Uveitis in Spondyloarthritis: An Overview

Fabrizio Cantini, Carlotta Nannini, Emanuele Cassarà, Olga Kaloudi, and Laura Niccoli

ABSTRACT. Autoimmune anterior uveitis (AU) accounts for at least half of the cases of noninfectious uveitis, and similarly to spondyloarthritis (SpA), its occurrence is related to HLA-B27 positivity. AU is significantly more frequently found in HLA-B27–positive subjects with SpA and is characterized by unilateral eye involvement, marked tendency to recur with involvement of both eyes in alternate fashion, and has good prognosis in the majority of cases. The estimated frequency of SpA in patients with AU is around 50%, whereas AU in SpA has been reported in at least 30% of cases. Across the SpA disease spectrum, AU has a frequency peak of 33.4% in patients with ankylosing spondylitis, while the estimated prevalence in psoriatic arthritis (PsA) and inflammatory bowel disease–associated SpA is 2%–25%, and 25%, respectively. In early PsA, the frequency of AU has been found in 9% of patients. The wide range of prevalence reported in PsA may be explained by the variable sets of classification criteria used for patient selection and the different length of followup. AU may precede the clinical features of SpA, may be present at diagnosis, or may complicate the SpA clinical course. However, the occurrence of AU in SpA as well as AU flares has been reduced through treatment of SpA with anti-tumor necrosis factor-α agents. (J Rheumatol Suppl. 2015 Nov;93:27–9; doi:10.3899/jrheum.150630)

Key Indexing Terms:
ANTERIOR UVEITIS SPONDYLOARTHRITIS ANKYLOSING SPONDYLITIS
PSORIATIC ARTHRITIS INFLAMMATORY BOWEL DISEASE

Noninfectious uveitis, anterior, posterior or both, with or without associated retinal vasculitis, are autoimmune inflammatory conditions of the uvea with an estimated prevalence in Western countries ranging from 38 to 150 per 100,000 per year, and an incidence of 17 to 52 per 100,000 per year[1]. Anterior uveitis (AU), also called iridocyclitis, is an autoimmune condition that accounts for at least 50% of the cases of noninfectious uveitis in all reported clinical series, and may be distinguished as either idiopathic (when occurring in an isolated pattern), or associated with rheumatic or nonrheumatic conditions including spondyloarthritis (SpA), Behçet disease, juvenile idiopathic arthritis, sarcoidosis, inflammatory bowel disease (IBD), and psoriasis[2,3,4].

As reported more than 40 years ago, AU is characterized by a genetic predisposition expressed by positive HLA-B27 in more than 50% of cases[5]. Other genes located in the class I MHC may be implicated in the pathogenesis of AU, but current knowledge suggests that the HLA-B27 allele plays a pivotal role[5]. Depending on the frequency of HLA-B27–positive subjects, HLA-B27–associated AU is more frequent in Western countries than in Africa or in Japan, where idiopathic anterior uveitis predominates[2]. HLA-B27 positivity seems to condition the phenotypic expression of AU in terms of type of onset and severity. In HLA-B27–positive subjects, AU onset is acute, with full expression of the clinical picture within 1 to 2 days; it is unilateral in most cases, but with a marked tendency to recur with alternate involvement of both eyes[5]. Patients complain of globe pain, photophobia, tearing, marked eye redness; and in more severe cases, vision blurring due to abundant inflammatory precipitate in the anterior chamber. When neutrophil infiltrate is particularly intense, hypopyon may occur. AU is characterized by a good prognosis, with rapid response to local antiinflammatory drugs added to cycloplegic therapy, and HLA-B27–associated AU seems to differ from the HLA-B27–negative AU only for its greater burden of inflammatory infiltrate in the anterior chamber, with more frequent hypopyon development, but not for a favorable longterm prognosis[5].

AU shares with the SpA complex the genetic predisposition related to HLA-B27 positivity, and this explains the association between the 2 conditions[5].

The aim of this review was to evaluate the frequency and clinical characteristics of AU associated with SpA through assessment of the frequency of SpA in clinical series of patients with AU, and conversely, the frequency of AU in patients with SpA.

Frequency of SpA in patients with AU. As expected, HLA-B27 positivity significantly increases the frequency of SpA in patients with AU. In a large clinical series of 154 patients with AU followed up for 6 years, 41 (26.1%) had ankylosing spondylitis (AS) and 39 (25.3%) had other SpA. The HLA-B27 allele was typed in 40 of 154 subjects (26%),

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and clinical features of SpA occurred in all 35 HLA-B27–positive and in none of 5 patients negative for HLA-B27[6]. This finding was confirmed in another study where 66% of 119 patients with HLA-B27–positive AU had associated SpA compared to 6% of 35 HLA-B27–negative patients[7].

SpA represents the most frequent extraocular manifestation observed in patients with HLA-B27-associated AU. In a large clinical series of 175 patients with HLA-B27-associated AU, AS was diagnosed in 81 subjects (46.3%), and undifferentiated SpA in 21 (12%)[8]. Of note, in an Italian cohort of 165 consecutive patients, AU preceded the onset of AS in 57% of cases[9].

Overall, the prevalence of SpA in subjects with HLA-B27–positive AU reportedly ranges from 13% to 58.3%[8,10]. The reasons for the wide range may be explained by different study design, classification criteria used for the diagnosis of SpA, intraobserver variability in pelvic radiography readings to detect sacroiliitis, and duration of followup.

There is general agreement in the literature that HLA-B27 positivity represents a shared genetic background between AU and SpA, with an average occurrence of SpA in at least 40% of patients with HLA-B27–associated AU.

Frequency of AU in SpA. The SpA group comprises several pathologic conditions including AS, preradiographic axial SpA, psoriatic arthritis (PsA), IBD-associated SpA, peripheral SpA, and reactive arthritis. It is widely accepted that AU uveitis represents the most frequent extraarticular manifestation of SpA, with some differences among the various entities. An overall prevalence of AU in SpA of 32.7% was reported in a systematic review of the literature published in 2007[11], with a frequency peak of 33.2% in patients with AS, and as expected, with a higher occurrence in HLA-B27–positive subjects with an OR of 4.2. AU was unilateral in 87.3% of cases, with recurrent attacks in 50.6%; and visual impairment was found in 8.6% of patients. Similar results were observed in a French observational study on patients satisfying the European Spondylarthropathy Study Group and/or Amor's classification criteria for SpA[12]. In the same report, the overall prevalence of AU in 885 patients with SpA was 32.2%, 38.1% in 657 HLA-B27–positive subjects, and 14.7% in those who were HLA-B27–negative. AU occurrence was significantly associated with HLA-B27 positivity (OR 3.58), radiologic sacroiliitis (OR 1.83), and disease duration (10–20 yrs: OR 1.73; > 20 years: OR 3.15), whereas no significant association resulted with disease activity measured by the Bath Ankylosing Spondylitis Disease Activity Index (OR: 0.98). Moreover, in a metaanalysis of 143 articles reporting data of 44,732 patients with SpA[13], AU was found to be the most frequent extraarticular manifestation, with a pooled prevalence of 25.8%; followed by psoriasis (9.3%) and IBD (6.8%). Confirming other reports[9,10], in an analysis of 514 cases of AU, 117 (22.7%) patients had some type of SpA, and uveitis preceded the onset of AS symptoms in 40 (53.3) out of 75 patients[14].

Interestingly, a recent ultrasonography (US) controlled study of 100 patients with idiopathic AU performed to evaluate the inflammatory involvement of enthesis demonstrated that 38 HLA-B27–positive subjects without SpA features had US findings of enthesitis comparable with those seen in controls with AU and associated SpA[15]. Although these findings should be confirmed in a larger number of patients, this study seems to suggest that HLA-B27–positive patients with recurrent AU have an abortive or incomplete form of SpA, thus confirming the central pathogenic role of HLA-B27 in both AU and SpA.

The prevalence of AU is variable among the different types of SpA. Considering the 3 most frequent SpA (AS, PsA, and IBD-associated SpA), there is a general agreement on the higher frequency of AU in patients with AS compared to the other 2 disorders, probably reflecting the higher frequency of HLA-B27–positive subjects in AS. Indeed, AU at onset or complicating the disease course has been reported in 33% of patients with AS, while the reported percentages are lower in PsA and IBD-associated SpA[11].

Concerning PsA, the reported prevalence of AU ranges from 2% to 25% of cases, and it is more frequently observed in axial PsA and in HLA-B27-positive patients[16]. The wide range of prevalence may be related to the different sets of classification criteria used for patient selection and the different disease duration. In keeping with other reports[16], in a prospective, followup study on 242 patients with early PsA, of whom 38 (15.7%) were HLA-B27–positive, the frequency of AU was 9%, with a significant association with dactylitis ($p = 0.032$), and no association with HLA-B27 positivity[17].

IBD are associated with SpA in 6.8% of cases[13]. Conversely, SpA features are the most frequent extraintestinal manifestation in patients with IBD, with an approximate prevalence of 20% to 30% of cases, depending on the settings, the classification criteria used for patient selection, and the radiological methods used to detect sacroiliitis[18]. The frequency of different clinical patterns of SpA is higher in patients with Crohn disease than in those with ulcerative colitis, and the relationship with HLA-B27 is more variable and weaker compared to other SpA[19]. AU in IBD-associated SpA has been reported, with an estimated frequency of 25% of cases, and in around half of the cases it precedes both the intestinal and articular manifestations[19].

Regarding therapy, AU usually responds well to topical antiinflammatory drugs in combination with mydriatics, and only rarely requires short-term systemic low-dose corticosteroids. However, the clinical course and the frequency of recurrences have been greatly improved by the use of monoclonal anti-tumor necrosis factor-α (TNF-α) agents for the treatment of SpA[20].

AU is the most frequent extraarticular manifestation of SpA, and the frequency of this association is related to the

shared genetic background as expressed by positive HLA-B27. Its prevalence is higher in AS compared to PsA and IBD-associated SpA. Clinically, AU in SpA is characterized by unilateral onset, but with marked tendency to recur affecting both eyes in alternate fashion. The prognosis is good, and permanent visual impairment is observed only in a minority of patients. Over the last 10 years the treatment of SpA with anti-TNF biologic drugs has reduced the frequency of onset and recurrence of AU.

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