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The Eye in Spondyloarthritis

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Abstract

Acute anterior uveitis is the most common extra-articular clinical manifestation of spondyloarthropathy. Rheumatologists should be aware of uveitis, know how it presents, understand the differential diagnosis of uveitis and arthritis, and be familiar with the role of systemic medications in the treatment or prevention of uveitis.

Summary

Uveitis is the most common, non-articular, clinical manifestation of ankylosing spondylitis. Rheumatologists need to be familiar with uveitis because of its association with various arthritides and because eye inflammation can sometimes be a dominant clinical manifestation in patients with rheumatic disease.

Keywords

ankylosing spondylitis; spondyloarthropathy; uveitis; iritis; acute anterior uveitis; TNF inhibitors; sulfasalazine

What is uveitis?

Uveitis describes inflammation in or adjacent to the uvea, which is the middle layer of the eye sandwiched between the outer coat or sclera and the inner tissue or retina. Uveitis can be divided into subsets based on anatomy: anterior, intermediate, or posterior [1]. Some patients have a combination of locations involved such as anterior and intermediate or all portions can be affected as in panuveitis. An anterior uveitis affects the iris and is diagnosed by a slit lamp or biomicroscope examination that discovers leukocytes in the anterior chamber of the eye adjacent to the iris. An intermediate uveitis is defined by an increase in leukocytes in the vitreous humor. Just as synovitis is diagnosed by finding increased leukocytes in synovial fluid, an ophthalmologist diagnoses uveitis by detecting leukocytes in fluid near the uveal tract rather than seeing the leukocytes in the uvea itself. A posterior uveitis is diagnosed by visualizing lesions in the choroid or adjacent retina. About 80% of all uveitis is anterior [2,

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3]. A sudden onset anterior uveitis is the phenotype most typically associated with spondyloarthritis. This form of uveitis is often called AAU for acute anterior uveitis.

What causes uveitis?

The differential diagnosis of uveitis can be divided into broad categories which include infections; immune-mediated syndromes generally confined to the eye; masquerade syndromes such as a B cell lymphoma that could be mistaken for an inflammation; reactions to medications; trauma; and systemic immune-mediated diseases. Representative examples of each type are shown in Table 1. Despite the multiple diagnostic categories for uveitis, and despite the ability to examine the eye such that the pathology is often visualized, idiopathic uveitis is usually the most common diagnosis in series published from tertiary care centers [4]. Other terms to describe idiopathic uveitis include non-classifiable or undifferentiated [5]. Of the systemic, immune-mediated diseases associated with uveitis, many are also capable of causing joint disease. Therefore, the differential diagnosis of uveitis in association with arthritis is quite broad as shown in Table 2. Although uveitis is an obscure term to the lay public and to many physicians, it accounts for about 10% of acquired blindness [6, 7]. Well known causes of vision loss such as macular degeneration and diabetic retinopathy usually occur near the end of life. In contrast, uveitis can begin in infancy and commonly affects patients many years before death. Consequently, uveitis is comparable to diabetes or macular degeneration in terms of years of visual morbidity.

Animal models of uveitis

One of the most common laboratory models of uveitis is called EAU for experimental autoimmune uveitis [8]. It is triggered by immunization with a retinal antigen such as IRBP (inter-photoreceptor retinoid-binding protein). The model has many analogies to the mouse model of demyelinating disease or experimental autoimmune encephalomyelitis (EAE). Uveitis can also be triggered by activation of the innate immune system. For example, a footpad of injection of endotoxin (lipopolysaccharide) induces a bilateral acute anterior uveitis in most strains of rat [9]. Several animal models of uveitis including aggrecan-induced arthritis [10], adjuvant arthritis [11], and multisystem inflammation in the SKG mouse [12] have been noted to cause both uveitis and arthritis. It is not known why both uveitis and arthritis should co-exist so frequently. The proteoglycan, aggrecan, hyaluronic acid, and type II collagen are common to both the uvea and the joint. Since uveitis is diverse, a single explanation is unlikely to explain the co-existence of inflammation in two disparate tissues for all diseases.

The Relationship between uveitis and spondyloarthritis

The first publications that recognized that HLA B27 predisposed to ankylosing spondylitis were published in the New England Journal of Medicine [13] and The Lancet [14] in April, 1973. In November, 1973, the association between HLA B27 and acute anterior uveitis was first reported [15]. Studying an English cohort, Brewerton and colleagues reported that 52% of patients with AAU were B27 positive compared to 4% among controls. It is now clear that many genes affect susceptibility to ankylosing spondylitis [16], although HLA B27 has

the greatest impact. Many of these same genes affect the likelihood to develop AAU, although there are also genes which affect susceptibility to AAU without affecting the likelihood to develop ankylosing spondylitis. Implicated genes which affect susceptibility to AAU but not AS include the genes for IL-18R1, IL-10, and EYS [16]. The latter gene codes for a protein implicated in retinal degeneration.

The characteristic phenotype of uveitis in association with HLA B27 is sudden onset, unilateral and recurrent [17]. Recurrences can occur in the contralateral eye, but it is rare for both eyes to be inflamed simultaneously. The intraocular pressure is usually lower in the affected eye. This contrasts HLA B27-associated disease from another cause of unilateral, recurrent, anterior uveitis, that due to herpes simplex infection. Fibrin in the anterior chamber, posterior synechiae, and hypopyon [18] are additional clinical findings that can help diagnose HLA B27-associated uveitis. Although inflammation within the eye can be fulminant in B27-associated diseases, visual acuity between attacks is often excellent {Feltkamp, 1968, 1991}. Estimates of the likelihood that a patient with ankylosing spondylitis will have experienced uveitis vary widely, in part because this number depends greatly on the duration that the cohort is followed. The likelihood is roughly 50% if follow up exceeds forty years [16]. Non-radiographic spondyloarthropathy is also associated with uveitis, although this is addressed by many fewer studies {de Winter, 26745, 2016; Erol, 2018, 26746}.

Rheumatologists are sometimes referred patients with uveitis to assess if a systemic disease is present. Accordingly, it is critical to know if a patient has HLA B27 associated acute anterior uveitis, how likely is spondyloarthropathy also present. The author addressed a slightly different question thirty years ago in reporting that two thirds of patients with AAU in association with spondyloarthropathy are unaware that they suffer from a spondyloarthropathy [17]. In other words, iritis is often the clue that leads to a diagnosis of spondyloarthritis. In a French study of 175 patients with B27-associated uveitis evaluated at an ophthalmology clinic, 78% were felt to have spondyloarthropathy including 46% with ankylosing spondylitis, 10% with presumed ankylosing spondylitis, 12% with undifferentiated spondyloarthropathy, and 10% with joint disease associated with psoriasis or inflammatory bowel disease [19]. This study was published in 2004, well before classification criteria for non-radiographic spondyloarthropathy were proposed [20]. With this broader recognition of spondyloarthritis, several studies have reconsidered the likelihood of spondyloarthritis in a patient with uveitis. This includes one study based on emergency room treatment in Dublin, Ireland [21] and one known as Sentinel that evaluated 798 uveitis patients in Spain [22]. In this latter study on acute anterior uveitis, subjects were excluded if they had known spondyloarthritis. HLA B27 negative subjects were included only if they had suffered more than one episode of AAU. Among the 475 subjects with HLA B27-associated AAU, the authors concluded that 71% had axial disease and 22% had peripheral disease. (The study does not make clear how many had both axial and peripheral disease.) Spondyloarthropathy was also prevalent among those with HLA B27 negative AAU. 19.5% of these patients were thought to have axial disease and 11% had peripheral joint disease. The detection of HLA B27 in a patient with uveitis does not, of course, prove a cause and effect relationship. A corollary to this is that the author does not recommend testing for HLA B27 in a patient who has bilateral uveitis or who has chorioretinitis. Uveitis

does have an increased incidence among patients with either inflammatory bowel disease (IBD) [23] or psoriatic arthritis (PsA) [24]. In both diseases, the likelihood of uveitis is far lower than the likelihood of uveitis in patients with ankylosing spondylitis. Approximately 50% of patients with IBD or PsA who develop uveitis are HLA B27+ [23, 24]. And the phenotype of the uveitis is far more varied than that which is typical of AS. For example, bilateral, chronic, and/or intermediate uveitis is sometimes diagnosed.

The treatment and prevention of acute anterior uveitis

The treatment of acute anterior uveitis is usually just topical corticosteroids and a dilating drop to relieve spasm in the ciliary muscle and to lessen the likelihood that the iris will become stuck to the anterior lens capsule. The latter phenomenon is called posterior synechiae. If patients have very severe disease, locally injected corticosteroid or even a brief course of oral corticosteroid can be considered.

Most patients with acute anterior uveitis do not require prophylactic therapy to prevent future attacks of uveitis. A small percentage of patients, however, have disease which is sufficiently frequent or severe such that it merits preventative medication. Monoclonal antibodies that neutralize tumor necrosis factor consistently reduce the incidence and severity of AAU [25, 26]. These data are derived from trials in which the indication for the TNF inhibitor was the spondyloarthropathy. Etanercept can also reduce the incidence of uveitis, but the data are less consistent in showing benefit [26]. Limited data show that secukinumab can reduce the likelihood to develop uveitis in a patient with spondyloarthritis (Deodhar et.al., EULAR abstract, presented 2018, Low incidence of both new-onset and flares of uveitis in secukinumab-treated patients with ankylosing spondylitis: clinical trial and post-marketing safety analysis). A prospective study indicated that methotrexate effectively reduced the incidence of AAU in patients with AS [27]. Retrospective data suggest that non-steroidal anti-inflammatory drugs might have a similar benefit [28]. Arguably the strongest data for an approach other than a biologic are randomized controlled trials using sulfasalazine to prevent AAU [29–31]. In patients whose joint disease is not severe enough to warrant a biologic, sulfasalazine offers an excellent alternative strategy for prevention.

Medications can induce uveitis. Paradoxically TNF inhibitors can probably cause uveitis [32], just as this class of medication can paradoxically cause either psoriasis or sarcoidosis. The argument that the medication rather than the underlying disease has caused uveitis includes bilateral inflammation and occasionally a case in which dechallenge/rechallenge has been assessed.

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Table 1:

Causes of uveitis and representative examples

Infections such as herpes simplex, herpes zoster, tuberculosis, and syphilis
Syndromes confined primarily to the eye such as pars planitis, sympathetic ophthalmia, and punctate inner choroidopathy
Masquerade syndromes such lymphoma, leukemia, and retinal detachment
Reactions to medications such as checkpoint inhibitors for cancer and rifabutin
Trauma such as after cataract surgery
Systemic immune mediated diseases such as ankylosing spondylitis and inflammatory bowel disease

Table 2

Examples of disease that could cause arthritis and uveitis

Ankylosing spondylitis
Behcet's syndrome
Blau syndrome (Familial synovitis, granulomatous uveitis, and dermatitis)
Crohn's disease
Juvenile idiopathic arthritis
Kawasaki's disease
Lyme disease
NOMID (Neonatal onset multisystem inflammatory disease)
Non-radiographic spondyloarthropathy
Psoriatic arthritis
Reactive arthritis
Relapsing polychondritis
Rheumatic fever
Rheumatoid arthritis with scleritis and secondary uveitis
Sarcoidosis
Sjogren's syndrome
Sweet's syndrome
Systemic lupus erythematosus
Ulcerative colitis
Vasculitis
Whipple's disease

Comments on Table 2: Despite the length of this table, it is not meant to be exhaustive. For example, other infections could conceivably be present in eye and joint. Some of the diseases listed such as ankylosing spondylitis are relatively common and commonly cause uveitis. Others such as rheumatoid arthritis are also relatively common but rarely cause uveitis. Some like Blau syndrome are rare but when it occurs, it commonly causes uveitis. If a patient has both uveitis and arthritis, the differential diagnosis can be narrowed considerably by knowing the phenotype of the uveitis (such as anatomic location, unilateral or bilateral presentation, and suddenness of onset) and symptoms outside either the eye or joint.