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The eyes have it: uveitis in patients with spondyloarthritis

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Abstract

Although systemic lupus erythematosus is the prototype multisystem disease, many other inflammatory diseases are also promiscuous, with symptoms manifesting in many organs. Now, new data emphasize the extra-articular involvement in spondyloarthritis, predominantly affecting the eye; however, the factors that account for the observed organ involvement remain unknown.

Canouï-Poitaine *et al.*¹ recently conducted a survey of French rheumatologists to identify extra-articular manifestations in patients with spondyloarthritis (SpA). Dubbed EXTRA and reported in *Arthritis Care & Research*,¹ their survey identified 902 patients, 71% with ankylosing spondylitis (AS) and the rest with psoriatic arthritis or another form of SpA. They concluded that 32.2% of those in the survey had a history of uveitis,¹ a term used to describe intraocular inflammation, which is a topic that often lies outside of general rheumatology training. Indeed, uveitis was 44% more prevalent than psoriasis in this cohort, almost four times more frequently observed than clinically identified inflammatory bowel disease, and substantially more common than heart, lung, or genitourinary associations.¹ Canouï-Poitaine and colleagues' findings strongly agree with the results of a 2008 meta-analysis, which demonstrated a 32.7% prevalence of uveitis among patients with SpA.² These data raise a question: why do uveal disease and sacroiliitis, spondylitis, enthesitis or other articular manifestations of SpA coexist?

SpA is not unique in affecting both joints and the uveal tract. For example, the subset of juvenile idiopathic arthritis that is characterized by typically pauciarticular disease, female predominance, and antinuclear antibody positivity is also often associated with uveitis. Whipple's disease, which results from *Tropheryma whippelii* infection, resembles AS, ulcerative colitis, reactive arthritis and Crohn's disease by having a predilection for bowel, joint, and eye involvement. Lyme disease is another infectious disease with the potential to cause uveitis and arthritis. Furthermore, Behçet disease, sarcoidosis, relapsing polychondritis, Kawasaki disease, other forms of vasculitis, and systemic lupus erythematosus also belong to the differential diagnosis of uveitis and arthritis. In addition, Blau syndrome, an autosomal dominant disease caused by a mutation in *NOD2* (also known as *CARD15*), a gene that has a role in innate immunity, is characterized by uveitis and arthritis. The mystery surrounding the link between the eye and the joint is exemplified by *NOD2*, as alterations in this gene can not only cause the monogenic Blau syndrome, in which the bowel is typically unaffected,³ but can also predispose to Crohn's disease.⁴ Although the polymorphisms in *NOD2* associated with Crohn's disease are distinct from the mutations responsible for Blau syndrome,⁴ these observations clearly demonstrate that the

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Competing interests

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site where the gene is expressed is not sufficient to explain the predominant organ involvement in these conditions.

Presumably more than one mechanism accounts for the link between eye and joint inflammation (Figure 1). Genetic factors such as *HLA-B27* or polymorphisms in the gene encoding the IL-23 receptor (*IL23R*) are common both to patients who develop AS⁵ and those who develop acute anterior uveitis (T. M. Martin, unpublished work). Presumably shared genetic factors contribute to coincidental eye, joint, bowel and skin disease, but this does not preclude identification of genetic factors that are unique for specific organs. For example, data from studies in mice suggest that genes that predispose to peripheral arthritis can be distinguished from the genes that promote axial disease.⁶

The existence of an antigen expressed in all the affected but not the unaffected organs would provide a simple explanation for the organ involvement seen in SpA. Indeed, eyes and joints both contain potential shared antigens such as aggrecan, type II collagen, and hyaluronic acid; however, evidence suggesting that *HLA-B27*-associated diseases represent an autoimmune response against one of these antigens or any other antigen is limited. Furthermore, these antigens are not restricted to the eye and joint.

Environmental factors such as bacillary dysenteries are strongly implicated in some forms of SpA, such as reactive arthritis. Components of bacterial cells have been detected in the inflamed synovium,⁷ and might activate the innate immune system and enable ingress of leukocytes, including T cells, into the joint tissue. Whether a similar phenomenon occurs in the uvea remains unknown. Nevertheless, adhesion molecules do vary between different tissue beds,⁸ and these 'addresses' could conceivably be shared between the uvea and the synovium, directing inflammatory cells to both locations.

Animal models could help clarify the mechanism underlying the dual vulnerability of the eyes and joints in SpA. However, we are aware of only two such models describing this combination of organ involvement, perhaps because the majority of investigators do not meticulously examine the eye for evidence of inflammatory disease. Adjuvant arthritis can be induced in specific strains of rats by an injection of Freund's adjuvant, which consists of killed mycobacteria in mineral oil. The affected rodents develop many features characteristic of SpA including spondylitis, new bone formation and even nongonococcal urethritis;⁹ uveitis is also well described in this model.⁹ In adjuvant arthritis, granulomas can be detected in the uveal tract and the inflammation is often bilateral.⁹ These features differ from uveitis associated with AS, as eye inflammation is typically unilateral and is clinically described as nongranulomatous in this disease.

We and our colleagues have also detected uveitis in an established model of arthritis, in which BALB/c mice are immunized with aggrecan.¹⁰ Aggrecan is the main proteoglycan in entheses, the tendinous insertions in bone, which are a major target for inflammation in SpA. This model of eye disease is more consistent in transgenic mice whose T-cell receptors specifically recognize the G1 epitope of aggrecan.¹⁰ Aggrecan is detectable in synovial and peripheral joints along with the uveal tract, but expression of this proteoglycan is not limited to these sites. Moreover, although the uvea and synovium are both affected in this model, the cytokine dependence of inflammation in each of these organs is substantially different; the absence of IFN- γ ameliorates joint disease while markedly exacerbating eye disease.¹⁰ Nevertheless, this model could be useful in determining whether T cells that migrate into the eye use the same adhesion molecules as those that infiltrate the joints, and will enable further investigation into the link between joint and uveal inflammation.

Ironically, in a clinical sense uveitis and spondylitis are opposites: in patients with AS, uveitis typically has a sudden onset, affects only one eye at a time, and resolves completely

between episodes; sacroiliitis has an insidious onset, is bilateral, and persists continuously. Thus, these features of SpA make an odd couple. Unraveling the mystery of their association could help us better understand the pathoetiology of SpA.

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Figure 1.

The skin, eyes, spine, peripheral joints, tendons and bowel can be simultaneously inflamed in spondyloarthritis. Factors that could contribute to this multiorgan manifestation include genes such as *HLA-B27* and *IL23R*, environmental factors such as bacteria, shared antigens such as aggrecan, and common 'addresses'—such as adhesion molecules—or chemotactic stimuli. Factors that are as yet to be identified undoubtedly contribute to this amalgamation of inflammation.