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ORIGINAL ARTICLE

Uveitis in spondyloarthritis including psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease

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Abstract Uveitis is a common complication of spondyloarthritis. The "phenotype" of the uveitis characteristic of ankylosing spondylitis (sudden onset, anterior, unilateral, recurrent, more often male) may differ from the phenotype often seen with either psoriatic arthritis or inflammatory bowel disease (insidious onset, anterior and intermediate, bilateral, chronic, and/or more often female). The frequency of uveitis is also much greater in association with ankylosing spondylitis than with either inflammatory bowel disease or psoriasis. Uveitis may affect the choice of therapy and can rarely be a complication of therapy. Uveitis and arthritis also co-exist in several animal models.

Keywords Ankylosing spondylitis · Crohn's disease · HLA B27 · Iritis · Psoriatic arthritis · Ulcerative colitis · Uveitis

Introduction

Uveitis is the most common, clinically important extra-articular manifestation of ankylosing spondylitis [1]. It is also an important association with psoriatic arthritis [2] and with inflammatory bowel disease [3]. This review discusses the relevance of uveitis to these diseases.

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Uveitis: background and definition

The term uvea derives from the Latin word for grape. The uvea is sandwiched between the outer layer of the eye (the cornea and sclera) and the inner layer of the eye (the retina). The most anterior portion of the uvea is the iris. An anterior uveitis is synonymous with an iritis. The ciliary body is posterior to the iris. It is also part of the uveal tract and it is the site where aqueous humor is synthesized. The posterior uveal tract is the choroid, which is highly vascular and helps to supply oxygen to the retina. Anatomic subsets of uveitis include iritis, iridocyclitis when the ciliary body is also inflamed, choroiditis, retinochorodoiditis, and panuveitis when inflammation involves the entire uveal tract. A working group called SUN, Standardization of Uveitis Nomenclature, endorsed the term intermediate uveitis for inflammation primarily in the vitreous humor and posterior uveitis when inflammation involves the choroid or retina [4]. Inflammation within the eye is recognized by biomicroscopy as with a slit lamp or indirect ophthalmoscope. Cells in the anterior chamber typify an anterior uveitis, but technically the anterior chamber is not part of the uveal tract. Cells in the vitreous humor typify an intermediate uveitis, but the vitreous humor is also not a portion of the uveal tract. For these reasons, some experts prefer the term intraocular inflammation over uveitis, although there is an excellent correlation between cells in either the aqueous or vitreous humor and uveal tract inflammation. Leukocytes in the aqueous humor or the vitreous humor could result from an infection or one of the so-called masquerade syndromes described below.

Differential diagnosis

Uveitis has multiple potential causes which include infections, immune-mediated syndromes confined to the eye, and

systemic, immune-mediated diseases. Uveitis can also be caused by medications. A lymphoma, leukemia, retinal detachment, or retinal degeneration could mimic a uveitis by causing leukocytes to be visible on exam. These latter conditions are often referred to collectively as uveitis masquerade syndromes. The systemic immune-mediated diseases that cause uveitis encompass a large number of diseases that cause arthritis. This list includes ankylosing spondylitis, reactive arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, Behcet's disease, subsets of juvenile idiopathic arthritis, sarcoidosis, relapsing polychondritis, systemic lupus erythematosus, and rare genetic conditions such as Blau syndrome and neonatal onset multisystem inflammatory disease (NOMID). Some infections such as Lyme disease and Whipple's disease also fall within the differential diagnosis of co-existent uveitis and arthritis.

The phenotype of uveitis with spondyloarthritis

The different etiologies of uveitis generally have consistent patterns. For example, uveitis associated with ankylosing spondylitis tends to have a sudden onset [5, 6]. Patients might experience a 1- to 2-day prodrome before cells in the anterior chamber can be detected by slit lamp examination. Most of the inflammation is usually anterior although a variable amount of cells in the vitreous humor can appear. Chorioretinal lesions are not characteristic. The iritis associated with ankylosing spondylitis can be intense with hypopyon [7] (pus in the anterior chamber of the eye), fibrin, or posterior synechiae (the pupil becoming attached to the lens posterior to it). However, the visual prognosis associated with this form of uveitis is excellent, and most patients recover full vision after an attack subsides, usually within 2 months.

Uveitis prevalence in spondyloarthritis

Uveitis occurs in up to 50 % of patients with ankylosing spondylitis [8]. A series that includes long follow-up will generally find a higher prevalence of uveitis relative to other reports. In comparison, uveitis affects roughly 2 to 5 % of patients with inflammatory bowel disease [9–13] and approximately 7 % of patients with psoriatic arthritis [14, 15]. Uveitis in association with ankylosing spondylitis affects males slightly more commonly than females [5]. Uveitis in association with inflammatory bowel disease usually affects females [3]. In psoriatic arthritis, based on experience with a limited number of patients, uveitis is predominantly a male disease if there is axial arthritis and a female disease if there is peripheral arthritis [2]. As a consequence, the phenotypic characterization of uveitis in association with IBD or psoriatic arthritis is less complete and based on smaller numbers of patients than studies on ankylosing spondylitis. In general, uveitis in either IBD or psoriatic arthritis appears very similar [2, 3]. The phenotype of the uveitis seems to have a bimodal type distribution. About half of those who develop uveitis tend to be HLA-B27 positive. Some of these individuals will have sudden, recurrent, unilateral, anterior uveitis. But about half of individuals with either psoriatic arthritis or inflammatory bowel disease who develop uveitis have disease which is bilateral, sometimes posterior to the lens in the form of a vitritis, and sometimes insidious in onset. These individuals are sometimes B27 positive. Their disease tends to be much more persistent and is more likely to be associated with cataract or glaucoma. Several studies have identified genetic loci that affect the predisposition to uveitis in association with ankylosing spondylitis separately from affecting predisposition to joint disease [16, 17]. These loci have not as yet been studied in the uveitis in association with psoriatic arthritis or IBD, and the rarity of these entities makes such a study difficult. In addition to HLA B27, several genetic factors such as polymorphisms in the IL-23R are common to ankylosing spondylitis, inflammatory bowel disease, psoriatic arthritis, and uveitis [16, 17].

Prevention of uveitis

Several strategies have been employed to prevent episodes of uveitis in patients with spondyloarthropathies. The most intensely studied strategy is the use of a TNF inhibitor in a patient with ankylosing spondylitis. A variety of TNF inhibitors is effective in this regard [18–20]. Some evidence suggests that etanercept may be less effective as a prophylactic measure relative to the monoclonal antibodies. Data, which are usually anecdotal, also support the concept that a monoclonal antibody to TNF is more effective than a soluble receptor for treating uveitis in most patients [21]. Sulfasalazine [22, 23], methotrexate [24], and perhaps oral nonsteroidals anti-inflammatory drugs [25] can also help to reduce the frequency or intensity of attacks of uveitis in B27-positive patients. These drugs have less cost and less risk than biologic therapies.

Treatment of uveitis

How to treat uveitis is a complex subject that extends beyond the scope of what can be covered thoroughly in a brief review. Anterior uveitis is usually treated successfully with topical therapy that includes corticosteroids and often a dilating drop to prevent posterior synechiae and to reduce spasm of the ciliary muscle. Very severe, unilateral disease with a sudden onset may require locally injected corticosteroids or a brief course of oral prednisone. Disease which is bilateral or posterior to the lens can present additional clinical challenges. Management options might include prednisone, systemic immunosuppression as with methotrexate, or rarely a TNF inhibitor. The clinical recommendation depends in part on the

severity of the disease and the impact which it is having on activities of daily living.

TNF inhibitors have also been reported to cause uveitis. For the most part, the reports are anecdotal, but a report based on a registry of drug-induced side effects also supported this conclusion [26]. It also found that etanercept was a more likely culprit than the monoclonal antibodies. It is very difficult to attribute the induction of uveitis in a patient with ankylosing spondylitis, psoriatic arthritis, or inflammatory bowel disease to a medication since uveitis is common with the underlying disease. Uveitis, however, is not commonly associated with rheumatoid arthritis. The best evidence is based on the development of uveitis in patients without a disease that predisposes to uveitis. The situation is analogous to psoriasis where the data are convincing that a TNF inhibitor can treat psoriasis, but it can also be a rare cause of psoriasis.

Animal models of uveitis and arthritis

The explanation for the co-existence of uveitis and joint disease is not known although overlapping genetic factors have been discovered as noted above. Some proteins and proteoglycans including aggrecan, hyaluronic acid, and type II collagen are shared by both the eye and joint. Uveitis has not been reported in association with arthritis induced in rodents by type II collagen, but not every study includes a careful examination of the eyes. Uveitis does co-exist in arthritis induced in mice by immunization with aggrecan [27]. This model has several aspects that mimic spondyloarthritis including sacro-iliac and spinal involvement. Interestingly in this model, treatment that benefits the arthritis, such as deletion of the gene for gamma interferon, can markedly worsen the uveitis [28]. Clinically, a parallel might be a patient with inactive inflammatory bowel disease who has active uveitis. Uveitis is also a component of several other models of arthritis including adjuvant arthritis induced by immunization with killed mycobacteria [29] and the SKG model due to a mutation in the transmembrane signaling molecule, ZAP70 [30]. Both adjuvant arthritis and the SKG model have elements that resemble spondyloarthritis such as spinal involvement. The uveitis in adjuvant arthritis tends to be granulomatous which is not characteristic of B27-related disease. The HLA B27/beta 2 microglobulin transgenic rat that develops an illness characterized by diarrhea and arthritis has been studied for uveitis with negative results [31].

Conclusion

In summary, uveitis is a common extra-articular manifestation of ankylosing spondylitis. It is less common in association with inflammatory bowel disease or psoriatic arthritis. It is also less consistent in the manner in which it presents in these diseases. Uveitis is an important clinical finding from the perspective of both therapy and the need to understand the etiology of spondyloarthritis.

Conflict of interest None

Disclosures The author has consulted for Abbvie, UCB, Allergan, EMD Serono, Novartis, Regeneron, Xoma, Santen, Genentech, and Sanofi.

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