male who had experienced his first uveitis attack in childhood. He was diagnosed as having RA during follow-up based on typical arthritis patterns and imaging findings.

A review of treatments used in the treatment of non-infectious uveitis showed that 44.3% of patients ($n=47$) received only topical treatment, while others required systemic treatment. The use of topical steroids and cycloplegic agents was more common ($p=0.003$ and $p<0.001$, respectively) in the treatment of anterior uveitis, whereas the use of oral steroids, azathioprine, and intravitreal steroid administration was more common ($p=0.002$, $p<0.001$, and $p=0.038$, respectively) in the treatment of panuveitis. Monoclonal TNF- α agents such as adalimumab (24.1%, $n=11$) and infliximab ($n=3$) were the preferred agents in the treatment of posterior uveitis.

DISCUSSION

Uveitis is an important clinical problem that causes visual morbidity and should be managed in collaboration with ophthalmologists and rheumatologists. IRDs were detected in approximately one-third of our patients presenting with different types of uveitis. SpA was diagnosed in 20% of patients presenting with anterior uveitis. BD was detected in 27% of patients referred with panuveitis and in 33.3% of patients whose first clinical manifestation was posterior uveitis.

In a multicenter Spanish study, the prevalence of uveitis in all age groups was 56.2 per 100,000. In terms of anatomical distribution, anterior uveitis was the predominant form with a rate of 83.2%, followed by panuveitis (9.8%) and posterior uveitis (4.3%). In this study, although idiopathic cases (48.4%) constituted the largest group, the main etiology was autoimmune disorders (23.5%) in the group with any cause. The most common autoimmune disorder leading to uveitis was AS (43.2%), followed by sarcoidosis (10.7%), other SpA (8.3%), psoriatic arthritis (7.1%), BD (7.1%), ANCA-associated vasculitis (2.4%), and RA (2.4%) [11]. Anterior uveitis was also the most common form in our study. However, unlike this study, only adult patients with noninfectious uveitis were included in our study. We found that the most frequent systemic IRDs underlying uveitis were BD (48.5%) and SpA (28.5%), respectively. The higher incidence of BD compared with other autoimmune etiologies in our study may be related to geographic or ethnic differences. In a recent study conducted in Iran, anterior uveitis was the most common (35.8%) in patients referred to rheumatology, while the most common IRD was BD (21.7%) [12]. This may also be related to the fact that posterior or panuveitis is referred to rheumatology more often compared to anterior uveitis in the first attack.

The predominance of unilateral uveitis in our study sample may result from the higher rate of anterior uveitis (42.5%) in the group. The tendency of panuveitis to recur more frequently than other forms and the higher frequency of IRD in patients with recurrent uveitis attacks can be explained by their higher systemic inflammatory load.

The presence of the HLA-B27 antigen may be associated with acute anterior uveitis or it could be associated with underlying SpA. The prevalence of HLA-B27 may differ between ethnic groups. HLA-B27 carriage rates are highest in Caucasians and vary from 8 to 10% [13].

Approximately 78% of patients with HLA-B27 uveitis have an extraocular disease and the most common of these diseases is SpA [14]. In our cohort, 80% of patients with SpA were HLA-B27 positive and these higher rates may be associated with ethnic trends.

Le Scanff et al. [15] demonstrated that lumbar and SIJ X-rays were not beneficial in determining the etiology of uveitis if clinical manifestations were absent. In our study, sacroiliitis was detected in five out of 79 patients (6.3%) and these patients were diagnosed as having SpA. Therefore, pelvis radiographs taken for screening purposes may not provide additional benefit in the etiologic tests for uveitis in asymptomatic patients. Haroon et al. [16] developed a diagnostic algorithm to determine which patients should be referred to a rheumatologist in two cohorts including 101 and 72 patients with acute anterior uveitis, respectively. According to this algorithm, patients with symptoms lasting ≥ 3 months, arthralgia and/or psoriasis, and HLA-B27 positivity were referred to a rheumatologist. The sensitivity and specificity of the algorithm in establishing a diagnosis of SpA were found as 96% and 97%, and the positive and negative predictive values were 41.5% and 0.03%, respectively. It has been reported that uveitis is more common in patients with both axial and peripheral disease than in those with peripheral involvement alone [17]. In our study, axial SpA was more common (80%) than peripheral SpA in patients who presented with noninfectious uveitis.

Behçet's uveitis is a recurrent, non-granulomatous, progressive, sight-threatening disease [18]. In the cohort of 880 patients (1,567 eyes), 11% of cases had anterior uveitis, 28.8% posterior uveitis, and 60.2% panuveitis involvement. Ocular involvement was bilateral in 78.1% [19]. 58.8% of our BD patients had panuveitis and the rest had posterior uveitis.

The prevalence of ocular involvement in GPA was found as 26% in a meta-analysis [20]. Uveitis is a rare ocular manifestation of GPA, occurring in up to 10% of patients [21]. In this study, GPA was detected in 1.9% of the patients whose first clinical finding was uveitis.

Two-thirds of patients presenting with sarcoid uveitis have no known history of sarcoidosis at presentation. In a study evaluating 362 patients with sarcoid uveitis, the rates of anterior and intermediate uveitis were 47.8% and 46.4%, respectively, the rate of multifocal choroiditis was 43.1%, and both eyes were affected in 86.5% of patients [22]. In our study, uveitis

was bilateral in both patients with sarcoidosis; one patient had anterior uveitis and the other had panuveitis. Of 200 patients with new-onset (<1 year) uveitis of unknown origin, 15% had abnormal chest X-rays and 11% had biopsy-confirmed sarcoidosis [23].

In our study, topical treatments were used in patients with anterior chamber involvement, and systemic agents were predominantly used in posterior uveitis. This result is consistent with the recommended treatment algorithm for patients with noninfectious uveitis [24].

The wide variability in the prevalence and incidence of uveitis between studies may be due to ethnic differences, diagnosis and inclusion criteria, follow-up period, and/or missing data. The limitations of our study included its retrospective design and relatively small sample size from a single center.

Conclusion

Systemic IRD was found in one-third of the patients whose presentation finding was uveitis. The high rate of IRD in patients with uveitis as the first clinical finding may be secondary to geographic features or the collaboration of ophthalmology and rheumatology in a tertiary center. A detailed interrogation for potential systemic rheumatic inflammatory diseases is of paramount importance because it may change treatment and prognosis. Prospective, multicenter studies with larger sample sizes are needed on this topic.

Ethics Committee Approval: The Dokuz Eylul University Non-invasive Clinical Research Ethics Committee granted approval for this study (date: 21.05.2021, number: 2021/15-23).

Authorship Contributions: Concept – TYI, GS; Design – TYI, GS; Supervision – TYI, GS, MK; Materials – EO; Data collection and/or processing – EO, MK; Analysis and/or interpretation – TYI, GS, EO, MK; Literature review – TYI, EO; Writing – EO, TYI; Critical review – GS, TYI.

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