Uveitis in Adult Patients with Rheumatic Inflammatory Autoimmune Diseases at a Tertiary-care Hospital in Mexico City

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ABSTRACT. ***Objective.*** Our aim is to describe the frequency of uveitis associated with rheumatic inflammatory autoimmune diseases (RIAD) in adult patients admitted to the Rheumatology Department at a tertiary-care hospital in Mexico City. We also describe the clinical features, seasonal distribution, treatment, and ocular complications associated with this disease.

Methods. We reviewed 1332 charts of patients with RIAD and selected those that had a diagnosis of uveitis. We obtained the following data: age, sex, type of uveitis and relationship with diagnosis of RIAD, recurrences, seasonal distribution, treatment, and residual visual deficit.

Results. We found 57 (4.27%) cases of uveitis in 1332 charts, including 38 men and 19 women (M:F ratio 2:1), aged 47 ± 16 years. Nongranulomatous acute anterior uveitis (NGAAU) comprised 90.52% of cases (52/57). In 64.91% of cases (37/57), uveitis preceded the diagnosis of RIAD by 12 ± 9 years, more frequently in winter (35.96%; p = NS). Uveitis was found in 40/93 patients with ankylosing spondylitis (AS), in 7/11 patients with relapsing polychondritis (RP), in 8/16 patients with Behçet's disease, in 1/16 patients with polyarteritis nodosa, and in 1/590 patients with rheumatoid arthritis (RA). Ninety-six percent of the patients were treated with steroids. Upon a mean followup of 60 days (range 7–4745 days), reduction of visual acuity (≤ 20/200) was associated with recurrence of uveitis in 3/7 cases with AS, in 4/8 cases with Behçet's disease, in 3/7 with RP, and in 1 case of uveitis and seronegative RA.

Conclusion. NGAAU frequently precedes RIAD and is found predominately in men, with a tendency to occur in winter. (First Release Dec 1 2010; J Rheumatol 2011;38:325–30; doi:10.3899/jrheum.100015)

Key Indexing Terms:
UVEITIS RHEUMATIC DISEASES ANKYLOSING SPONDYLITIS
RELAPSING POLYCHONDRITIS BEHCET SYNDROME

Uveitis is a term describing a group of inflammatory diseases that affect almost all structures of the eye. Causes range from traumatic, infectious, and parasitic to drug-induced; in some cases uveitis is associated with rheumatic inflammatory autoimmune disease (RIAD)[1].

The International Uveitis Study Group has classified uveitis according to duration as acute (≤ 3 months) and chronic (> 3 months); according to the anatomical location as anterior, intermediate, posterior, and panuveitis; and according to inflammatory type as granulomatous and nongranulomatous.

Information regarding the frequency of uveitis associated with adult RIAD largely originates from ophthalmology departments of tertiary hospitals where 9% to 40% of uveitis is associated with RIAD[2,3,4]. RIAD associated with uveitis in adults includes spondyloarthropathies[5], Behçet's

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disease (BD)[2,3,6,7,8], sarcoidosis[3,4,6], and rarely, seronegative rheumatoid arthritis (RA)[3].

Uveitis is considered idiopathic if an ophthalmologist does not detect systemic involvement at the time of initial manifestation[9]. In some patients, uveitis is associated with infection and parasitic disease, depending on geographic location, race, and climate[10,11,12,13,14]. Our aim was to describe the frequency of uveitis associated with RIAD in adult patients seen in the Rheumatology Department in a tertiary hospital in Mexico City, and to describe their clinical characteristics, seasonal distribution, treatment, and eye complications.

MATERIALS AND METHODS

We reviewed records of 1332 consecutive adult patients with RIAD seen in the outpatient clinic of the Rheumatology Department over 3 months (June to August) without regard to the time of diagnosis. Thus a patient was not necessarily diagnosed with uveitis during the study period; it is possible that the diagnosis occurred months or years before. We selected records of patients with a previously established diagnosis of uveitis that met the diagnostic criteria of the International Uveitis Study Group[1] certified in the Uveitis Section of the Ophthalmology Department, and who in addition were diagnosed with RIAD that fulfilled the accepted classification criteria[15,16]. The following data were obtained from patient records: age, sex, type of uveitis, and age at presentation of the first episode of uveitis. On the first visit to the ophthalmologist the type of uveitis and visual acuity were determined. During followup with the ophthalmologist, the type of uveitis, number of recurrences of uveitis per patient, and duration of monitoring were recorded, and at the final ophthalmic evaluation, ocular sequelae and whether there was a decrease in visual acuity (≤ 20:200) were recorded[17]. For all events of uveitis the following information was collected: number of eyes involved for each patient, time delay between symptoms of uveitis and the onset of treatment, time of year in which symptoms occurred, treatment received, and the time between the first event of uveitis and diagnosis of RIAD. Excluded from the study were records from foreign patients, patients with degenerative rheumatic diseases and metabolic diseases, and uveitis caused by other etiologies. The data analysis was executed using descriptive statistics, ± standard deviation, and trend analysis, with OR and 95% CI.

RESULTS

Of 1332 patients' records with RIAD, 57 (4.27%) had uveitis, 38 men and 19 women (ratio 2:1) with a mean age of 47 ± 16 years. The first episode of uveitis occurred at 40 ± 15 years of age (range 9 to 71). Uveitis was documented in 40 of 93 (44.44%) patients with ankylosing spondylitis (AS), in 7 of 11 (63.63%) patients with relapsing polychondritis (RP), in 8 of 16 (50%) patients with BD, in 1 of 6 (16.66%) patients with polyarteritis nodosa (PAN), and in 1 of 590 patients with RA (0.16%; this patient had onset of uveitis at 9 years of age and later developed seronegative RA as an adult). We found no cases of uveitis in 600 records of patients with systemic lupus erythematosus (SLE) or in 16 charts of patients with Wegener's granulomatosis (Table 1). In 89 of 95 (93.68%) cases of uveitis (initial and relapse events), the season of occurrence was determined: 14.6% of the uveitis occurred in spring, 26.97% in summer, 22.47% in autumn, and 35.96% in winter (p = NS; Table 1).

In 37 of the 57 cases (64.91%), uveitis was the first symptom prompting consultation with the ophthalmologist. In the total of 57 cases of uveitis there were 95 episodes documented (2 ± 1 episodes per patient; range 1–5). Fifty-two of the 95 episodes of uveitis (54.73%) affected the right eye and 43 (45.27%) the left eye. In 3 cases with initial onset of uveitis in only 1 eye, relapse occurred simultaneously in both eyes.

Eighty-six of 95 (90.52%) episodes of uveitis were a type of acute nongranulomatous anterior uveitis (NGAAU) and 8/95 (8.42%) were panuveitis. In 7 cases the initial ophthalmic evaluation found sequelae from previous episodes of uveitis. There was a delay of 30 ± 64 days (range 1–365) to establish the diagnosis of uveitis, treated with local steroids (drops or subtenonian) and/or systemic steroids in 96% of cases; immunosuppressive agents were administered in some patients. The final ophthalmic examination showed a reduction of visual acuity in 11 eyes of 57 patients (19.29%), due to more than one of the following sequelae: 7 eyes with synechiae; 4 with glaucoma, 2 with cataract, 1 with retinitis, 1 with aphakia, 1 with traces of pigment in the anterior lens capsule, and in 2 cases the causes of visual deficits were not documented.

Uveitis associated with AS. Ninety-six percent of the uveitis in patients with AS was NGAAU and the remaining 4% was panuveitis. The uveitis was unilateral in the majority of patients, with only 2 cases documented as bilateral; recurrence occurred in 19 of 40 (47.5%) of these patients, for a mean of 2.77 ± 1.18 uveitis episodes per patient (range 2–5 episodes); 35.71% of the uveitis occurred in winter (Table 1). Uveitis in AS was diagnosed within 16 ± 26 days (range 1–180 days) of symptom onset. These patients had received treatment with prednisolone eye drops (PED) in 12 cases, PED + oral prednisone (PDN) in 9 cases, PED + oral PDN + subtenonian steroids in 8 cases, and PED + subtenonian steroids, with oral PDN dose of 15 ± 20 mg/day (range 5–65) in 6 cases. In 3 cases the ophthalmologist administered PDN + immunosuppressants, and 1 case each with azathioprine, cyclophosphamide, and methotrexate (Tables 2 and 3). The monitoring by an ophthalmologist was documented in 42 of the 70 episodes of uveitis (60.0%). The episodes resolved in 30 to 120 days, leaving as sequelae synechiae in 7 eyes, glaucoma in 5 eyes, pigment in the anterior lens capsule in 3 eyes, and cataract in 1 eye. The cause of amaurosis was not specified in 1 case and there was severe visual impairment in 2 cases (Table 3).

Uveitis associated to Behçet's disease. Eight of 16 cases were diagnosed with BD (50%). Five women and 3 men had experienced more than 1 episode of uveitis, 2 with NGAAU, 1 with hypopion, and 2 with panuveitis. Forty percent of the uveitis occurred in summer (Table 1). Seven of 8 patients (87.5%) were followed for up to 61 ± 72 months by an ophthalmologist with recurrences and were severely visually impaired in 4 eyes because of cataracts and glaucoma,

Table 1. Demographic data, recurrence, and seasonal distribution of 89 episodes of uveitis in patients with rheumatic inflammatory autoimmune diseases. All data are n (%).

Data	RP	BD	AS	PAN	RA	SLE	WG	Total
No. patients	11 (0.82)	16 (1.2)	93 (6.98)	6 (0.46)	590 (44.3)	600 (45.04)	16 (1.2)	1332 (100)
Uveitis cases	7 (63.63)	8 (50)	40 (44.44)	1 (16.66)	1 (0.16)	0	0	57 (4.27)
Men/women	2/5 (28.57)	3/5 (37.5)	31/9 (77.5)	1/0 (100)	1/0 (100)	0/0	0/0	57
No. patients with recurrence	2/7 (28.57)	5/8 (62.5)	19/40 (45.5)	0	0	—	—	26/57 (45.61)
Episodes of uveitis in								
Spring	1 (14.29)	1 (10)	11 (15.71)	0	0	0	0	13 (14.6)
Summer	2 (28.57)	4 (40)	17 (24.29)	1 (100)	0	0	0	24 (26.97)
Autumn	0 (0)	2 (20)	17 (24.29)	0	1 (100)	0	0	20 (22.47)
Winter	4 (57.14)	3 (30)	25 (35.71)	0	0	0	0	32 (35.96)*
Total episodes	7	10	70	1	1	0	0	89

* Trend analysis, p = nonsignificant. RP: relapsing polychondritis; BD: Behçet's disease; AS: ankylosing spondylitis; PAN: polyarteritis nodosa; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; WG: Wegener's granulomatosis.

Table 2. Number of patients receiving various treatments for uveitis associated with rheumatic inflammatory autoimmune diseases.

Disease	POS	POS + TIP	POS + TIP + PDN	PDN + Tip	POS + PDN	PDN	PDN Dosage, mg, (range)	AZP	CYC	POS + PDN + MTX	PDN + MTX	PDN + Chlorambucil	No Treatment*
AS	12	6	8	0	9	2	15 ± 20 (5–65)	1	1	1	0	0	4
BD	4	0	1	0	4	4	18 ± 20 (10–70)	1	0	0	1	1	3
RP	3	0	1	0	1	2	27 ± 25 (20–60)	0	0	0	0	0	0
RA	0	0	1	0	0	0	60	0	0	0	0	0	0
PAN	1	0	0	0	0	0	0	0	0	0	0	0	0

* These patients did not receive treatment as they had only sequelae of uveitis. POS: prednisolone opthalmic solution; PDN: oral prednisone; TIP: tenonian-injectable prednisolone; AZP: azathioprine; CYC: cyclophosphamide; MTX: methotrexate; AS: ankylosing spondylitis; BD: Behçet's disease; RP: relapsing polychondritis; RA: rheumatoid arthritis; PAN: polyarteritis nodosa.

Table 3. Number of events of uveitis, duration of uveitis before diagnosis, and initial and final evaluation of visual acuity (VA) for patients with uveitis associated with rheumatic inflammatory autoimmune diseases.

Disease	No. Events of Uveitis/patients (ratio)	Days of Evolution Before Diagnosis (range)	1st Evaluation VA ≥ 20:200	1st Evaluation VA < 20:200 (%)	Months of Followup By Ophthalmologist (range)	Final VA > 20:200	Final VA ≤ 20:200 (%)
AS	70/40 (1.8)	16 ± 26 (1–180)	8	34 (80.95)	6 ± 17 (1–120)	39	3 (7.14)
BD	15/8 (1.9)	90 ± 123 (1–365)	2	7 (77.77)	61 ± 72 (0.5–156)	6	4 (40)
RP	7/5 (1.4)	168 ± 403 (1–1080)	1	4 (80)	17 ± 29 (1–60)	2	3 (60)
RA	1/1 (1.0)	120	1	0 (0)	6	0	1 (100)
PAN	1/1 (1.0)	2	0	1 (100)	1	1	0 (0)

AS: ankylosing spondylitis; 70 episodes of uveitis, 2 patients with disease of both eyes. Only 42 episodes of uveitis had final evaluation of VA by an opthalmologist. BD: Behçet's disease; of 15 uveitis cases, only 9 episodes of uveitis had followup and documented VA; in 1 patient with disease initially in only 1 eye, uveitis occurred in the other eye during the followup. RP: relapsing polychondritis; the final VA was documented in only 5/7 of these patients' charts; PAN: polyarteritis nodosa.

despite having received up to 70 mg/day of PDN and 2 immunosuppressive agents (Tables 2 and 3). Four patients with delayed diagnosis of 3 months to 1 year had a worse prognosis than those diagnosed within 15 days (Table 3). Uveitis was associated with mucocutaneous manifestations of BD in 4 patients (50%).

Uveitis associated to relapsing polychondritis. Seven of 11 cases of RP (63.63%; 5 women and 2 men) had uveitis and scleritis; 6 cases exhibited NGAAU type, in which 1 case was accompanied by orbital pseudotumor while the other patient had panuveitis. Recurrences occurred in 2/7 (28.57%), with 57.14% of episodes of uveitis during winter (Table 1). Uveitis in these patients had a delayed diagnosis of 168 ± 403 days (range 1–1080) and they had received

PDN at oral doses of 27 ± 25 mg/day (Tables 2 and 3). In these patients the initial episode of uveitis was associated with mild pain from articular and costochondral cartilage, dysphonia, and painless joint effusion, resulting in delayed diagnosis of RP. In 5 patients, PDN treatment eased the symptoms of RP, but a chronic uveitis developed. The ophthalmic followup showed that after 17 ± 29 months (range 1–60), 3 patients had a reduction of visual acuity ≤ 20:200. One of these patients (with a 3-year delay in diagnosis) was able to count fingers at 50 and 20 cm using each eye, respectively (Table 3). The ear deformity that occurred after multiple relapses and ear cartilage biopsy confirmed the diagnosis of RP.

Uveitis associated to RA and PAN. The only RA-associated uveitis developed unfavorably because of delayed diagnosis and persistent ocular inflammatory activity. This patient had uveitis at 9 years of age and later developed seronegative RA as an adult. The other case of uveitis was associated with short development and PAN that responded to treatment without sequelae.

DISCUSSION

The records of patients were selected consecutively over a period of 3 months, as patients were cited for that time interval for followup, and only patients in whom ophthalmologists suspected that uveitis was associated with rheumatic disease were directed to our study. For this reason a large number of cases of primary uveitis or uveitis associated with infection were not included. The most common diagnoses in the outpatient clinic of our Department of Rheumatology were SLE, RA, and AS. Other autoimmune rheumatic diseases such as scleroderma and vasculitis were also seen.

This retrospective report based on patient records from the Rheumatology Department of a tertiary hospital in Mexico City shows the association of uveitis in adults (age > 16 years) with various RIAD. Infection as a cause of uveitis was initially ruled out, and because of peripheral joint pain and/or low intensity back pain, asthenia, and adynamia, the patients were initially seen by a general practitioner, who diagnosed infectious or allergic conjunctivitis, resulting in a delay of weeks or months before examination by an ophthalmologist specializing in ocular inflammatory diseases. Upon the diagnosis of uveitis, the ophthalmologist began treatment with oral steroids and directed patients to the rheumatologist. Because of the large number of patients being treated in the rheumatology outpatient department, the delay to see the rheumatologist was 7 to 15 days. At the time of rheumatologic evaluation, extraocular symptoms had disappeared and laboratory and image studies were normal, thus it was not usually possible to establish the diagnosis of RIAD from the outset (or at first episode of uveitis). RIAD was diagnosed up to 12 ± 9 years (range 1–40) after the initial uveitis episode.

Differentiating the uveitis associated with infectious disease from that associated with RIAD is easier in countries where infection and parasitic disease are endemic[18]; diagnostic problems concerning the etiology of uveitis arise when it is presented in communities where infectious disease, idiopathic uveitis, and uveitis associated with systemic disease occur with a similar frequency. The comprehensive search for infection in these populations usually shows negative results[2,3,6,7].

Uveitis may precede the development of RIAD by months or years[5,19], especially in Mestizo Mexican patients with AS[20], making it difficult to associate an isolated event of uveitis with the development of RIAD years later. However, in our study the initial episode of uveitis was accompanied by arthralgia, myalgia, pain in ear cartilage, or mild intensity lower back pain, which decreased with the PDN prescribed by the ophthalmologist, being normal upon initial rheumatologic evaluation. Thus it was impossible to establish the diagnosis of RIAD upon the first episode of uveitis[9]. Over time, and with suspension of the PDN, clinical signs and symptoms led to a diagnosis of RIAD[5,19,20].

The Mexican population is mostly Mestizo (mixed Amerindian and Spanish), with a minority of mulattos, white Europeans, Arabs, and black Africans[21,22]. The low frequency of genes associated with the development of uveitis in Mexican Mestizo patients[11,23,24] explains the lower frequency of uveitis associated with RIAD found in our study (4.27%) in comparison to that reported in hospitals in other countries (9% to 40%)[2,3,4]. However, the most common type of uveitis and the association with AS was similar to that reported in hospitals in the Middle East[6,8]. This is in contrast to the uveitis that occurred in men in our study, which showed a tendency toward repetition and high association with the AS, while in the eastern regions of Europe and North America, 1 type of uveitis was not dominant in any sex[11,12,13].

Steroid treatment in our patients with NGAAU was effective, with residual reduction of visual acuity present in a minority of patients[17]; in patients with panuveitis, steroid therapy did not prevent any visual deficit.

Sixty percent of patients with RP developed an eye condition: conjunctivitis, scleritis, episcleritis, keratitis, or keratoconjunctivitis sicca[16], and 26% exhibited iritis[16]. Despite this, RP-associated uveitis was not mentioned in the series of cases of uveitis associated with systemic diseases of tertiary hospitals or in a review of the literature[2,3,4,6,7,8,11,19], thus the association of uveitis and RP continues to be documented as case reports[25]. In our study, there were only 2 cases with uveitis secondary to "severe" scleritis.

There have been 16 cases of RP in Mexican Mestizos reported to date and 50% exhibited an eye condition[26]. Unlike AS, RP-associated uveitis frequently tended toward a chronic course in a population with a low frequency of genes associated with uveitis[11,23,24], suggesting that environmental factors favor the development of chronic uveitis in the RP population in Mexico City.

Patients in Mexico City with BD more frequently have genes associated with the development of BD as compared to the general population of Mediterranean origin[27]. The association of uveitis and BD (50%) was similar to that reported in hospitals in Valencia, Spain (42.5%)[23], and Korea (50.9%)[28] and higher than that reported in hospitals in New York (34%)[29] and Istanbul (21.9%)[30]; the association was lower than that reported in a hospital in Naples, Italy (82.7%)[31]. Cases of uveitis associated with BD showed a poor response to treatment with PDN. Also, because of its tendency to recur, this association caused a visual deficit (40%) more often than reported in patients with BD at a hospital in Tunisia (12.5%)[8], at a similar level to that reported in Finland (37%)[3], and less frequently than in Tehran (63.1%)[6]. In BD the eye inflammation is often severe and prompt treatment is needed. The prognosis may be poor.

The absence of cases of uveitis associated with sarcoidosis in our series was due to the near absence of sarcoidosis in the Mexican population[32]. This suggests that aside from genetic factors, environmental factors appear to favor increased frequency and severity of uveitis in patients with BD.

Mexico City has a cold, dry winter with temperatures between –2°C to 25°C during the day, with high pollution. These conditions were associated with a greater number of episodes of uveitis in patients with AS and RP. Chronic uveitis among our patients in Mexico City was associated with greater severity of RP and BD. In BD, uveitis left more visual sequelae (40%) than that reported in patients with uveitis and BD in US hospitals (3%)[33] and in several Middle Eastern locations and Tunisia (23%–24.8%)[8,33]. It is possible that not only the cold, polluted weather but also the delayed diagnosis and suboptimal therapy may have influenced the greater number of observed sequelae.

The use of immunosuppressants is indicated, and in cases with uveitis associated with RIAD, cooperative treatment between the ophthalmologist and rheumatologist is critical to conserve vision. In more advanced cases, steroid therapy may be the first step, but proper immunosuppressive treatment must be arranged.

RIAD-associated uveitis observed in the Rheumatology Department at a tertiary hospital for adults in Mexico City frequently precedes the diagnosis of RIAD. Most likely for genetic reasons, this population exhibits a lower frequency of uveitis associated with RIAD than that reported in hospitals of other countries, NGAAU being the most frequently found disorder in men with AS. Chronic uveitis associated to RP and BD followed in frequency and severity. The winter climate of the city appears to influence the incidence of uveitis.

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