Psoriatic Eye Manifestations

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ABSTRACT

The relationship between the eye and psoriasis has been recognized for decades, but the precise eye manifestations in patients with psoriasis and psoriatic arthritis are only recently coming to light. Psoriatic eye findings may include conjunctivitis, dry eye, episcleritis, and uveitis, all of which may precede articular changes. Uveitis, seen in 7% to 25% of psoriatic arthritis patients, may be recognized by the presence of conjunctival injection, photophobia, pain, lid swelling, or otherwise unexplained visual changes. Early recognition is paramount because its natural course may lead to vision loss. Immunopathogenesis has shown evidence for T-helper cell (Th) type 1 (Th1) and Th17 involvement in the pathogenesis of uveitis according to the murine experimental autoimmune uveitis model. Corticosteroids are the primary treatment modality; however, increasing emphasis has been placed on immunomodulators and biologics for more intractable cases. Referral to an ophthalmologist is essential for definitive diagnosis and treatment.

INTRODUCTION

The relationship between the eye and psoriasis has been recognized for decades, but the precise eye manifestations in patients with psoriasis are only recently coming to light.¹-⁴ Psoriatic eye findings may include conjunctivitis, dry eye, episcleritis, and uveitis. Eye findings in conjunction with psoriatic arthritis were reported in 1976 by Lambert and Wright, who noted the presence of ocular inflammation in 31.2% of 112 patients with psoriatic arthritis, with conjunctivitis the most common lesion (19.6%), followed by iritis (7.1%).⁵ Psoriatic arthritis has traditionally been thought to precede psoriatic eye manifestations, but a minority of cases are seen in the reverse order.⁶-⁸

Uveitis is a loose term that refers to a large group of diverse diseases. The International Uveitis Study Group classifies intraocular inflammation into anterior (iris or ciliary body), posterior (choroid or retina), intermediate (vitreum, peripheral retina, and pars plana of the ciliary body), or panuveitis (generalized inflammation of entire uvea).⁹,¹⁰ Uveitis may manifest solely in the eye, or it may be associated with a systemic disease. Multiple studies quote the prevalence of uveitis in psoriasis and psoriatic

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Key words: psoriatic uveitis, uveitis, psoriasis, uveitis treatment, biologics, conjunctivitis, psoriatic arthritis, ocular inflammation

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Other diseases that may present with uveitis in conjunction with arthritis include ankylosing spondylitis, Reiter syndrome, juvenile rheumatoid arthritis, inflammatory bowel disease, Behçet disease, Lyme disease, Whipple disease, vasculitides, Kawasaki disease, familial granulomatous uveitis, and sarcoidosis. The pattern of ocular involvement can be distinctive in each of the aforementioned conditions.

Eye

Although many eye structures are not clearly visible to the naked eye, knowledge of eye structure (Figure 1) is necessary to understand more clearly the ocular effects of psoriatic disease. The eye is a neurosensory organ composed of specialized cells and chambers that function to focus, sense, process, and signal incoming light to the visual cortex and other portions of the brain. The most anterior portion of the eye, the cornea, provides refraction and protection for the posterior structures. Immediately posterior to the cornea is the anterior chamber, a space filled with aqueous humor, bound by the iris and lens posteriorly. Light is focused by the lens before passing through the vitreous chamber, which is filled with vitreous humor. Light is then focused on photosensitive receptors on the retina.

Spondyloarthropathies and the eye

Much of the published literature examines psoriatic uveitis within the larger class of spondyloarthropathies (SpAs), which include ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease, and undifferentiated SpA. In the largest analysis of its kind, Zeboulon and colleagues performed a systematic literature search analyzing MEDLINE-listed publications up to 2006. They identified 26,168 patients with SpA, of which 9,757 patients (32.7%) were reported as having one or more flares of uveitis. Articles before the one by Zeboulon’s group had cited uveitis prevalence rates as high as 50% in all SpA patients. The cumulative lifetime incidence of acute anterior uveitis in all SpA patients is 0.2%, except in human leukocyte antigen (HLA)-B27–positive patients in whom the incidence rises to 1% (OR 4.2, 95% CI 3.3-5.3). The onset of uveitis was noted to be at an average of 37 years of age. Patients with SpA show increasing prevalence rates of uveitis with the duration of the articular disease.

Psoriasis and the eye

For patients with psoriasis, uveitis had been commonly thought to occur only in conjunction with psoriatic arthritis; however, there have been many case reports of psoriatic uveitis presenting independent of joint disease. Furthermore, the temporal relationship of these two entities has been disputed. Some recent studies suggest that for most...
SpAs, inflammatory joint manifestations precede uveitis. Nevertheless, some cases of uveitis have been reported to occur even before psoriatic skin disease, and uveitis has been reported as the first presenting sign of SpAs in 0% to 11.4% of cases. The severity of ocular inflammation does not necessarily correlate with extent of joint findings but may correlate with skin disease.

Presentation

Acute uveitis attacks typically present with pain, intense photophobia, red eye, blurred vision/miosis (pupil constriction), and varying degrees of lid edema. Conjunctival injection in acute anterior uveitis begins at, and is most intense around, the edge of the cornea (Figures 2A, B, C). Eyes affected by uveitis may have smaller pupils than on the unaffected side because inflammation may trigger muscle spasm of the iris sphincter, or the pupil could be distorted by posterior synechiae. However, the actual predictive value of symptoms in diagnosing uveitis is unknown. The only warning sign may be unexplained poor vision. Thus, patients who show no evidence of inflammatory changes should nevertheless be referred to an ophthalmologist if symptoms worsen.

Psoriatic uveitis is most commonly anterior, although it can be associated with posterior uveitis as well. It is also more likely than other forms of spondyloarthropathy-associated uveitis to be insidious in onset, bilateral, with periodic flares. All complaints should be referred to an ophthalmologist for evaluation.

Conjunctivitis

Conjunctivitis is a commonly occurring eye condition that can be caused by psoriasis, but it is more commonly due to allergies, bacterial infection, or viral infection. The most common presentation is generalized conjunctival injection (Figure 2D) with mild photophobia, gritty discomfort, and possible discharge. Visual acuity is rarely affected. Allergic conjunctivitis often presents with conjunctival swelling and large cobblestone papillae under the upper lid. Muculopurulent discharge is a hallmark of bacterial infection. Bilateral watery discharge, which may present with swollen preauricular lymph nodes, characterizes viral infection. Increased rates of obstructive meibomian gland dysfunction were noted in psoriatic patients, possibly suggesting an underlying cause for the relationship between conjunctivitis and psoriasis.

Published articles have suggested conjunctivitis prevalence rates in psoriasis patients as high as 64.5%, but otherwise discussion of this relationship has been limited, as shown in the paucity of results in a PubMed search (2011) of psoriasis and conjunctivitis. Uveitis, however, is studied much more frequently in the literature, possibly owing to the more serious sequelae of this particular inflammation.

Dry eye (keratoconjunctivitis sicca)

Keratoconjunctivitis sicca has been cited at a prevalence rate of 2.7% of psoriatic arthritis patients. Some studies suggest prevalence rates of dry eyes as high as 18.75% of psoriasis patients; however, studies have also shown no significant difference in tear-film production between psoriasis patients and controls, although the breakup time of tear film may be decreased.

Episcleritis

Episcleritis (inflammation of the tissue layer covering the sclera) may also occur in conjunction with psoriasis and presents with hyperemia (increased blood flow) that may be pink or even blue, tenderness (although significant tenderness should be cause to suspect scleritis, a more serious condition), and watering (Figures 2E, F).

Course of Disease

Uveitis is the fifth leading cause of visual loss in Europe. Long-term ocular complications of psoriatic uveitis have been poorly studied. Acute
Figure 2. Eye diseases associated with psoriasis. A-C. Uveitis. D. Conjunctivitis. E, F. Episcleritis

Sources: A, B, D-F, Courtesy of the National Eye Institute, David C. Cogan Ophthalmologic Pathology Collection, National Institutes of Health. C, Courtesy of Stephen Foster, M.D., Ocular Immunology and Uveitis Foundation
anterior uveitis is the most common form of uveitis in psoriasis and is the most common uveitis overall. A retrospective study of a cohort of patients with uveitis, irrespective of underlying cause, found that 91% of patients with acute anterior uveitis had normal visual acuity at a final follow-up visit, compared with 64% of those with other forms of uveitis. In B27-associated uveitis, the rates of blindness are up to 11%. Other possible changes secondary to uveitis include secondary glaucoma, retinal vascular occlusions, inflammatory optic neuropathy, retinal detachment, posterior synechiae (adhesions between the iris and the anterior surface of the lens), and hypopyon (a collection of pus inferiorly in the anterior chamber).

Immunopathogenesis
Although the exact underlying mechanisms contributing to the link between psoriasis and uveitis remain poorly understood, there are common etiologic pathways involved in the pathogenesis of both entities.

Psoriasis
Immune responses are largely modulated by CD4+ T-helper (Th) cells with effector CD8+ cells. Naïve CD4+ cells are directed to differentiate into subtypes Th1, Th2, and other newly described types, such as Th17. Th1 cells are traditionally associated with cell-mediated responses to viral and bacterial infections, and Th2 cells are traditionally associated with antibody-mediated responses to parasite activity, such as helminthes.

Psoriasis was initially described as a “Th1 disease” because of the presence of interleukin (IL) 1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon-γ, which are classically produced by Th1 cells. Recent research into psoriasis highlights the T-cell population called Th17 cells. The process is thought to be mediated in part by interferon-alpha, a proinflammatory cytokine, which stimulates myeloid dendritic cells to produce IL-12 and IL-23, which are Th17-promoting cytokines.

Both Th1 and Th17 T cells are involved in the pathogenesis of psoriasis. TNF-α is a key inflammatory mediator that is produced by both Th1 and Th17 reactions and is found at elevated levels in psoriatic skin and in joint fluid from patients with psoriatic arthritis. TNF-α acts by activating a few possible pathways, such as nuclear factor-kappa B (NF-κB), an inflammatory gene transcription factor, or mitogen-activated protein kinase (MAPK), which activates cellular inflammatory activities. There is notable cross-talk in the affected pathways, ensuring that TNF-α activation can incite an inflammatory response. Studies of psoriasis patients treated with TNF-α inhibitors have shown significant clinical response in psoriasis and psoriatic arthritis treatment.

Uveitis
Much of the immunology research into uveitis focuses on the experimental autoimmune uveitis (EAU) and endotoxin-induced uveitis (EIU) models. EAU is induced by immunization of species such as mouse, rat, or rabbit with purified retinal antigens such as retinal soluble antigen (i.e., arrestin) and the interphotoreceptor retinoid-binding protein (IRBP). Immunization results in a uveitis that strongly resembles a Th1-induced reaction with strong dependence on TNF-α, similar to traditional theories of psoriatic uveitis. TNF mRNA expression was increased by 16 times in EAU mice. Notably, intravitreal injection of TNF in rabbits induces uveitis, which is characterized by a cellular infiltrate in the aqueous humor consisting primarily of lymphocytes and monocytes. Treatment of EAU-afflicted rats with soluble TNF receptor to inhibit TNF activity inhibited macrophage activity and decreased photoreceptor damage. In a separate open-label study, TNF inhibitor treatment improved visual acuity in refractory posterior segment intraocular inflammation by leading to an increase in IL-10 expression in the peripheral blood CD4+ T cells.

For EAU, investigation has shown that CD4+ cells are necessary for the development of that type of uveitis, but CD8+ cells are not specifically needed. Mice depleted of CD8+ cells will still develop EAU when immunized with a uveitis-inducing antigen. Although retinal antigen-specific CD8+ cells may induce retinal pathology in rodents, they are not needed for EAU.
Recent studies\(^6\) suggest that Th1, IL-17, and Th17 are also involved in the EAU model, as in psoriasis. Neutralization of IL-17 cytokine by monoclonal antibody prevents and reverses EAU.\(^6\) Interferon-\(\gamma\), on the other hand, exacerbates EAU.\(^6\) EAU induced by components such as complete Freund’s adjuvant, a bacterial adjuvant, has been shown to be IL-17 dependent and is neutralized by IL-17–specific antibodies. However, uveitis induced with antigen-pulsed mature dendritic cells appears to require a Th1 response.\(^6,6^9\) Notably, polarized Th1 or Th17 cells can both produce EAU independently in mice, even without the ability to produce the reciprocal effector cytokine.\(^6^7,7^0\)

**Treatment of Uveitis**

Given the immune-mediated nature of both psoriasis and noninfective uveitis, pharmacotherapy has aimed to suppress the inflammatory response implicated in these diseases. Psoriatic uveitis may be anterior or posterior or both and thus may require different treatment strategies. Acute anterior uveitis may often be treated with a dilating eyedrop to keep the pupil mobile and prevent formation of synechiae (adhesions between the iris and lens).\(^7^1\) Posterior uveitis, although it may be difficult to appreciate on examination, is more commonly responsible for loss of vision,\(^7^2\) increasing the urgency for inflammation treatment. Recommended pharmacotherapy has evolved as understanding of the pathogenesis has improved and as specific inflammatory mediators have been identified. Although the traditional treatment has involved corticosteroids or immunomodifying drugs, in recent years, the use of drugs that target the TNF pathway has been suggested for use in the more intractable cases.

**Corticosteroids and immunomodulators**

Corticosteroids can be administered locally via eyedrops, using periocular or intravitreal injections, or as an intravitreal implant. A randomized, controlled trial found prednisolone acetate 1% eye drops to resolve acute anterior uveitis in 80% to 90% of cases by 4 weeks.\(^7^3\) However, eyedrops are not recommended in the treatment of posterior uveitis because of poor penetration, whereas injections can penetrate more favorably for use in posterior uveitis.\(^7^4\) Intravitreal implants improved visual acuity and inflammation in a long-term follow-up study of patients with noninfectious posterior uveitis.\(^7^5\) Local steroid use for uveitis is associated with complications that deter extensive use. Despite the efficacy of topical eyedrops in the treatment of anterior uveitis, there is a reported risk of increased intraocular pressure in 33% to 42% of patients, induction of cataracts, and increased risk of corneal infection.\(^7^3\) Furthermore, injections combine these side effects with the possibility of globe perforation, orbital fibrosis, ptosis, and endophthalmitis.\(^7^4\) Cases of increased intraocular pressure, cataracts, and retinal detachment have been reported in patients who have received the intravitreal implant.\(^7^5\) Notably, some of the complications associated with these treatment modalities may be hard to disentangle from the inherent risk of these complications from uveitis itself.

The efficacy of systemic corticosteroids was described in some of the earliest reports of psoriasis-associated intraocular inflammation.\(^7\) Systemic corticosteroids may be used in the treatment of both acute and chronic uveitis. The long-term toxicity of systemic corticosteroids warrants consideration of other immunomodulators if doses are too high or are continued for too long, particularly if those doses exceed 10 mg per day. Immunomodulators are also recommended in refractory cases after 1 month of high-dose systemic corticosteroid treatment and when corticosteroids must be tapered because of side effects.\(^7^6\) Tapering of systemic corticosteroids is essential, particularly in those uveitis patients with psoriasis. In addition to the characteristic adrenal suppression in all patients who are not properly tapered from systemic corticosteroids, cessation of systemic corticosteroids has been repeatedly noted to flare skin lesions and may trigger an eruption of pustular psoriasis.\(^7^7\)

Immunomodulators used in the treatment of uveitis include the antimetabolites azathioprine, methotrexate, and mycophenolate mofetil; T-cell inhibitors such as cyclosporine and tacrolimus; and the alkylating agents cyclophosphamide and chlorambucil. The side-effect profile for these classes of drugs includes hematologic abnormalities, liver dysfunction, and gastrointestinal upset. In one study examining the use of these agents in ocular inflammatory disorders, mycophenolate mofetil resulted in remission quicker than methotrexate, whereas azathioprine was associated with more side effects compared with methotrexate and
mycophenolate mofetil. These treatments typically take a long time to achieve effect, during which time corticosteroid use is recommended. Duration of treatment with immunomodulators typically ranges from 6 to 24 months.

**Biologics**

Several studies have considered the efficacy of biologics, namely, TNF inhibitor treatments against ocular inflammatory disease. The three main biologics studied are infliximab, etanercept, and adalimumab, all of which have demonstrated success in treating the cutaneous and articular manifestations of psoriasis.

Although the literature typically focuses on treatments for uveitis caused by a range of SpAs, one psoriasis-specific study, looking at the success of infliximab and adalimumab in treating ocular inflammation, found that seven of eight patients achieved remission of inflammation within an average time of 3.84 ± 0.07 months. Visual acuity improved in two of eight patients, deteriorated in two patients, and remained stable in four patients. The ocular inflammation examined in this study was in the form of panuveitis, scleritis, and anterior uveitis. Of the four patients who were given infliximab, one received a monthly dose of 800 mg, one received a monthly dose of 500 mg, and two patients received monthly doses of 400 mg, although it is unclear how dosages were determined. The remaining patients received one 40-mg dose of adalimumab every 2 weeks, with one patient receiving a 40-mg injection every week. For five of the eight patients, methotrexate was used concomitantly. In addition, one patient was concomitantly receiving both methotrexate and prednisone.

Given the effectiveness of TNF inhibitors in treating uveitis, several studies have examined the role of these agents in preventing uveitis flares in patients treated for systemic disease. Braun and colleagues aggregated data from several studies to obtain a sample size of 717 patients with ankylosing spondylitis (AS). The incidence of anterior uveitis in patients receiving placebo was 15.6 per 100 patient-years versus an incidence rate in infliximab-treated patients of 3.4 per 100 patient-years and an incidence rate in etanercept-treated patients of 7.9 per 100 patient-years. Overall, there was a statistically significant difference between patients receiving placebo and patients receiving TNF blocker therapy ($P = .01$). The statistical significance appeared to be more attributable to infliximab than to etanercept ($P = .005$ vs. $P = .05$). Notably, in this study, the difference between the effectiveness of infliximab and etanercept in preventing flares was not statistically significant ($P = .08$).

Adalimumab was studied in a cohort of 1,250 patients with AS and demonstrated a statistically significant reduction in uveitis flares. Whereas there was a 15/100 patient-years flare rate before treatment, there was a 7.4/100 patient-years flare incidence rate during treatment ($P < .001$). In the pediatric population, several studies have been published that corroborate adalimumab's effectiveness in the treatment of noninfectious uveitis and reduction of flares.

Findings from other studies have challenged the effectiveness of etanercept in preventing uveitis flares. A randomized study of 20 patients being tapered from methotrexate found no statistical difference in the prevention of flares between etanercept- and placebo-treated patients. A separate 46-patient retrospective study examining SpA patients used each patient as his or her own control. Patients reported uveitis flares before and after TNF inhibitor treatment with etanercept, infliximab, or adalimumab. Overall, results from this study demonstrated a statistically significant reduction of flares during TNF inhibitor therapy compared with before TNF inhibitor therapy ($P = .03$). However, subanalysis of this study demonstrated that patients treated with etanercept alone did not show a statistically significant change in incidence of flares compared with patients before etanercept treatment ($P = .92$).

Additional studies looking at the uveitis recurrence rate have found statistically significant differences between the different TNF blocker treatments in effectiveness in decreasing uveitis recurrences rates. Galor and colleagues found a 59% versus a 0% reduction in patients treated with infliximab and etanercept, respectively ($P = .004$). Similarly, Cobo-Ibanez and associates found that the incidence of uveitis flares decreased from 61.73 cases per 100 patient-years to 2.64 in patients receiving infliximab therapy. However, the incidence changed from 34.29/100 patient-years compared with 60 cases...
per 100 patient-years once etanercept treatment was initiated ($P = .041$). These findings conflict with those of Braun’s study. Although Braun’s study was sufficiently powered (717 patients) to detect a 5% difference in the incidence rates of infliximab versus etanercept more than 99% of the time, it did not identify a significant difference between the two drugs in their ability to prevent flares. Kakkassery and colleagues reported the resolution of uveitis when patients formerly taking etanercept were switched to infliximab. 

In the pediatric noninfectious uveitis population, adalimumab was compared with infliximab in an open-label prospective cohort study. Findings suggested that adalimumab and infliximab were comparable in short-term treatment efficacy ($P < .001$) but that adalimumab was superior to infliximab in maintaining remission on treatment (60% vs. 18.8%, $P < .02$), albeit with a small sample size of 33 total patients.

Although TNF inhibitor therapies may be promising methods to treat uveitis or prevent uveitis flares in patients with psoriasis, their use is not undisputed. Their side-effect profile requires diligent drug-safety monitoring as well as the need to exclude multiple sclerosis as the cause of uveitis before initiation. Lim and associates interpreted the results from two drug event databases and concluded that TNF inhibitor therapy, particularly etanercept, may actually be a potential inciter of uveitis. Lim and associates interpreted the results from two drug event databases and concluded that TNF inhibitor therapy, particularly etanercept, may actually be a potential inciter of uveitis. The authors also pointed out that the findings of their study did not corroborate avoiding treatment with etanercept altogether. Rather, if patients receiving etanercept develop uveitis, the authors conclude that it is reasonable to switch to a different TNF blocker.

**CONCLUSION**

Psoriatic eye manifestations, uveitis in particular, can lead to serious consequences, including vision loss. These manifestations have been reported more frequently in psoriasis patients with arthritis, but they have also been reported in psoriatic patients without arthritis. Psoriatic eye manifestations may precede articular changes. Uveitis may be recognized by the dermatologist by the presence of conjunctival injection, photophobia, pain, lid swelling, or otherwise unexplained visual changes. Referral to an ophthalmologist is essential for definitive diagnosis and treatment. Corticosteroids are the primary treatment modality. However, increasing emphasis has been given to immunomodulators and TNF blockers for the more intractable cases. TNF blockers may be promising for the prevention of induction and recurrence of uveitis in psoriasis patients.

More research on the relationship between uveitis and psoriasis is needed. In particular, a greater understanding of the frequency of psoriasis-specific uveitis may shed light on the importance of surveillance. Current experimental eye models for the study of uveitis do not specifically address the pathophysiology of psoriatic uveitis. Long-term follow-up of psoriasis patients with eye manifestations would provide more insight into treatment methods.

Given the serious nature of untreated disease, the dermatologist should have a high index of suspicion for eye findings in psoriasis patients. We recommend regular surveillance of psoriasis patients for visual changes and eye symptoms. Collaboration between ophthalmologists and dermatologists is essential to optimize disease management.

**REFERENCES**


