ORIGINAL RESEARCH PAPER

Ophthalmology

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MULTIRESISTANT ULCER

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ABSTRACT

To present a case of severe corneal ulcer and its medical and surgical treatment.

INTRODUCTION

According to the International Dry Eye Workshop, 2007: 'Dry eye is a multifactorial disease of the tears and ocular surface that results in ocular discomfort, visual disturbance and tear film instability with potential damage to the ocular surface'.

There are many causes for dry eye disease, but all share the existence of a self-perpetuating cycle of decreased outflow / high evaporation of tears that leads to ocular surface inflammation/ lesion, which in turn causes further decreased outflow/high evaporation of tears.

Interruption of this cycle it's not always simple, allowing for ocular changes to happen. Filamentous keratitis and corneal ulcers are some of the complications of long-standing dry eye disease.

Tear substitutes have a relatively simple formulation that cannot match the complex number of components and structure of the normal tear film. Also, their delivery is periodic, rather than continuous. Improvement of ocular surface inflammation is another option.

CASE PRESENTATION

We present the case of a sixty-nine year old white woman with severe dry eye disease and filamentary keratitis.

Past medical history of salivary gland extraction in 1970, hypertension, cerebrovascular accident in 2008, diabetes since 2013 and major depressive disorder for many years. She was medicated with pantoprazole, irbesartan, nifedipine, perindopril, spironolactone and furosemide. Antidepressants and anxiolytics were likely to be used (but the patient didn't know).

Since the diagnosis, in 2009, she experienced multiple episodes of acute disease, with the need of artificial tears and topical antibiotics (with or without topical steroids).

In her initial observation, the patient had a best-corrected visual acuity of 20/20 Snellen (0 LogMAR) in the right eye and 20/32 Snellen (0.2 LogMAR) in the left eye.

She would usually complain of decreased visual acuity, foreign body sensation, ocular pain and red eye. The lesions ranged from diffuse superficial punctate keratitis with filaments to white interstitial stromal infiltrates. Periods of acute conjunctivitis were also common. With time, these lesions resulted in important corneal scarring and thinning.

The first episode of perforated ulcer happened on May 2012 (FIGURE 1). There was worsening of the usual complaints and also a water-like secretion. The right eye biomicroscopy revealed purulent exudate in the inferior fornix, conjunctival hyperemia, inferomedial paracentral corneal ulcer showing signs of seidel, partial iris protrusion through the defect, shallow anterior chamber and flare. She was admitted in our hospital. Specimens for bacterial and fungal culture were made (results were negative). There was a good response to the therapeutic contact lens, topical gentamicin plus moxifloxacin drops and oral ciprofloxacin. During the time in the hospital, she developed a superficial ulcer in the other eye (probably self-inflicted due to excessive scrubbing), which was treated with moxifloxacin drops and artificial tears. Despite some improvement, after a few follow-up visits, we started the patient on autologous serum drops. The patient felt better, and best-corrected visual acuity was 20/32 Snellen (0.2 LogMAR) in the right eye and 20/50 Snellen (0.4 LogMAR) in the left eye. On the biomicroscopy there was only a discrete superficial punctate keratitis in the right eye. Autologous serum drops were applied for about a month, and then we kept her only on artificial tears. One month later, the clinical condition got worse again, with foreign body sensation in the left eye and corrected visual acuity of 20/100 Snellen (0.7 LogMAR). The biomicroscopy revealed severe dry eye on both eyes (break-up time < 2s; Shirmer's test < 4mm in 5 minutes) and the left eye was starting to develop a new ulcer in the center of the previous scar. She was medicated with ciprofloxacin ointment.

Throughout the next year, the situation had a fluctuating course. Periods of worsening and need of topical antibiotics were frequent. She restarted the autologous serum drops and topical fluorometholone, oral prednisolone and oral pilocarpine were introduced (FIGURE 2). The absence of response to these medical treatments led us to occlude the lacrimal puncta, with little effect on the break-up time. Considering the few options left, oral cyclosporine (daily dose of 25 mg) was started and the patient showed signs of improvement.

The second perforated ulcer happened on November 2013. She complained of pain in the right eye and blurred vision. The right eye biomicroscopy revealed inferomedial paracentral corneal ulcer showing signs of seidel, athalamia and partial iris protusion through the defect. We applied a therapeutic contact lens and the patient was medicated with moxifloxacin and ketorolac drops (besides the usual artificial plus autologous serum drops). Oral cyclosporine and topical steroids were stopped. Medical treatment wasn't enough, so one week later the patient was scheduled for a surgical procedure (suture of the defect plus fibrin glue seal, air bubble injection in the anterior chamber and reintroduction of a therapeutic contact lens). There was loss of the contact lens and suture dehiscence after one week. The resulting anterior synechia was helping to maintain anterior chamber integrity. Another

surgical procedure so close to the previous one was considered inappropriate. We allowed healing of the defect with supportive measures (reapplication of a contact lens and antibiotic coverage). Two weeks later, the patient was feeling better with right eye visual acuity of 20/200 Snellen (1.0 LogMAR). The biomicroscopy showed loss of therapeutic contact lens, conjunctival hyperemia, diffuse superficial punctate keratitis, corneal thinning (in the place where the ulcer was before), good anterior chamber without Seidel and anterior synechia. A new ulcer started to develop, four weeks after the previous one. The patient was medicated with methotrexate (7,5mg once weekly). The response was promising but the drug had to be stopped due to important side effects (diarrhea and oral ulcers).

During the next six months, the clinical situation was maintained similarly. Following the Internal Medicine Physician advice, we prescribed a dose of methotrexate that didn't cause side effects and helped to control the clinical situation.

The third perforated ulcer happened on July 2014. The patient complaints were similar to the previous episodes, and right eye visual acuity was counting fingers by this time. She underwent an application of multiple layers of amniotic membrane to cover the entire right cornea. We sutured the amniotic membrane to the cornea and sclera and applied a therapeutic contact lens in the end. Four days later there was loss of the amniotic membrane and contact lens, with shallow of the anterior chamber, seidel and iris protruding to the defect. On the next day, we did a surgical repair of the ulcer using the modified Gunderson conjunctival flap technique and applied fibrin glue plus a therapeutic contact lens. The flap proved to be insufficient in preventing seidel and we scheduled the patient for application of amniotic membrane one week later. The right eye evolved favorably in the subsequent follow-up visits. However, three weeks after the procedure, she started to develop a central and profound deep ulcer in the other eye. We could manage the ulcer with the standard measures of eye occlusion and topical antibiotics.

Currently, the lesion is stable (FIGURE 3). The patient presents with best-corrected visual acuities of hand motion on the right eye and 20/63 Snellen (0.5 LogMAR) on the left eye. Right eye biomicroscopy reveals an anterior synechia, preserved but shallow anterior chamber depth and maintained ocular tonus. Left eye biomicroscopy reveals diffuse superficial punctate keratitis and central dellen. She is medicated with both artificial and autologous serum drops and oral methotrexate (5 mg once weekly).

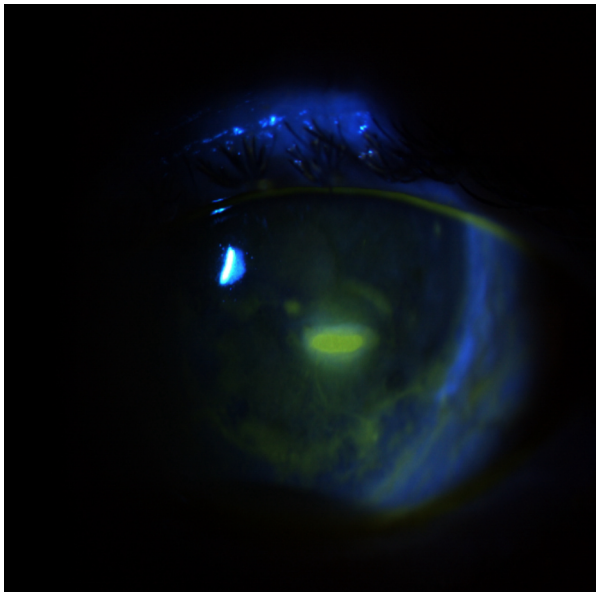

FIGURE 1 – First episode of perforated ulcer

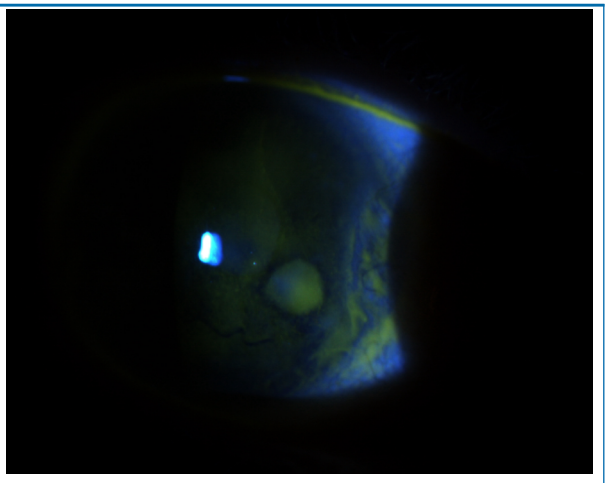

FIGURE 2 – Before restarting autologous serum drops

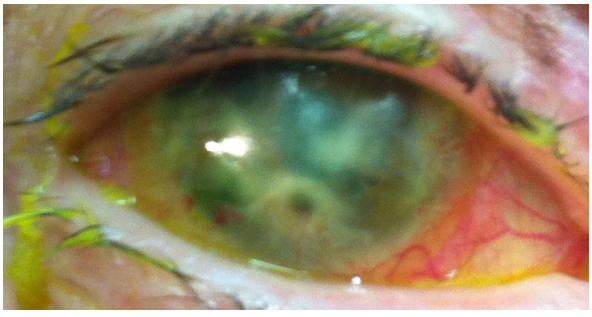

FIGURE 3 – After several episodes of perforation

DISCUSSION

Besides the age, there are other important factors that may be involved in the dry eye disease of this patient. The fact that the patient has diabetes can lead to reflex hyposecretion of the lacrimal gland. On the other hand, the existing psychiatric pathology could have influenced significantly the course of the disease. The patient was non-compliant with the prescribed treatments or sometimes started to do topical steroids without medical advice. A frequent side effect of the drugs used for depressive disorder is also hyposecretion of the lacrimal gland.

CONCLUSION

This clinical case gathers in one patient almost all medical and surgical treatments available by now to treat dry eye disease and manage its complications. It is unfortunate to see that, despite all efforts, visual acuity inevitably decreases to a point where actions are taken just to preserve the eye. However, we must weight the benefit of such measures versus the risk for the patient.

In our case, before the development of an ulcer, autologous serum drops appear to be the medical treatment that has the most impact in the regression of corneal lesions occurring as a consequence of long-standing dry eye disease. This is probably due to blood serum composition, which includes factors such as epidermal growth factor, transforming growth factor , vitamin A, fibronectin and neuropeptides namely substance P and insulin-like growth factors. Although the proportion of components is different from the natural tear, these factors lack in the artificial tears currently being commercialized.

Transplantation of preserved human amniotic membrane can be considered an important development in surgery of the ocular surface. It is applied to the eye as a basement membrane substitute or as a temporary graft / patch to promote epithelial wound healing on the surface of the eye. Amniotic membrane contains different kinds of growth factors that are responsible for its anti-inflammatory and anti-scarring effects. The exact mechanism and role of each of these growth factors are yet to be found. In addition to amniotic membrane's clinical properties, the easiness on how it

can be obtained and stored makes its use quite appealing. Besides, it has the potential to be used in several clinical contexts as an alternative to the existing treatments.

We need controlled clinical trials to improve the quality of evidence for the use of autologous serum drops and amniotic membrane in ocular disease and comparative studies regarding its use and standard treatments.

New medical treatment options are under investigation and show promising results.

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