REFRACTORY CHILDHOOD OCULAR ROSACEA TREATED BY INFLIXIMAB

Introduction

Childhood ocular rosacea is a rare and often misdiagnosed disorder associated with chronic blepharitis, and in many cases, chalazia and phlyctenular keratoconjunctivitis [1]. It is also known as blepharokeratoconjunctivitis [2, 3].

Childhood ocular rosacea is believed to be the consequence of chronic meibomian gland dysfunction, which is responsible for chronic inflammation of the ocular surface. Stagnation of the meibum, due to an increase in its liquefaction temperature, encourages secondary bacterial infection. In addition, the bacterial lipases affecting the meibum increase its viscosity. A cell-mediated delayed hypersensitivity reaction to bacterial exotoxins and to bacterial parietals is at the origin of phlyctenular keratoconjunctivitis [4].

Childhood blepharokeratoconjunctivitis is known to be a rare condition whose diagnosis is often delayed. It is commonly asymmetrical without any associated cutaneous signs [5], making diagnosis even more challenging. Its clinical spectrum is polymorphous including conjunctival hyperemia, superficial punctate keratitis, anterior blepharitis, recurrent chalazia, phlyctenular keratoconjunctivitis and corneal infiltrates [2, 6].

Populations of India, Pakistan and the Middle East have been shown to be more seriously affected by this disease. There is an added risk of neovascularization and corneal perforation in its most severe forms [7]. In young patients, we must also consider the amblyogenic potential of the pathology, particularly irregular astigmatism linked to corneal scarring [8]. Thus, stepladder management must be advocated, including eyelid hygiene, warm compresses, a combination of oral and topical antibiotics, topical steroids, and steroid sparing strategies such as topical cyclosporine A, which may be necessary depending on the severity of the disease [9]. Appropriate and sometimes more aggressive treatments of this chronic condition are essential to avoid amblyopia, blinding corneal scars and other complications [10].

Biologic agents have revolutionized the care management of many autoimmune diseases. Infliximab is a chimeric monoclonal antibody biologic systemic drug targeting tumor necrosis factor alpha (TNF-α). It has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis.

We report a case of refractory childhood ocular rosacea, which required an increased course of treatments leading to biologics.

Case report

The case concerns an 11-year-old girl referred in 2009 for bilateral keratoconjunctivitis and recurrent chalazia with a history of facial dermatitis. Clinical investigation revealed a previous history of acne rosacea in the patient's mother and atopy in the patient's sister. The initial clinical findings showed large limbal phlyctenules in both eyes (Figure 1). Best-corrected visual acuity was measured at 20/32 in both eyes. There was no sign of ocular allergy such as giant papillary conjunctivitis or Trantas dots.

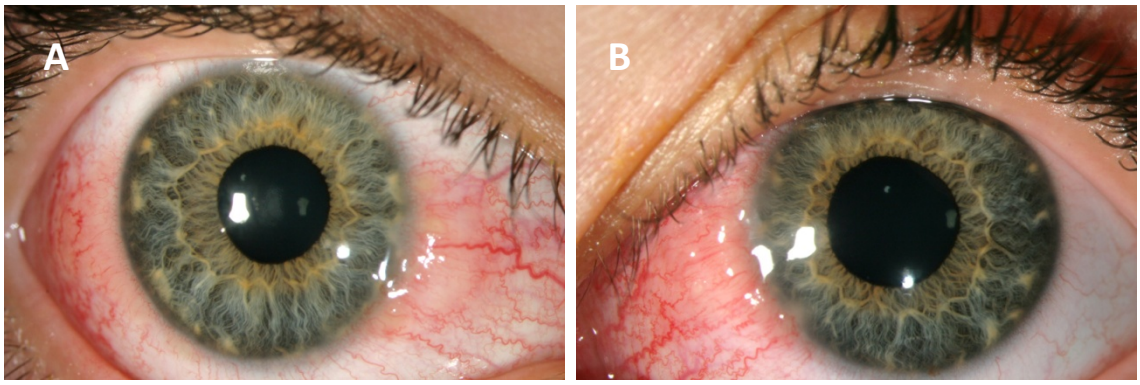

Figure 1 : Right eye (a) and left eye (b). Initial slit lamp images demonstrating large bilateral limbal phlyctenules.

Blepharokeratoconjunctivitis associated with rosacea was suspected. Cutaneous rosacea was confirmed by histological analyses of cutaneous biopsy showing numerous non-necrotizing epithelioid granulomas with giant cells sometimes centered on hair follicles in keeping with granular rosacea.

Sarcoidosis, the main differential diagnosis as regards histological analyses was ruled out by performing a chest abdomen pelvis computed tomography scan, by angiotensin converting enzyme dosing and respiratory functions tests looking for a restrictive syndrome. Lupus was also ruled out by performing a biological check-up. Clinical cutaneous signs were not compatible with psoriasis or atopic dermatitis.

Despite systemic treatment combining doxycycline 100 mg per day, local corticosteroid therapy with topical dexamethasone 6 drops per day, topical azithromycin 1.5%, topical cyclosporine A 2% (2 drops per day) and regular eyelid hygiene, this young girl remained steroid dependent. Therefore, the symptoms recurred when the local corticosteroid therapy dexamethasone was decreased to 2 drops per day (Figure 2). On the contrary, the cutaneous inflammation regressed with doxycycline treatment alone.

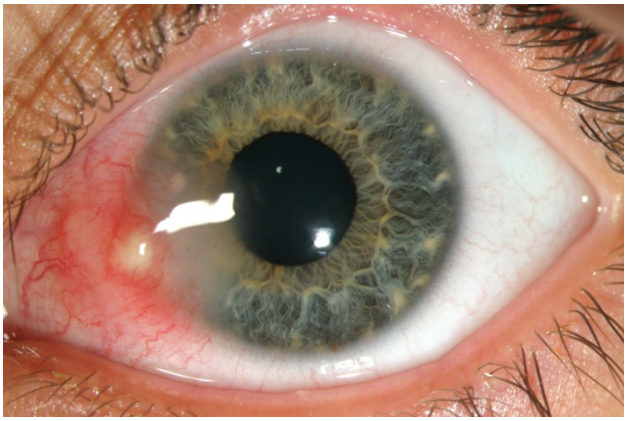

Figure 2 : Large limbal phlyctenule recurrence in the left eye despite doxycycline treatment, topical dexamethasone 2 drops per day and topical cyclosporine A 2% (2 drops per day).

In April 2011, at the age of 13 years, given the potential involvement of a sight-threatening corneal disease, systemic corticosteroid therapy was started at 0.5 mg/kg of prednisone per day without success. The symptoms recurred when the local corticosteroid therapy dexamethasone was decreased to 3 drops per day and prednisone 10 mg a day (Figure 3). Then, azathioprine (125 mg per day) was added. Unfortunately, this did not prevent the worsening of the condition in the right eye, which until then had been less affected (Figure 4). Visual acuity in her right eye was limited to counting fingers and to 20/200 in her left eye.

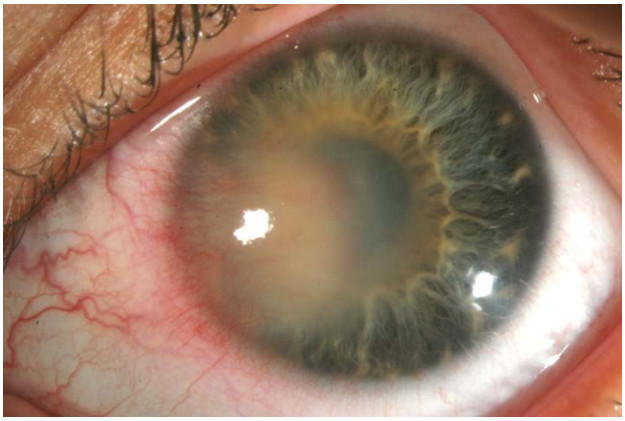

Figure 3 : Recurrence of corneal involvement in the left eye despite doxycycline treatment, topical dexamethasone 3 drops per day, topical cyclosporine A 2% (2 drops per day) and prednisone 10 mg a day.

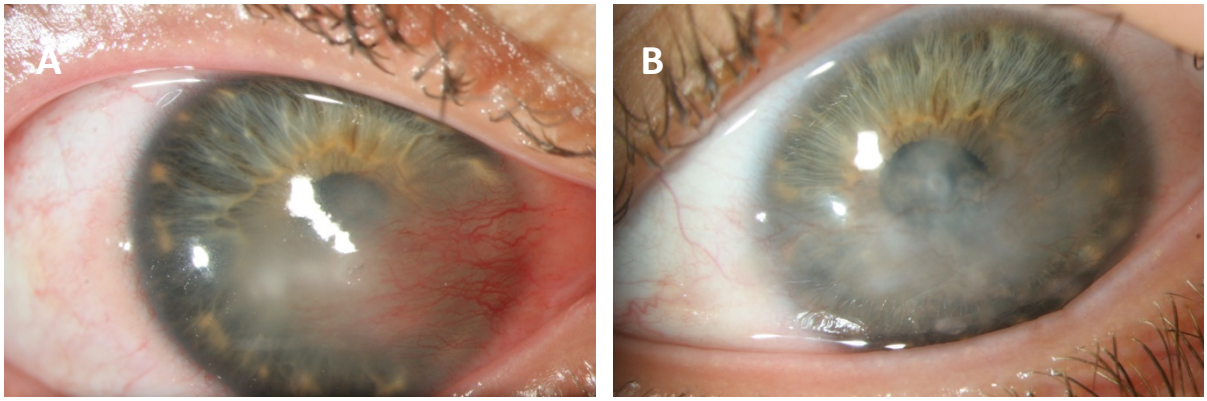

Figure 4 : Right eye (a) and left eye (b). Corneal involvement worsening in both eyes despite doxycycline treatment, topical dexamethasone 8 drops per day, topical cyclosporine A 2% (2 drops per day), prednisone 15 mg a day and azathioprine 125 mg per day.

The case of our young patient with sight-threatening ocular surface disease thought to be an exceptionally severe case of childhood ocular rosacea was presented in multidisciplinary meeting. In July 2013, intravenous treatment by anti TNFα (infliximab, 5 mg/kg every 8 weeks) and weekly 12.5 mg methotrexate were introduced, in combination with steroid therapy increased to 1 mg/kg of prednisone per day. This treatment provided complete remission with weaning off steroid therapy. However, best-corrected visual acuity remained limited to 20/63 in the left eye due to corneal opacity but increased to 20/25 in the right eye (Figure 5).

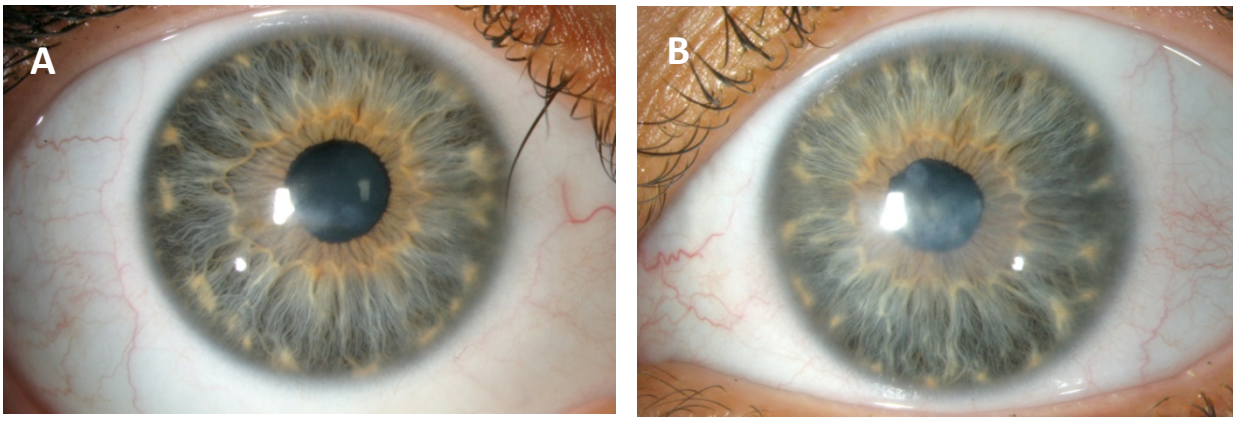

Figure 5 : Right eye (a) and left eye (b). Slit lamp images demonstrating complete remission in both eyes 4 months after treatment introduction including intravenous infliximab, weekly oral methotrexate and prednisone 10 mg.

In July 2015, infliximab was stopped after two years of treatment. Three months later, the ocular surface inflammation recurred with reappearance of corneal neovascularization (Figure 6). The patient was still treated with oral doxycycline and methotrexate. Infliximab was started again providing complete regression of symptoms (figure 7) and withdrawal of local and systemic corticosteroids. The patient remained in steroid-free remission.

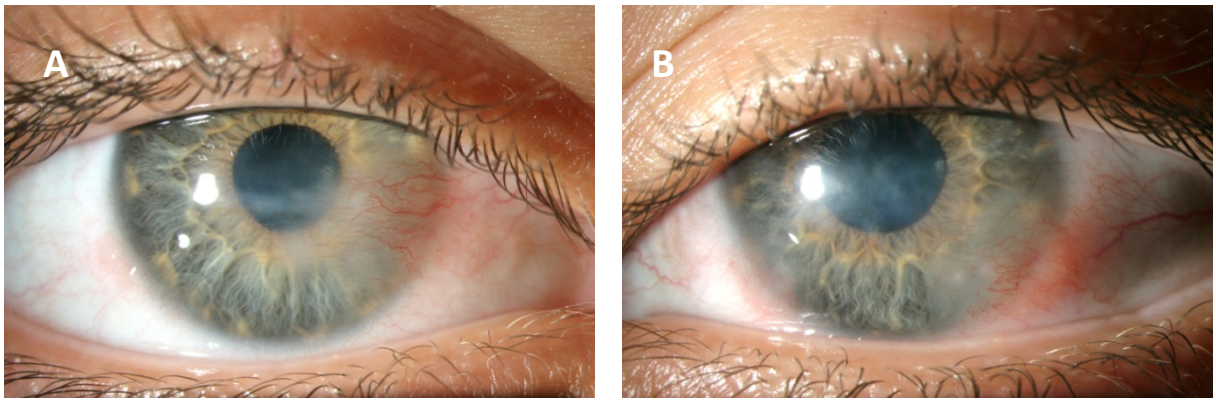

Figure 6 : Right eye (a) and left eye (b). Recurrence of corneal involvement in September 2015 after withdrawal of infliximab.

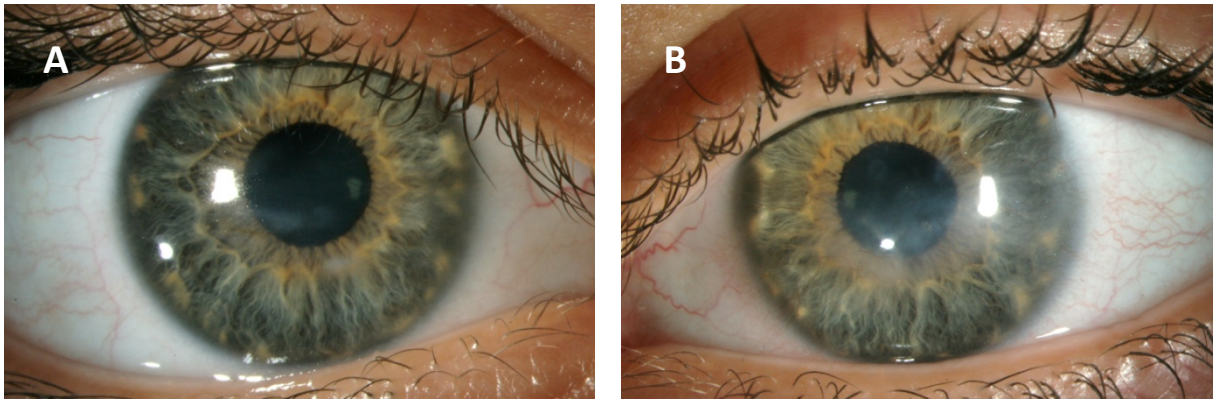

Figure 7 : Right eye (a) and left eye (b). Remission in both eyes after infliximab reintroduction.

Discussion

The treatment of childhood ocular rosacea is based on its presumed physiopathogenic mechanisms and relies on lid hygiene and antibiotics to control bacterial proliferation and to improve meibomian gland function. Oral cyclines may induce the reduction of lipases produced by the commensal staphylococci diminishing the liberation of toxic fatty acids produced by the hydrolysis of meibomian lipids [7]. This treatment is authorized for children over eight years of age due to risk of tooth staining [11]. For children under eight years of age, antibiotic treatment by macrolide (erythromycin or josamycin) might be suggested. However, these last two antibiotic treatments have now been replaced by local azithromycin, whose simplified therapeutic approach encourages observance in children [3]. Corticosteroid eye drops [12] or cyclosporine A eye drops as corticosteroid-sparing agent are associated in the most severe forms of disease [9].

Although ocular manifestations usually respond well to antibiotic therapy and local therapy, systemic immunosuppressive therapy is required in extreme cases, as reported here. In particular, a more severe form of the disease, with a greater likelihood of developing corneal vascularization, marginal corneal ulceration, and corneal phlyctenules has been reported in Asian and Middle Eastern children [7, 13]. Among fifty-one Asian patients, diagnosed with pediatric blepharokeratoconjunctivitis, one patient had severe inflammatory disease that required systemic control with oral prednisolone and five patients required surgical treatment. Among these five patients, three required deep lamellar keratoplasty (2 tectonic and 1 optical), and two had cornea gluing alone [13]. However, destructive phenotype has been described in white children, which may require systemic immunosuppression. Indeed, due to persistent active disease, three among ten white European adolescents with an aggressive condition, were started on systemic immunomodulatory treatments (azathioprine, mycophenolate mofetil or prednisolone), despite ongoing treatment with local steroid therapy [14]. These treatments achieved disease remission within three months with no adverse events reported.

In the case reported here, corticosteroid use and the addition of azathioprine failed to control ocular surface inflammation because our patient remained steroid dependent. Therefore, treatment had to be intensified with biologics. The off-label use of infliximab, by analogy with treatments used for severe cases of mucous membrane pemphigoid [15], was started after multidisciplinary discussion with pediatricians and dermatologists. As far as we know, there have been no other reports in the literature of childhood ocular rosacea in children or in adults treated by biologics.

Corneal complications of rosacea, such as phlyctenules and corneal infiltrates are thought to be caused by means of an immunological specific T-cell response [3]. There is substantial evidence that TNFα has protective effects against T-cell-mediated autoimmunity, which may explain its efficacy here [16].

Nonetheless, a male patient with a granulomatous variant of cutaneous rosacea was treated with adalimumab for 3 months without any improvement on dermatological lesions [17]. Furthermore, the development of severe cutaneous rosacea in a patient treated with infliximab for ulcerative colitis was reported in 2009 [18]. Hence, studies are required to evaluate the efficacy and tolerance of anti-TNFα in the management of ocular and dermatological rosacea.

Lastly, topical anti-TNFα known as ESBA105, although not currently available commercially, could be a future option in the management of ocular complications of rosacea [19].

Conclusion

Severe forms of blepharokeratoconjunctivitis or childhood ocular rosacea are well known, though fortunately rare. This pediatric case of exceptionally serious blepharokeratoconjunctivitis underlines the importance of appropriate and sometimes aggressive treatments.

References

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