Uveitis as the Initial Clinical Manifestation in Patients with Spondyloarthropathies

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ABSTRACT. ***Objective.*** To investigate the frequency and pattern of presentation of uveitis as the first clinical manifestation to prompt diagnostic evaluation in patients with spondyloarthropathies (SpA).

Methods. Patients with uveitis were attended simultaneously by ophthalmologists and rheumatologists in our Uveitis Clinic between June 1997 and October 2000. An established clinical protocol based on the pattern of uveitis and the patient's symptoms was used to determine diagnosis. Evaluation included clinical history, ophthalmologic examination, hemogram, biochemistry, erythrocyte sedimentation rate, the fluorescent treponemal antibody absorption test, urinalysis, and chest radiograph. Additional studies were requested according to the protocol.

Results. Data from 394 patients were recorded in our database. Seventy-two (18%) had some type of SpA; their mean age was 44.7 years (SD 15.7) and 51 (71.8%) were men. Forty-two patients (59%) of the SpA group had been previously diagnosed. In the 30 (41%) who were undiagnosed, uveitis was the first manifestation to prompt diagnostic evaluation. The most frequent clinical pattern was acute unilateral anterior uveitis. The 2 main keys to confirm the diagnosis of SpA were the presence of recurrent acute unilateral uveitis and low back or joint pain, in addition to the uveitis flare. HLA-B27 was found in 94% of patients.

Conclusion. In 41% of the patients diagnosed with SpA, uveitis was the first clinical sign, suggesting that collaboration between ophthalmologists and rheumatologists greatly aids the diagnosis and treatment of these patients. When this close collaboration is not possible, all patients with rheumatic complaints and recurrent acute unilateral uveitis should be referred to a rheumatologist. (J Rheumatol 2004;31:524–7)

Key Indexing Terms:
UVEITIS SPONDYLOARTHROPATHY DIAGNOSIS

Ocular involvement is common in rheumatic diseases. Some patients may present with nonspecific signs and symptoms, and ocular inflammation may be the first manifestation and the clue to a difficult diagnosis. Uveitis is a general term used to define inflammation in the uveal tract. An underlying systemic disease, often autoimmune, is identified in up to 40% of patients with uveitis[1], and may be the initial presentation of spondyloarthropathies (SpA). The pathogenic relationship between uveitis and related systemic diseases, particularly SpA, remains undetermined. Patients with acute anterior uveitis are frequently referred to a rheumatologist for an opinion concerning the presence of an underlying disorder. About one-third of patients attending a uveitis clinic with any type of SpA have an undiagnosed condition, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), spondyloarthritis associated with inflammatory bowel disease (IBD), undifferentiated SpA (USpA)[2], and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis). For this reason, we have been bringing ophthalmologists and rheumatologists together in our uveitis clinic since 1997. The 2 specialties work together to diagnose and treat patients with uveitis.

Although it seems to be well known that uveitis can be the presenting sign of SpA, when we started this study there were no reports confirming this. Thus, we investigated the frequency of previously undiagnosed SpA in a large series of patients with uveitis.

MATERIALS AND METHODS

Patients. In this prospective study, we included 394 patients with a diagnosis of uveitis who underwent evaluation in our Uveitis Clinic in La Paz Hospital, Madrid, between June 1997 and October 2000. The Uveitis Clinic is attended simultaneously by a team of ophthalmologists and rheumatologists.

An established clinical protocol based on the pattern of uveitis and the patient's symptoms was used to determine diagnosis in each case. Diagnostic evaluation included a careful history, ophthalmologic examination, hemogram, biochemistry, erythrocyte sedimentation rate, the fluorescent treponemal antibody absorption test, urinalysis, and chest radiograph. In patients with previous flares of uveitis, a pelvic radiograph was also done. Any additional studies were requested according to a protocol based on the report of Bañares, *et al*[2] (Table 1).

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Submitted October 4, 2002; revision accepted August 21, 2003.

Table 1. Clinical patterns of uveitis[2] and supplementary studies. All patients underwent a basic study as described in Materials and Methods.

Clinical Patterns	Most Frequent Diagnosis (excluding ophthalmologic syndromes)	Supplementary Studies
Anterior uveitis (AU)		
Recurrent acute unilateral	SpA (48%)	Sacroiliac radiograph
Without keratitis		HLA-B27
Recurrent acute bilateral	Idiopathic (45%)	
	Psoriasis (27%)	Clinical screening for psoriasis
	Tubulointerstitial nephritis uveitis syndrome (TINU) (9%)	Consultation with a nephrologist (if TINU is suspected)
Chronic AU	Idiopathic (41%)	
	JRA (4.6%)	Clinical screening for JRA,
	SS (4.6%)	SS and sarcoidosis
	Sarcoidosis (4.6%)	
Posterior uveitis		
Unilateral retinochoroiditis	Toxoplasmosis (92.6%)	Toxoplasma serology
Bilateral retinochoroiditis	Toxoplasmosis (23.1%)	Toxoplasma serology
	Masquerade syndromes (7.7%)	Ocular ultrasound (in elderly people and children)
Retinal vasculitis without systemic manifestations	Idiopathic (57%)	
	Behçet's disease (21%)	HLA-B51 (if suspected)
Intermediate		
	Idiopathic (89%)	
	Multiple sclerosis (3.7%)	Clinical screening for MS
Panuveitis		
With predominant retinochoroiditis	Toxoplasmosis (61%)	Toxoplasma serology
With predominant vitritis	Idiopathic (43%)	
	SpA (14%)	Sacroiliac radiograph
With predominant retinal vasculitis	Behçet's disease (37%)	HLA-B51
	Inflammatory bowel disease (10.5%)	Screening for IBD and
	Sarcoidosis (10.5%)	sarcoidosis
With predominant exudative retinal detachment	Vogt-Koyanagi-Harada (75%)	Spinal fluid analysis

SpA: spondyloarthropathy, JRA: juvenile rheumatoid arthritis; SS: Sjögren's syndrome, IBD: inflammatory bowel disease, MS: multiple sclerosis.

Data concerning age, sex, race, age at onset of uveitis, nature of onset, ocular complications, type of treatment, and associated diseases were collected in our database.

Diagnostic criteria. SpA was diagnosed and classified according to the criteria of the European Spondylarthropathy Study Group (ESSG)[3]; diagnosis of AS and ReA was based on the modified New York[4] and Calin[5] criteria; PsA was defined using Moll and Wright's criteria[6]; and a diagnosis of IBD was made when the endoscopic and/or gut histological picture was characteristic of ulcerative colitis or Crohn's disease. USpA was diagnosed when the ESSG criteria[3] were fulfilled but no specific disease entity could be diagnosed. We used the modified Khan criteria to define the SAPHO syndrome[7].

Classification of cases. A final diagnosis was achieved in every patient based on Bañares, *et al*[2]. We included patients with uveitis and final diagnoses of SpA in the study group. For the purpose of this report, these patients were divided into 2 groups: those previously diagnosed with SpA and those undiagnosed before attending the Uveitis Clinic.

Classification of uveitis. The International Uveitis Study Group classification system[8] was used for anatomic classification. Thus, uveitis was categorized as anterior when it involved the iris or the ciliary body (iritis or iridocyclitis); posterior when it affected the choroid or, by extension, the retina (choroiditis or retinochoroiditis); intermediate when the inflammation was limited to the vitreous, peripheral retina, and pars plana of the ciliary body; or panuveitis when 2 or more of these segments were affected.

The course of the uveitis was classified as acute (inflammation lasting < 3 months), chronic (inflammation persisting for ≥ 3 months), or recurrent when acute flares appeared after complete resolution of a previous flare. Uveitis can be unilateral, affecting only one eye at a given time (although recurrences may occur in the contralateral eye), or bilateral (both eyes involved simultaneously).

Variables. The following data were collected prospectively for each patient: (1) sex and age; (2) uveitis-related variables such as anatomic location, laterality, course, recurrence and clinical pattern, ocular complications, type of treatment received; (3) clinical symptoms of SpA such as low back pain (inflammatory spinal pain and buttock pain), synovitis, enthesopathy, or extraarticular involvement (psoriasis, urogenital symptoms, diarrhea); and (4) complementary tests such as HLA-B27 typing, sacroiliac radiography, and ileocolonoscopy.

RESULTS

From June 1997 to October 2000, 394 patients with uveitis were evaluated at our Uveitis Clinic. A wide spectrum of disorders, including infections, specific ocular syndromes, and systemic diseases, was found. In this study group, 188

of the 394 patients (48%) were diagnosed as having idiopathic uveitis. The systemic disorder most frequently found was some type of SpA (72 patients, 18.3%).

The most common pattern of uveitis in this SpA group was acute and unilateral. There were only 3 cases of chronic uveitis, 2 with IBD and one with AS; 5 of bilateral concurrent uveitis; 2 intermediate uveitis and 2 panuveitis. Demographic data, clinical patterns of uveitis, and final diagnoses are shown in Table 2.

In the SpA group, AS was the most frequent final diagnosis, found in 51 patients (70.8%). Of the remaining patients in this group, 7 had ReA, 5 IBD, 5 PsA, 2 USpA, and one SAPHO, and one had IBD and psoriasis.

The division of the SpA group into previously diagnosed cases and those previously unknown shows that 30 (41%), more than one-third of the cases in this series, had not been previously diagnosed (15 AS, 5 PsA, 3 ReA, 3 IBD, 2 USpA, one SAPHO, and one with psoriasis and IBD). In these patients, uveitis was the initial manifestation to be recognized by a physician. The other 42 patients (59%) had been diagnosed before the uveitis flare (36 AS, 4 ReA, 2 IBD; Table 3). HLA-B27 typing was positive in 94% of all patients (96% of those with AS, 71% of those with ReA, 80% of those with PsA). We found no significant differences in the clinical pattern of uveitis between patients previously diagnosed with SpA and those unidentified before the uveitis flare.

Table 2. Demographic data and clinical features in patients with uveitis and spondyloarthropathy.

Characteristic	n (%)
Male	51 (70.8)
Female	21 (29.2)
Age at first evaluation, yrs	
< 20	1 (1.4)
20 to 55	54 (75)
> 55	17 (23.6)
Type of uveitis	
Acute	70 (97.2)
Nonacute	2 (2.8)
Laterality	
Unilateral	67 (93)
Bilateral	5 (7)
Presence of SpA	
AS	51 (70.8)
ReA	7 (9.7)
PsA	5 (7)
IBD	5 (7)
Undifferentiated SpA	2 (2.7)
SAPHO	1 (1.4)
IBD/PsA	1 (1.4)

Table 3. Incidence of spondyloarthropathy (SpA) previously or not diagnosed.

	Total	Previously Diagnosed	Undiagnosed
Ankylosing spondylitis	51	36	15
Reactive arthritis	7	4	3
Psoriatic arthritis	5	0	5
IBD	5	2	3
Undifferentiated SpA	2	0	2
SAPHO	1	0	1
PsA/IBD	1	0	1

DISCUSSION

The relationship between uveitis and SpA, especially anterior, recurrent unilateral uveitis, has been well established[9–15]. The prevalence of uveitis in patients with AS was 40% in a previous study[16]. Although it is known that uveitis can be the first clinical manifestation of SpA, in our literature review we found only 2 articles confirming this, and one of them was published after we started our study[10,17]. Pato, *et al*[17] evaluated 514 patients with anterior uveitis, 22% diagnosed as having some type of SpA (AS was the most frequent). Fifty-three percent of the patients with SpA were diagnosed after the uveitis episode in a multidisciplinary outpatient uveitis clinic attended by rheumatologists and ophthalmologists.

In our series of 394 patients, SpA was the most common underlying disorder; it was present in 72 patients, 41% of whom had not been previously diagnosed. These results agree with those of Pato, *et al*[17]. We believe that the high percentage of new diagnosis of SpA in these patients could be achieved by close collaboration between the 2 specialities.

Acute anterior uveitis is the most common type of extraskeletal involvement in patients with AS, occurring in 25% to 40% of patients at some time during the disease course[9,10,18-20]. As shown in our study, this uveitis is usually anterior and unilateral and has a strong tendency to recur, not infrequently in the contralateral eye[10,17]. Bilateral involvement during a given attack is not frequent[21]. We found only 2 cases of bilateral uveitis and one of posterior uveitis in this group.

Acute uveitis is also common in reactive arthritis. Ocular lesions may be the major manifestation during the course of the disease, which is associated with HLA-B27, and they have a strong tendency to recur[21]. There were 7 patients with ReA in our series; 3 of these cases were diagnosed in our clinic after the uveitis flare, and only one was bilateral.

We found 5 patients with psoriatic arthritis, none of whom had been diagnosed until the uveitis flare. The first report of uveitis associated with PsA was a study[22] of 112 patients, in which anterior uveitis was found in 7.1%.

More than half the patients diagnosed with IBD in our study had previously remained undiagnosed. In a study by Lyons, *et al*, the uveitis associated with IBD was more likely to be chronic and bilateral[23]. The 2 cases of chronic uveitis that we found were in this group.

There were 2 cases of USpA and one of SAPHO syndrome; all 3 patients presented acute anterior unilateral uveitis that was diagnosed after the uveitis flare. The case of SAPHO syndrome was published as a case report[24]. This is the first report of the association of uveitis with this syndrome. Another patient was diagnosed in our uveitis unit as having IBD and psoriasis.

In agreement with previous series[2,10,17], the most frequent pattern of uveitis is highly characteristic in its clinical manifestations, which include anterior location, acute onset, unilateral recurrence, and good prognosis. There were no differences in the pattern of uveitis between previously diagnosed cases and those that were unidentified.

Over 50% of cases of acute anterior uveitis are associated with the HLA-B27 antigen[10,12]. We did not evaluate the frequency of HLA-B27 in all our patients with acute anterior uveitis; however, 94.4% of those with uveitis and some type of SpA were HLA-B27 positive. There were no significant differences between those with a previous diagnosis and those who had remained undiagnosed.

There are 2 keys to confirming diagnosis of previously unrecognized SpA: the recurrence of an acute unilateral uveitis without rheumatic symptoms and the presence of previously overlooked back or joint pain. Other manifestations such as enthesitis, diarrhea, or skin lesions in addition to the uveitis flare were also important clues for diagnosis.

In summary, uveitis may be the presenting symptom that draws attention to the diagnosis of SpA. For the longterm care of these patients, the ophthalmologist and rheumatologist should collaborate in identifying systemic diseases that may be present, to avoid unnecessary tests that can delay treatment or may occasionally be misleading. Close collaboration between these 2 specialties contributes to more effective diagnosis and treatment of patients. When this is not possible, all patients with recurrent acute unilateral uveitis, whether they present rheumatic symptoms or not, should be referred to a rheumatologist.

REFERENCES

1. Rosenbaum JT, Nozik RA. Uveitis: many diseases, one diagnosis. Am J Med 1985;79:545-7.
2. Bañares A, Jover JA, Fernández-Gutierrez B, et al. Patterns of uveitis as a guide in making rheumatologic and immunologic diagnoses. Arthritis Rheum 1997;40:358-70.
3. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218-27.
4. Van der Linden SM, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
5. Calin A, Fox R, Gerber RC, Gibson DJ. Prognosis and natural history of Reiter's syndrome. Ann Rheum Dis 1979;38:28-31.
6. Moll JMH, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
7. Khan MF, Khan MA. The SAPHO syndrome. In: Wright V, Helliwell P, editors. Psoriatic arthritis. Baillieres Clin Rheumatol 1994;8:333-62.
8. Bloch-Michel E, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. Am J Ophthalmol 1987;103:234-5.
9. Beckingsale AB, Davies J, Gibson JM, Rosenthal AR. Acute anterior uveitis, ankylosing spondylitis, back pain and HLA-B27. Br J Ophthalmol 1984;68:741-5.
10. Rosenbaum JT. Characterization of uveitis associated with spondyloarthritis. J Rheumatol 1989;16:792-6.
11. Rosenbaum JT. Acute anterior uveitis and spondyloarthropathies. Rheum Dis Clin North Am 1992;18:143-51.
12. Brewerton DA, Caffrey M, Nicholls A, Walters D, James DCO. Acute anterior uveitis and HLA-B27. Lancet 1973;2:994-6.
13. Salmon JF, Wright JP, Murray AD. Ocular inflammation in Crohn's disease. Ophthalmology 1991;98:480-4.
14. Rosenberg AM. Uveitis associated with juvenile rheumatoid arthritis. Semin Arthritis Rheum 1987;16:158-73.
15. Rothova A, Van Veenendaal WG, Linssen A, Glasius E, Kijlstra A, de Jong PTVM. Clinical features of acute anterior uveitis. Am J Ophthalmol 1987;103:137-45.
16. Edmuns L, Elswood J, Calin A. New light on uveitis in ankylosing spondylitis. J Rheumatol 1991;18:50-2.
17. Pato E, Bañares A, Jover JA, et al. Undiagnosed spondyloarthropathy in patients presenting with anterior uveitis. J Rheumatol 2000;27:2198-202.
18. Feltkamp TEW. HLA-B27, acute anterior uveitis, and ankylosing spondylitis. Adv Inflam Res 1985;9:211-6.
19. Van der Linden S, Rentsch HU, Gerber N, Cats A, Valkenburg HA. The association between ankylosing spondylitis, acute anterior uveitis and HLA B-27: the results of a Swiss family study. Br J Rheumatol 1988;27 Suppl 2:39-41.
20. Abel GS, Terry JE. Ankylosing spondylitis and recurrent anterior uveitis. J Am Optom Assoc 1991;62:844-8.
21. Hamideh F, Prete PE. Ophthalmologic manifestations of rheumatic diseases. Semin Arthritis Rheum 2001;30:217-41.
22. Lambert JR, Wright V. Eye inflammation in psoriatic arthritis. Ann Rheum Dis 1976;35:354-6.
23. Lyons JL, Rosenbaum JT. Uveitis associated with inflammatory bowel disease compared with uveitis associated with spondyloarthropathy. Arch Ophthalmol 1997;115:61-4.
24. Villaverde V, Muñoz-Fernández S, Hidalgo V, et al. Acute anterior uveitis in a patient with sacroiliitis and acne conglobata. Rheumatology Oxford 1999;38:797-8.