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Case Report

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Immunologic-allergic corneal infiltrate in atopic patient undergoing multidrug topical treatment for POAG: Diagnostic and therapeutic management

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Abstract

The authors present a case of ocular surface inflammation, Meibomian Gland Dysfunction (MGD), and marginal corneal ulcers that occurred in atopic patient with multitherapy topical treatment for POAG with products preserved with BAK. Restoration of ocular surface equilibrium was obtained by suspending all previously used drugs and using less toxic ocular hypotensive agents, and treating MGD with associated dry eye syndrome; low-dose hydrocortisone was administered after performing a conjunctival swab to rule out ongoing infections.

Keywords: Marginal corneal infiltrates; Iatrogenic keratitis; Glaucoma and ocular surface; Peripheral keratitis; NSAIDs ocular disease.

Introduction

Long-term use of topical glaucoma medications is known to be associated with ophthalmic complications, in particular ocular surface toxicity, most often due to the nature of the preservatives included in the medications [1,2]. The ocular surface is vulnerable also to other drugs and preservatives, traumatic injuries, microorganisms, dry eye and immuno-allergic reactions [3]. Furthermore, studies conducted via video recording, revealed that 20-60% of patients had inadvertently touched part of the eye either the ocular surface, eyelids or eyelashes while attempting to administer their eye drops [4,5] with further adverse consequences.

The authors present the clinical case of a patient affected by Primary Open Angle Glaucoma (POAG), in multi-treatment with topical drugs, characterized by intense ocular surface inflammation and marginal corneal infiltrates. The diagnostic hypotheses and the set therapy are presented. The results are discussed even considering literature data.

Patient case

Medical history

58 -year-old male patient, former smoker, affected by arterial hypertension for 6 years, dyslipidemia, and seasonal rhinitis. Systemic therapy with ACE inhibitors, diuretics, statins, antiplatelet agents, oral H-1 receptor antagonists in cycles, gastric protection (histamine type-2 receptor antagonists).

Therapy in both eyes for Primary Open Angle Glaucoma (POAG) for 7 years in initial tonometric compensation with beta-blockers; subsequent association of prostaglandin in multidose eye drops. For 9 months he has been reporting worsening hyperemia, tearing, frequent whitish secretion in the morning, burning, photophobia, itching, foreign body sensation, in both

eyes. He has carried out therapies with numerous eye drops containing different classes of antibiotics, antivirals, NSAIDs, and sodium hyaluronate for this inflammatory state, without appreciable benefits, indeed with progressive worsening of the symptoms.

In the last few weeks, an increase in ocular tone has also been noted, for which it was necessary to increase the hypotensive therapy. Multidose Diclofenac eye drops was administered for four days and accentuation of the inflammation and worsening of the visual acuity were noted.

Ocular examination

Right Eye (RE): Best Corrected Visual Acuity (BCVA): 20/20 (Snellen). Intraocular Pressure (IOP): 19 mmHg diffuse. Slit Lamp Exam (SLE): hyperemia, prevalent in the inferior-nasal sector of the bulbar conjunctiva; micropapillary reaction of the upper tarsal conjunctiva; lid margin hyperemia with Meibomian Gland Dysfunction (MGD); lower eyelid laxity with excessive scleral exposure (scleral show); increased blink frequency; neovascularization in the limbus from 4 to 6 o'clock; superficial epithelial defects and corneal infiltrates in the lower sectors. Fluorescein dye staining (Fluotest): peripheral epithelial defects at 5-6 o'clock (Figure 1*)*. Break up time (BUT): 2 sec.

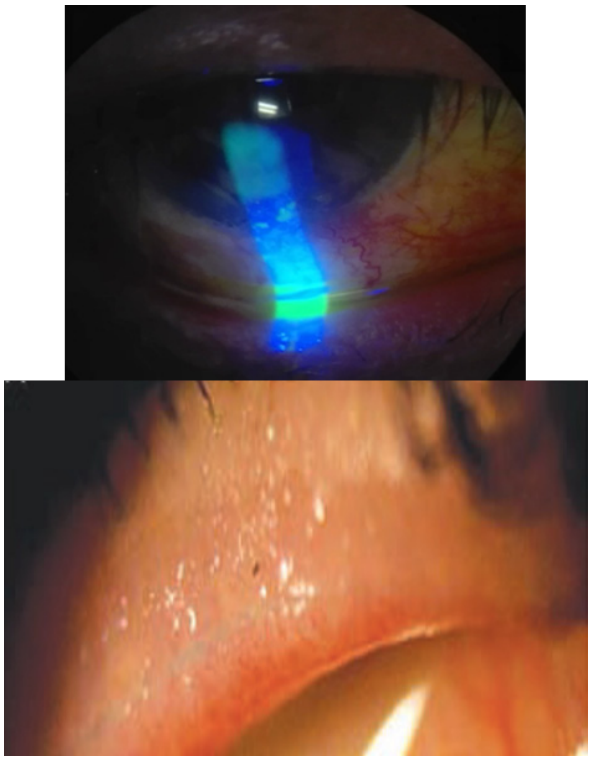

Figure 1: (A) Right eye: superficial epithelial defects and corneal infiltrates; (B) Meibomian gland dysfunction.

Left eye (LE): BCVA: 15/20 (Snellen). IOP: 21 mmHg. SLE: diffuse hyperemia of the bulbar and tarsal conjunctiva and of the palpebral margin; MGD; marginal infiltrate at 8 o'clock and a similar smaller lesion at 9 o'clock (Figure 2). Fluotes: diffuse superficial punctate keratitis; marginal ulcers at 8 and 9 o' clock (Figure 3). BUT: 0-1 sec.

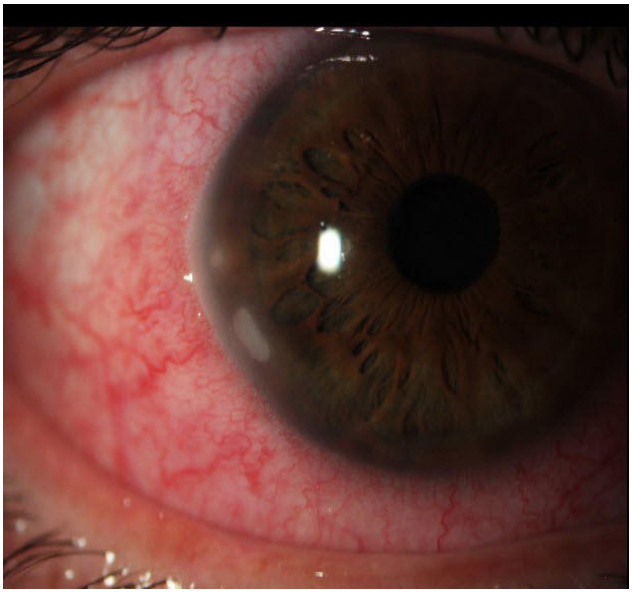

Figure 2: Left eye: marginal infiltrate at 8 and 9 o'clock; severe conjunctival hyperemia; reduced tear meniscus.

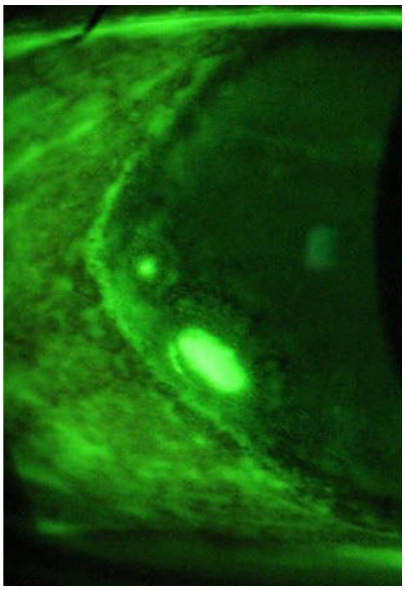

Figure 3: Left Eye: marginal ulcers at 8 and 9 o' clock (fluorescein staining at yellow filter).

Therapy in progress at the first observation

Ofloxacin 3 mg/ml (2 drops every 4 hours); Ganciclovir gel 1.5 mg/g (1 drop every 8 hours); Olopatadine (2 drops every 12 hours); Diclofenac sodium 1 mg/ml (2 drops every 8 hours); Timolol 5 mg/ml + Brimonidine 2 mg/ml (2 drops every 8 hours); Bimatoprost 0.1mg/ml (2 drops in the evening); multidose Sodium hyaluronate 0.15% (2 drops every 4 hours).

All the eye drops used were preserved with Benzalkonium chloride with concentrations from 0.05 to 0.2 mg/ml.

Clinical management

The therapies in progress were immediately suspended and only saline solution (0.9% NaCl) was administered: 2 drops every 3 hours; Acetazolamide cp 250 mg (1 cp every 12 hours) has also been associated.

After three days of wash out, a conjunctival swab was taken from each eye for culture research of bacteria and fungi; in addition, scraping of the superior tarsal conjunctiva was performed for cytological evaluation in light microscopy and Scanning Electron Microscopy (SEM).

After a further four days, negative results of the swabs for the microbiological tests were received and the SEM cytological examination showed serious suffering of the epithelial cells with disappearance of the microvilli and inflammatory infiltrate (Figures 3,4). A new therapeutic scheme was therefore undertaken.

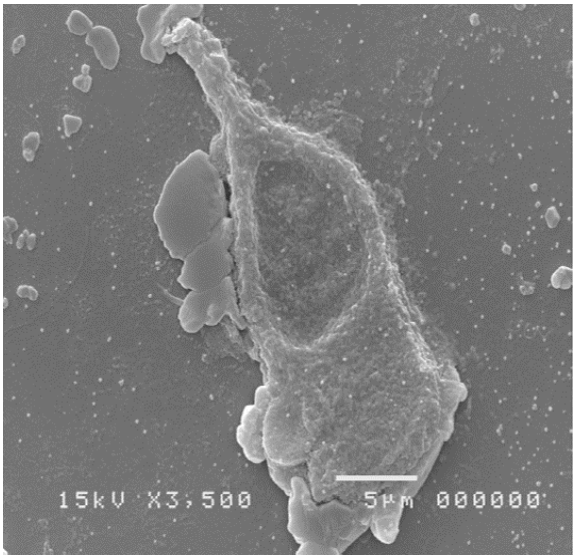

Figure 3: Scanning electron microscopy (SEM): Dysmorphic epithelial cell, without microvilli.

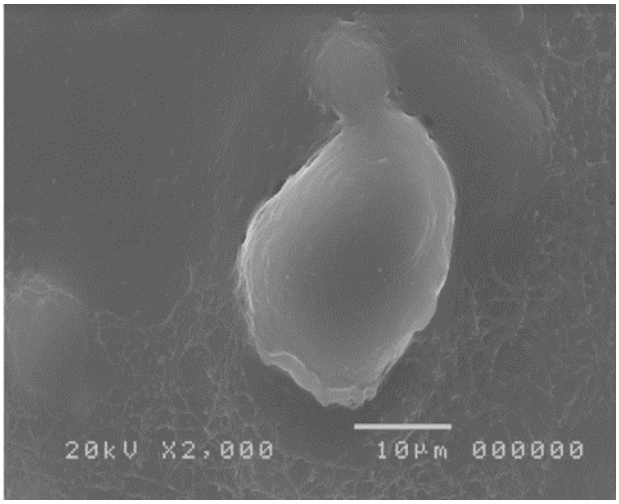

Figure 4: Scanning electron microscopy (SEM): Neutrophil granulocyte undergoing active phagocytosis.

New therapy

1. Eyelid hygiene (warm compresses and subsequent cleansing) with medicated eye gauze twice a day.
2. Doxycycline 100 mg, one tablet per day for 20 days.
3. Timolol 1 mg/g gel, 1 drop per day in the morning.
4. Latanoprost 0.05 mg/ml in multidose package without preservatives, 1 drop per day in the evening.
5. Hydrocortisone sodium phosphate 3.35 mg/ml single dose, 1 drop every 8 hours for 7 days, then every 12 hours for other 14 days.
6. Trehalose 3 g% + Sodium hyaluronate 0.15 g% + Carbopol 974P 0.25 g% gel, 1 drop every 8 hours.
7. Tetracycline 1 g% + Sulfamethylthiazole 5 g% ointment, to be applied at bedtime for 10 days.

None of the prescribed products contained BAK.

Follow up

After three weeks of therapy, complete re-epithelialisation of the cornea and regression of the inflammatory reaction was observed in both eyes.

Negative corneal fluotest in both eyes (Figures 5,6). BUT: RE: 10 sec; LE: 8 sec.

IOP: 18 mmHg in both eyes. BCVA: 20/20 in both eyes.

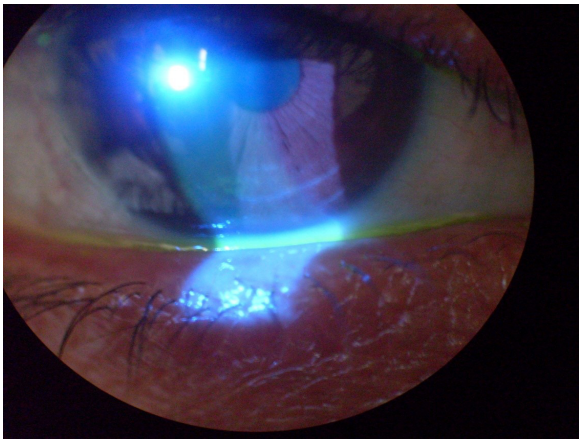

Figure 5: Right eye: Corneal fluotest negative.

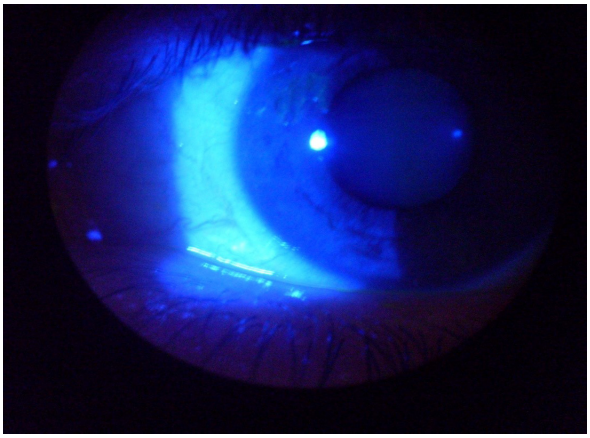

Figure 6: Left eye: Corneal fluotest negative.

Discussion

Autoimmune diseases generally involve the peripheral cornea: the most frequent are Mooren's ulcer and collagen vascular diseases, with or without scleritis [6]. In fact, the peripheral cornea is closer to the conjunctiva, where all the immunological mechanism necessary to generate an immune response are located. In the peripheral cornea there is a higher concentration of Langerhans cells, IgM and C1, the recognition unit of the classical pathway of complement, than in the central cornea. Antigen-antibody complexes, wherever they are formed (cornea, tears, aqueous humor, or limbal vessels), can activate complement more effectively in the peripheral than in the central cornea. Peripheral corneal diseases that often represent a hypersensitivity reaction to exogenous antigens, such as those of

the Staphylococcus aureus cell wall, include catarrhal infiltrates, ulcers, and phlyctenules [7].

Marginal corneal ulcers have been reported also in eyes having topical Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and other drugs (antibiotics, ocular hypotensives, antihistamines), but not topical corticosteroids [8,9]. The ulcers in PRK patients occurred with diclofenac sodium and ketorolac tromethamine eye drops; probably the use of a contact lens coupled with the epithelial defect after PRK leads to local concentrations high enough to damage keratocytes and white blood cells in the post-PRK eye, leading to the development of marginal infiltrates [10]. Persistent bilateral corneal marginal infiltrates may occasionally arise as a side effect of monoclonal antibody treatments for rheumatic conditions [11,12].

In the present case, presumably the chronic use of glaucoma drugs resulted in a severe condition of dry eye and lesions of the corneal and conjunctival epithelium. The appearance of corneal lesions had led to the addition of topical antibiotics and antivirals which probably aggravated the conditions of the ocular surface.

The subsequent administration of non-preservative-free diclofenac on an already damaged ocular surface must have triggered an immune reaction of the peripheral cornea which led to the formation of a marginal infiltrate and ulceration. The patient is also an atopic subject, with a history of seasonal rhinitis.

Suspecting a toxic and immune-allergic reaction to the eye drops used, a seven-day washing was carried out and, subsequently, a therapy with less toxic active ingredients for the ocular surface, BAK-free.

Inflammation of the lid margin and meibomian glands was treated [13] and a gel tear substitute containing hyaluronic acid, Carbopol and Trehalose was administered to restore the tear film. For the ocular surface inflammation, a soft steroid was used, to avoid the risks of an elevation of the IOP and a delay in the healing of corneal ulcers.

It is important to emphasize that, before administering steroids, microbiological examinations were carried out in the case in question to rule out ongoing infections, because the management of infectious keratitis is very different [14,15].

The therapy implemented resulted in a complete resolution of the inflammatory and ulcerative picture of the ocular surface and made it possible to rebalance the IOP and the precorneal tear film in just four weeks.

Conclusions

The patient who came to our observation, under chronic treatment with ocular hypotensive drugs, presented a complex clinical picture, characterized by severe inflammation of the ocular surface, dry eye, MGD and marginal corneal ulcers.

The disturbances appeared during multitherapy for POAG, with BAK-preserved products, and were exacerbated by the addition of antimicrobials and NSAIDs.

Understanding the etiopathogenetic mechanisms that underlie the processes is essential for establishing the therapeutic strategy. The suspension of the drugs used and the subsequent prescription of treatment for MGD and dry eye, associated with less toxic drugs for lowering IOP, allowed the restoration of the balance of the ocular surface; the use of soft steroids, after exclusion of active infections, allowed to rapidly reduce the inflammatory reactions, without interfering with the repair processes of the corneal ulcers and with the control of the IOP.

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