MANAGEMENT OF OCULAR CICATRICIAL PEMPHIGOID

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ABSTRACT
THE OCULAR CICATRICIAL PEMPHIGOID BELONGS TO A FAMILY OF CHRONICALLY PROGRESSIVE AUTOIMMUNE DISORDERS, PREDOMINANTLY AFFECTING MUCOUS MEMBRANES. THE KEY FEATURE IS THE CHRONICALLY ACTIVE CONJUNCTIVAL INFLAMMATION WITH CONSECUTIVE FIBROSIS, LEADING TO LOSS OF VISION. UNFORTUNATELY, THE EARLY LESIONS ARE SUBTLE AND HARD TO IDENTIFY, MANY PATIENTS BEING TREATED FOR CHRONIC CONJUNCTIVITIS FOR YEARS. THE TREATMENT IS GENERAL AND LOCAL, MEDICAL AND SURGICAL, CONDUCTED BY BOTH THE OPHTHALMOLOGIST AND THE DERMATOLOGIST. MULTIDISCIPLINARY APPROACH AND EARLY DIAGNOSIS ARE THE KEYS TO PREVENTING SERIOUS COMPLICATIONS.

KEYWORDS: PEMPHIGOID, OCULAR, MANAGEMENT

INTRODUCTION

Cicatricial pemphigoid is a rare inherited disorder characterized by erosive mucosal lesions that in time lead to fibrosis. The most common areas involved are the oral mucosa and the conjunctiva. Cicatricial pemphigoid is a chronic and progressive disease with severe long-term complications. [3] The first mention of pemphigoid lesions of the conjunctiva is in 1793 by Wichman. In 1878 Von Graefe first described the progressive nature of the disease to its final stage. The term ocular cicatricial pemphigoid refers to ocular lesions in cicatricial pemphigoid but the ophthalmologist must take into account that this is a systemic disease.[4] The purpose of this article is first of all to draw attention to this rare but debilitating disease and also to underline that the key to an early diagnosis is clinical suspicion.

EPIDEMIOLOGY

In literature the incidence varies between 1/20000 and 1/46000 with a women: men ratio of 2:1.[5] However, although the incidence is apparently low, it is considered that a much larger number of cases remain undiagnosed in the early stages and are being treated for

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[3] Harrisons's Principles of Internal Medicine 17th ed, 2008, McGraw-Hill, page 340
[4] Douglas S. Holsclaw "Ocular Cicatricial Pemphigoid" International Ophthalmology Clinics, 1998, vol 38, Issue 4, 89-106
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"chronic conjunctivitis" for several years until the condition progresses to the final stages. The average age at diagnosis is between 60-70 years but because of the nonspecific changes in the early stages, the lesions may occur as early as 40 years[6], although in our practice we have had a patient who started showing symptoms and subtle conjunctival lesions in her early 30's. In cicatricial pemphigoid, the most frequently involved is the conjunctiva (60-80%) and pharyngeal and oral mucosa (30-84%), and less the nasal, laryngeal, esophageal, anogenital mucosa.[7] Approximately 50% of patients with ocular cicatricial pemphigoid present extraocular lesions.[8]

PATHOGENESIS

Ocular cicatricial pemphigoid is an autoimmune disorder that is triggered in susceptible individuals by a precipitating factor. It is believed that patients presenting HLA-DQw7 gene have a 9.6% higher risk of developing ocular cicatricial pemphigoid scar.[9] The trigger can be conjunctival surgery in a predisposed individual or a drug. In 1970 a new antihypertensive agent called practolol triggered a series of ocular cicatricial pemphigoid cases.[10] It is also considered that topical glaucoma medications can induce subconjunctival fibrosis after long time usage (pilocarpine, timolol). [11] Immunohistochemically this disease is characterized by the formation of deposits of immunoglobulin A, G, M and complement (C3) at the basal membrane of the conjunctival epithelium, forming autoantibodies against various structures of the basal membrane. Autoantigens have been identified that are involved in the pathogenesis of ocular cicatricial pemphigoid, such as BP180, BP230, α6β4 integrin, laminin 5 and collagen type VII. Also, in the active phases of the disease elevated levels of interleukins 4, 5, 6, tumor necrosis factor alpha (TNF-α) have been found in the patients' serum suggesting a poor regulation of the immune system.

CLINICAL ASPECTS

Ocular cicatricial pemphigoid begins with nonspecific symptoms, patients complain of foreign body sensation, local irritation, burning and epiphora and there may be a recurrent papillary conjunctivitis. Some patients do not describe symptoms until advanced stages. Damage is initially unilateral but progresses within 2 years to the fellow eye.[12]

The progression of the disease is characterized by four stages. Stage 1 mimics a chronic conjunctivitis with discrete subepithelial fibrosis of the conjunctiva or erosions of the tarsal conjunctiva. Fibrosis is easily overlooked and can be best seen in the tarsal conjunctiva as fine, whitish striations (Fig1a, 1b).

[6]Albert&Jakobiec's Principles and Practice of Ophthalmology 3rd ed, Saunders-Elsevier 2008, vol 1, chapter 46
[7]Myron Yanoff&Jay S.Duker Ophthalmology 4th ed, Saunders-Elsevier 2013, section 4, chapter 4.10
[8] Elder MJ, Lightman S, Dart JK: Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. Br J Ophthalmol 1995; 79:246-264.
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[10]Wright P: Cicatrizing conjunctivitis. Trans Ophthalmol Soc UK 1986; 105:1.
[11]Hirst LW, Werblin T, Novak M, et al: Druginduced cicatrizing conjunctivitis simulating ocular pemphigoid. Cornea 1982; 1:121.
[12]Laforest C, Huilgol SC, Casson R, et al. Autoimmune bullous diseases: ocular manifestations and management. Drugs 2005;65:1767–79.

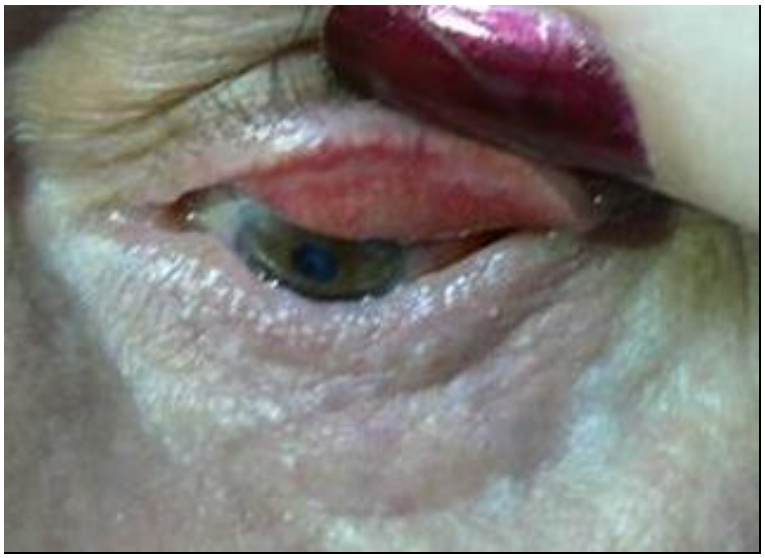

Fig 1a

Fig 1b

In stage 2 the fibrosis process continues and leads to fornixes shortening, more obvious in the lower conjunctival fornix. (Fig 2).

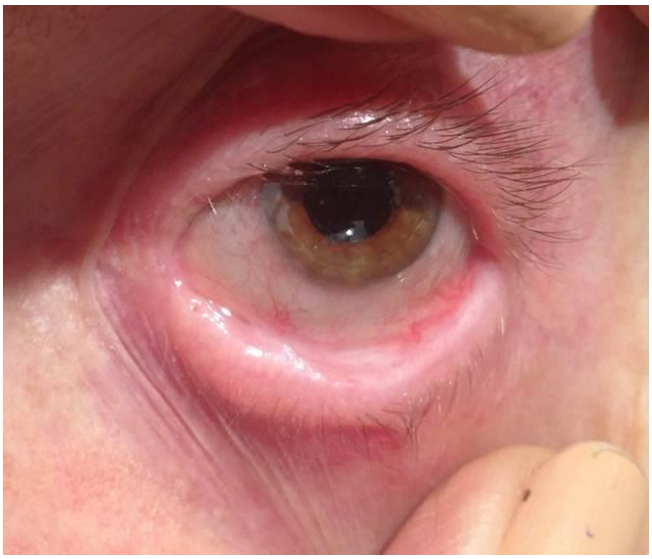

Fig 2

Stage 3 is characterized by the occurrence of symblepharon and stenosis of the lacrimal puncta and the lacrimal ducts. The disease is most commonly diagnosed in this stage. (Fig3)

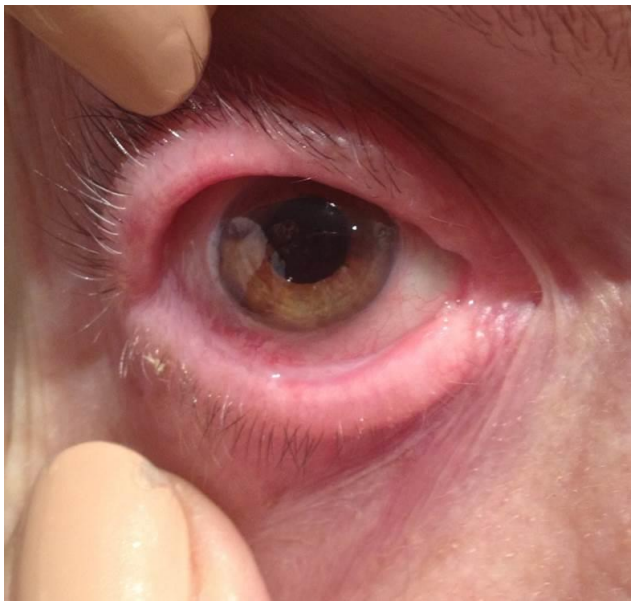

Fig 3

The last stage is considered the biggest therapeutical challenge with severe dry eye, ankiloblepharon and corneal keratinization. (Fig 4)

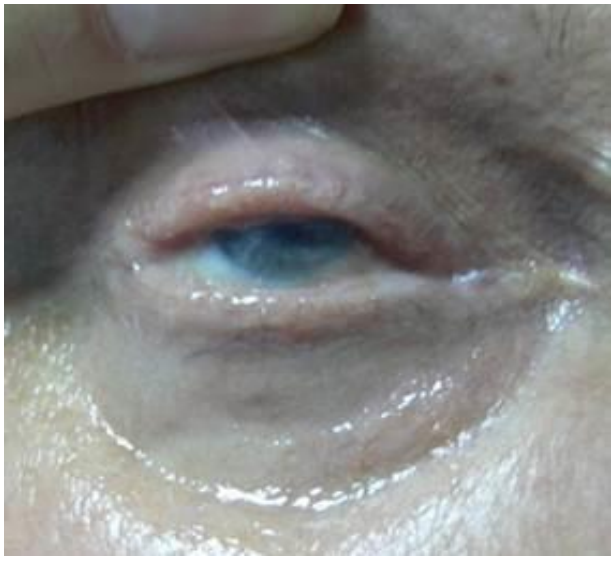

Fig 4

A noteworthy aspect is that this condition leads in time to severe dry eye syndrome. Due to the ongoing process of fibrosis, conjunctival tear glands are destroyed resulting in aqueous and mucin component deficiency in the tear film. Dry eye with simblepharon and trichiasis lead to corneal neovascularization and corneal injury with visual impairment.[13]

Systemic lesions occur, as mentioned, in the oral, laryngeal, esophageal, nasal, anogenital mucosa. Any patient with suspected ocular cicatricial pemphigoid requires a detailed history to find out if they present dysphagia or difficulty breathing.

[13]Albert&Jakobiec's Principles and Practice of Ophthalmology 3rd ed, Saunders-Elsevier 2008, vol 1, chapter 46

DIAGNOSIS

There are a wide variety of diseases that can cause lesions similar to ocular cicatricial pemphigoid, such as atopic keratoconjunctivitis, ocular rosacea, sequelae after chemical burns, Stevens-Johnson syndrome, trachoma, conjunctivitis with adenovirus or trauma but most of them can be excluded based only on the medical history of the patient. Positive diagnosis requires a conjunctival biopsy. Taking the biopsy requires experience as any surgical procedure can accelerate the fibrosis. Where possible the biopsy should include a damaged area and normal tissue. Direct immunofluorescence is used to highlight linear deposits of immunoglobulin and complement in basement membrane of the conjunctival epithelium. If the result is negative but clinical suspicion is high immunoperoxidase assay or electron microscope can be used. [14]

TREATMENT

Treatment of ocular cicatricial pemphigoid patients is difficult and requires an interdisciplinary approach with both ophthalmologist and dermatologist. The goal of the treatment is to control inflammation and to stop the process of fibrosis, which once installed, is not reversible. The ophthalmologist monitors and assesses inflammatory activity of the conjunctiva, performs surgery when necessary and the dermatologist initiates and monitors the systemic treatment.

Systemically, the first-line treatment is prednisone followed by dapsone, methotrexate or azathioprine. When the therapeutic response is incomplete or evolution is very fast cyclophosphamide is administered and for refractory cases or who have severe adverse reactions immunoglobulin (within 1 year) or biological therapy (rituximab) is recommended. This regimen is initiated and supervised by a dermatologist and it is not the purpose of this article.

Local treatment of ocular cicatricial pemphigoid lesions is primarily a supportive one. For dry eye syndrome artificial tears and ointments are prescribed and to relieve inflammation in the acute phase topical non-steroidal or steroidal anti-inflammatory drugs may be used, depending on the appearance of the cornea.

Any surgery is performed only when the systemic status of the patient is stable and the disease is kept under control with appropriate therapy for at least 6 weeks prior to surgery[15]. For trichiasis epilation can be performed but is doesn't offer good long-term results. Electrolysis or crioablation of lash follicles give better results. Dry eye can be managed by occlusion of the lacrimal puncta and for meibomian glands disfunction, eyelid massage and tetracycline orally. For fornixes retraction, if the inflammation is controlled and the disease is in an inactive phase, you can use an oral mucosal graft from an area without lesions or amniotic membrane to reconstruct the fornices and to provide better ocular motility. (Fig5a, 5b)

[14] Albert&Jakobiec's Principles and Practice of Ophthalmology 3rd ed, Saunders-Elsevier 2008, vol 1, chapter 46

[15] Heiligenhans A, Shore JW, Rubin PA, Foster CS. Long-term results of mucous membrane grafting in ocular cicatricial pemphigoid. Ophthalmology. 1993;100:1283.

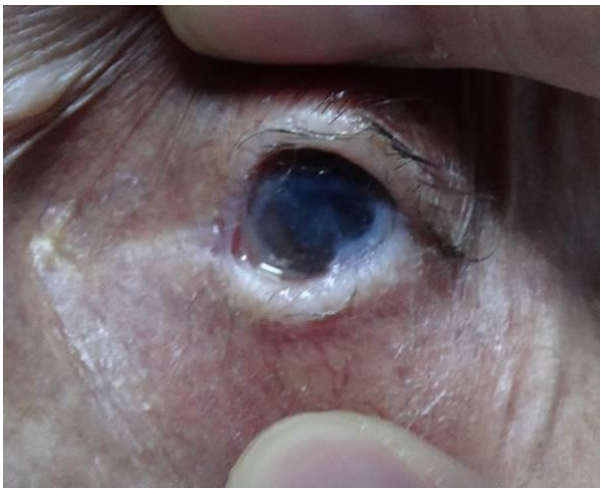

Fig 5a Stage 4 ocular cicatricial pemphigoid

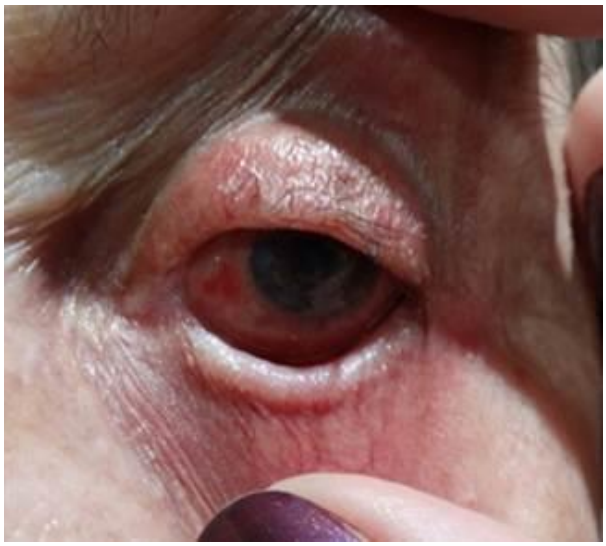

Fig 5b Same patient, after oral mucosa graft in the inferior fornix

Corneal surgery is contraindicated in patients with severe ocular cicatricial pemphigoid. Penetrating keratoplasty can be practiced only in certain patients with good eyelid function and without the tear film disorders. Unfortunately, most patients have corneal hypoesthesia, severe dry eye and altered eyelid dynamics. For these patients keratoprosthesis is the only surgical alternative that offers real opportunities for visual rehabilitation.[16]

CONCLUSIONS

Ocular cicatricial pemphigoid prognosis depends on how early it is diagnosed and treated. At the time of diagnosis up to 60% of patients are already in stage 3.[17] This condition remains very difficult to treat due to its progressive autoimmune character and the absence of early diagnostic methods. The best option for early diagnosis remains the clinical suspicion based on the physician's experience. Also, being a systemic disease, the patient should be investigated for evidence of other mucosal lesions, oral, esophageal, etc. Although there are multiple treatment options, the results are still unsatisfactory. Due to the autoimmune character, the ophthalmological treatment, both medical and surgical, is palliative, not curative.

[16] Albert&Jakobiec's Principles and Practice of Ophthalmology 3rd ed, Saunders-Elsevier 2008, vol 1, chapter 46

[17] Myron Yanoff&Jay S.Duker Ophthalmology 4th ed, Saunders-Elsevier 2013, section 4, chapter 4.10

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