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Psoriasis: An eye opener – A cross-sectional study in a Tertiary Care Hospital of South India

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ABSTRACT

Introduction: Psoriasis is a multi-system chronic inflammatory skin disease targeting 2% to 3% of the general population. It is a prototype of immune dysregulation mediated by TH1 proinflammatory cytokines such as TNF-α, IFN-gamma, IL-6, and IL-12 with far reaching systemic effects. There is growing and emerging evidence that psoriasis patients have a higher prevalence of associated comorbid diseases, with severe skin disease portends a serious risk for development of these comorbidities and are found to have a higher association of extracutaneous disease manifestations. **Aim:** To look for eye involvement in psoriasis patients and to evaluate the risk and prognostic factors of disease association. **Material and Methods:** 200 Patients with psoriasis were screened for any eye involvement after few unusual case presentations with eye complications during the period from September 2013 - August 2014. **Results:** First case was a post cataract sudden loss of vision secondary to development of uveitis in a female patient aged 52 years, with past history of psoriasis with minimal skin lesions and no arthritis. Another 5 cases of psoriasis with eye involvement were detected during the screening employed in a series of 200 psoriasis cases. **Conclusion:** The present report highlights the importance of psoriasis and eye involvement, need for collaboration between dermatologists and ophthalmologists for thorough examination and evaluation prior to any surgical intervention and also further long term follow-up studies are warranted for confirmation of this causal relationship.

Key words: Psoriasis; eye complications; opthalmological examination

INTRODUCTION

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 [1-4]. 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 of paramount because its natural course may lead to vision loss [5]. 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 [6-9]. Referral to an ophthalmologist is essential for definitive diagnosis and treatment. Herein we report our experience to highlight the importance of thorough evaluation of patients with psoriasis and involvement of eye, and coordination between dermatologists and ophthalmologists prior to any interventions.

METHODS AND RESULTS

Our first case, a 52 year old female was referred from ophthalmology OPD for opinion on her skin lesions present since 30 years. Patient had minimal lesions over the extremities with no itching. There was

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history of winter exacerbation. She gave history of local application of steroids and methotrexate intake for skin lesions 2 years back. There was no history of joint involvement. No long standing debilitating illness like diabetes, tuberculosis and hypertension. She underwent a cataract surgery, phacoemulsification with Intraocular (IOL) implantation for both eyes 1 week apart a month ago. Left eye postoperative was uneventful with visual acquity of 6/6, subsequently she was operated for right eye cataract. Postoperatively when the pad and bandage was removed on the next day she had pain, and no perception of light or projection of rays. The cause of sudden loss of vision could not be explained but on slit lamp examination there was severe anterior uveitis. On examination of right eye there was conjunctival congestion, presence of keratic precipitates with aqueous flare was seen. Upon fundus examination there was no fundal glow, B-scan showed vitreous haze behind the IOL (Fig. 1). Intraocular pressure was 36 mm of Hg. Optical coherence tomography (OCT) was normal in both eyes. Patients was started on antibiotic and steroid eye drops and also a short course of systemic corticosteroids.

On cutaneous examination there were hyperpigmented papules and plaques seen over both lower extremities (Fig. 2). Few post inflammatory hyperpigmentation macules over the back suggestive of old healed lesions. Palms and soles were normal. There were no lesions over the scalp and no nail changes were seen. Hence a clinical diagnosis of psoriasis vulgaris in remission was given. She was advised emollients for regular application.

Retrospectively a literature search was done to look for any association between psoriasis and eye involvement. There was no mention of eye involvement in psoriasis in any of standard textbooks of dermatology. But after extensive research in journals, many published articles of eye involvement in psoriasis with severity of skin lesions and joint involvement were mentioned. This made us to workup the case thoroughly and was referred back to ophthalmologist with relevant information. They investigated for any cause for uveitis and found to be non-infective. Patient was advised few blood investigations along with HLA-B27, but was not done due to logistical reasons. Finally the loss of vision was attributed to development of uveitis, secondary to psoriasis.

This prompted us to screen all our patients with psoriasis with or without joint involvement for any associated eye complications attending our outpatient department or referred cases. In this process over a period from 2013-2014, we screened around 200 psoriasis cases for any involvement of eye and coincidentally we were able to detect 5 cases with eye complications. Two cases had joint involvement, one was HLA-B27 positive. Two cases had extensive psoriasis which was present since more than 20 years (Table 1). All these patients were referred to ophthalmology department with these eye symptoms, they were extensively investigated for any systemic or secondary infective cause and had none. Slit lamp examination confirmed that the eye symptoms were due to anterior uveitis probably secondary to psoriasis. All the cases after initial evaluation were treated and were advised for regular eye follow up to avoid any complications.

Ethical Requirements for Studies Involving live human subjects or animal: Accepted by all authors.

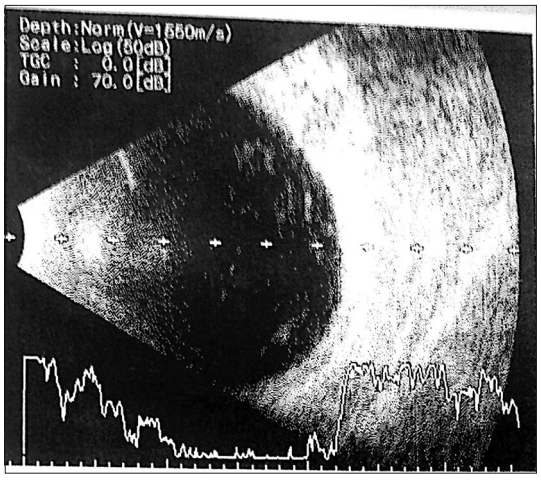

Figure 1: Fundus examination of right eye, there was no fundal glow with B-scan showing vitreous haze behind the IOL indicating anterior uveitis

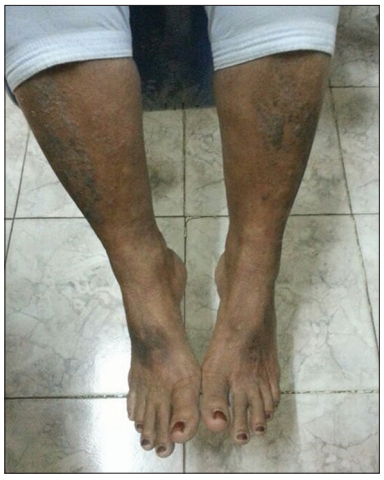

Figure 2: Minimal cutaneous lesions seen as hyperpigmented papules and plaques over both lower extremities suggestive of psoriasis

Table 1: Case details of patients with psoriasis and eye symptoms

S. no	Age/sex	Duration of psoriasis	Eye symptoms	Treatment and outcome
1.	52 yrs/F	30 years	Severe pain in Right eye post cataract. Left eye - normal	Right eye – loss of vision. Left eye – prophylactic antibiotic and steroid eye drops for 2 months. Systemic steroids – 1 week
2.	43 yrs/F	11 years	Redness in both eyes – 6 months	Antibiotic and NSAID drops for 6 weeks
3.	61 yrs/M	17 years with psoriatic arthritis	Pain in both eyes – on and off	Steroid and NSAID drops. Regular follow-up Plan to start – immunomodulatory drugs – Methotrexate
4.	56 yrs/F	22 years, Arthritis, HLA-B27+ve	Pain and photophobia – many years	Eye protection, NSAID Drops. Tapering course of systemic steroids
5.	49 yrs/M	8 years	Reddness in both eyes – 3 months	Antibiotic and NSAID drops for 6 weeks
6.	48 yrs/F	28 years	Watering of eyes, blurred vision – many years	Antibiotic and NSAID eye drops for 6 weeks

The study design was accepted by the Raja Rajeswari Medical College & Hospital.

All subjects gave their informed consent and ethical clearance was obtained from local ethical committee.

DISCUSSION

The relationship between the eye and psoriasis has been recognized for decades, but the precise eye manifestations in patients with psoriasis are only recent findings [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].

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) [7]. 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 arthritis [4,5,8,9].

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 [3,16]. Furthermore, the temporal relationship of these two entities has been disputed. Some recent studies suggest that for most spondyloarthropathies (SpAs), inflammatory joint manifestations precede uveitis [11,12,17]. Nevertheless, some cases of uveitis have been reported to occur even before psoriatic skin disease[6], and uveitis has been reported as the first presenting sign of SpAs in 0% to 11.4% of cases [3]. The severity of ocular inflammation does not necessarily correlate with extent of joint findings but may correlate with skin disease [18-20].

Presentation

Acute uveitis attacks typically present with pain, intense photophobia, red eye, blurred vision/miosis (pupil constriction), and varying degrees of lid edema [21]. Conjunctival injection in acute anterior uveitis begins at, and is most intense around, the edge of the cornea. 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. In fact, the only warning sign may be unexplained poor vision [22]. 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 [10,23]. It is also more likely than other forms of spondyloarthropathy-associated uveitis to be insidious in onset, bilateral, with periodic flares [5,10,23-25].

All complaints should be referred to an ophthalmologist for evaluation. Nonophthalmologists can assess a patient's visual acuity and examine the external eye for circumcorneal injection. Physicians may evaluate with a direct ophthalmoscope for evidence of decreased corneal transparency, keratic precipitates (inflammatory cells on the cornea), and posterior synechiae (adhesions of the lens and iris) [22]. However, the diagnosis of

uveitis must be confirmed with a slit-lamp examination performed by an ophthalmologist. HLA-B27, as noted, is not currently considered diagnostically useful [14].

Course of disease

Uveitis is one of the leading causes of visual loss [26]. Long-term ocular complications of psoriatic uveitis have been poorly studied. Acute 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 [22]. In B27-associated uveitis, the rates of blindness are up to 11% [27]. 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) [22,28].

Other common presentations of eye disease commonly associated with psoriasis include conjunctivitis, keratoconjunctivitis sicca, and episcleritis.

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

Psoriasis was initially described as a "Th1 disease" because of the presence of interleukin1 (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 [29]. 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 [29,30].

Th17 cells are CD4+ T cells that are developmentally and functionally distinct from Th1 and Th2 cells.45 Th17 cells produce IL-17, TNF, and IL-22, which are increased in psoriasis. 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 [31-33]. 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-link 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 [34,35].

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 [36,37], similar to traditional theories of psoriatic uveitis. TNF mRNA expression was increased by 16 times in EAU mice [38]. Notably, intravitreal injection of TNF in rabbits induces uveitis [39], 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 [34,35].

Treatment of uveitis

Given the immune-mediated nature of both psoriasis and non-infective 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 eye drops to keep the pupil mobile and prevent formation of synechiae (adhesions between the iris and lens) [40]. Posterior uveitis, although it

may be difficult to appreciate on examination, is more commonly responsible for loss of vision [41], 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.

Our experience in this study and review of literature shows that uveitis in patients with psoriasis may have distinct clinical features. It appears that in this subset of patients, uveitis is more often bilateral, persists for a long duration, and requires oral NSAID therapy more often than the two most common types of anterior uveitis, idiopathic and HLA-B27-associated anterior uveitis. Bilateral attacks have been reported to occur in 7% to 21% of idiopathic and HLA-B27 associated uveitis patients [11]. Observations of a mean attack duration of 11.2 weeks and the high incidence of oral NSAID use compared with the mean attack duration of 6.2 to 5.3 weeks in idiopathic anterior and HLA-B27-associated anterior uveitis and substantially decreased requirement of supplemental therapy seem to underline the fact that uveitis in psoriasis may have a different clinical course and be more recalcitrant than idiopathic or HLA-B27-associated types [50]. The mean age at diagnosis reported for idiopathic and HLA-B27-associated uveitis is 30 to 40 years, in contrast to almost 44 years mean age in our study population of psoriatic uveitis patients [49,50]. This may indicate that uveitis occurs at a later age in this population, perhaps resulting from the fact that the prevalence of psoriasis increases with age, and psoriatic uveitic patients may be older because psoriasis in general occurs in an older population [3].

We believe that psoriasis is indeed a systemic disease with a propensity for skin, joint, and eye involvement. Knox [3], in his review of 10 patients with psoriasis and uveitis, noted that arthritis was present in none. This has been supported by a mounting number of case reports of an anterior uveitis antedating or occurring after the development of psoriatic skin lesions [44-48]. It has been postulated that HLA-B27 positivity may be associated with greater severity of uveitis in patients with psoriasis; demonstrates a significant difference in the maximum grade of cells demonstrated on clinical examination, and the HLA-B27 patients required systemic nonsteroidal anti-inflammatory drugs more often for the control of intraocular inflammation than did HLA-B27 negative patients. These findings are almost certainly indicative of more resistant, difficult to control, recurrent uveitis in psoriatic patients who are HLA-B27 positive. Indeed, HLA-B27 positivity may contribute to disease expression in patients with psoriatic arthritis as well and has been associated with an earlier age of onset of psoriasis, arthritis, and bilateral sacroileitis [50].

Posterior involvement (retinal vasculitis, cystoid macular edema, and papillitis) was a frequent occurrence. This contrasts with Knox's [3] observation of boggy retinal congestion and edema and pigmentation of both maculae seen in his series of patients with psoriasis. Our study suggests that psoriatic uveitis is usually anterior, recurrent, often bilateral, and may be associated with a high incidence of posterior involvement. Anterior uveitis in such patients typically requires oral nonsteroidal anti-inflammatory drug therapy to achieve and maintain remission of ocular inflammation. Further epidemiologic studies are required to determine the strength of association between psoriasis and uveitis; definition of such an association may allow more frequent ophthalmic monitoring in patients with psoriasis, allow the institution of appropriate treatment with NSAIDs or systemic immunomodulators early on in their treatment, and prevent vision loss in patients with psoriatic uveitis.

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.

CONSENT

The examination of patients is conducted according to the Declaration of Helsinki principles. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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