

# Phlyctenular keratoconjunctivitis – an atypically severe case treated with systemic biologic immunosuppressive therapy

## Abstract

**Purpose:** To report an atypically severe and refractory phlyctenular keratoconjunctivitis case treated successfully with systemic biologic immunosuppressive therapy.

**Methods:** A 10-year-old female was followed in the ophthalmology clinic for three years for a severe form of bilateral PKC. The patient was treated for blepharitis and intestinal parasitosis, and underwent topical corticosteroid therapy, followed by subconjunctival injections and systemic corticosteroids with no clinical improvement. An association of topical cyclosporine A and oral methotrexate had no clinical response either. Phlyctenae of the cornea remained evident with neovascularization, progressive peripheral corneal thinning and occasional anterior chamber reaction.

**Results:** The patient was treated with a combination of infliximab and methotrexate and corticosteroid therapy was tapered, with a fast and sustained resolution of the symptoms and corneal signs. Eleven months past initiation of the treatment, the patient remains asymptomatic and without any recurrence of the disease.

**Conclusion:** Phlyctenular keratoconjunctivitis may present with a broad spectrum of symptoms and signs, and its severity varies significantly. In cases of severe PKC, which are refractory to conventional therapy, systemic biologic immunosuppressive therapy may be a valuable alternative.

**Keywords:** phlyctenular keratoconjunctivitis, biologic immunosuppressive therapy

Joana Valério Sequeira  
Valadares<sup>1</sup>

Ana Bastos-Carvalho<sup>1</sup>

José Manuel Pedroso  
Franco<sup>1</sup>

Ana Filipa Mourão<sup>1,2</sup>

Manuel Monteiro-Grillo<sup>3</sup>

1 Centro Hospitalar Lisboa Norte, Hospital Santa Maria, Lisbon, Portugal

2 Centro Hospitalar Lisboa Ocidental, Egas Moniz Hospital, Lisbon, Portugal

3 Department of Ophthalmology, Centro Hospitalar Lisboa Norte, Hospital Santa Maria, Lisbon, Portugal

## Introduction

Phlyctenular keratoconjunctivitis (PKC) is a non infectious inflammatory process, presumably resulting from type IV hypersensitivity reaction to systemic antigens [1], [2]. It usually occurs in children and young adults, with predominance in young women [3], [4]. While the condition has been described as a complication of staphylococcal blepharitis, *Mycobacterium tuberculosis* and intestinal parasites are other possible causes [1], [3], [5].

Phlyctenular keratoconjunctivitis can be unilateral or bilateral and is characterized by phlyctenae of the conjunctiva and cornea [6]. Conjunctival phlyctenae are often transient and are associated with mild to moderate symptoms [7]. Corneal lesions tend to be more severe, spreading centripetally and perpendicularly to the limbus. These lesions may be associated with neovascularization and may ulcerate leaving corneal opacities, thinning and permanent vision impairment [1]. Another rare but possible complication is corneal perforation [2], [6], [7].

The treatment approach depends on the aetiology. The majority of cases associated to staphylococcal blepharitis respond to eyelid hygiene and oral antibiotics, while more

severe cases may require topical corticosteroids [1], [7]. When this therapy is insufficient or associated to complications, topical immunosuppressive agents as cyclosporine A (CsA) and tacrolimus may be an option [2], [6]. Phlyctenular keratoconjunctivitis seems to be an expression of altered immune mechanisms and the use of systemic immunosuppressive therapy in patients with ocular inflammation, including children, has been investigated and documented in a variety of recalcitrant forms of uveitis [4], [8]. Infliximab, an antitumor necrosis factor  $\alpha$  (anti-TNF- $\alpha$ ) agent, has shown to be effective in HLA-B27-associated anterior uveitis, uveitis and scleritis associated with rheumatic disease, ocular Behçet's syndrome, refractory posterior uveitis, sarcoidosis and in uveitis associated with oligoarticular juvenile idiopathic arthritis [8].

## Case description

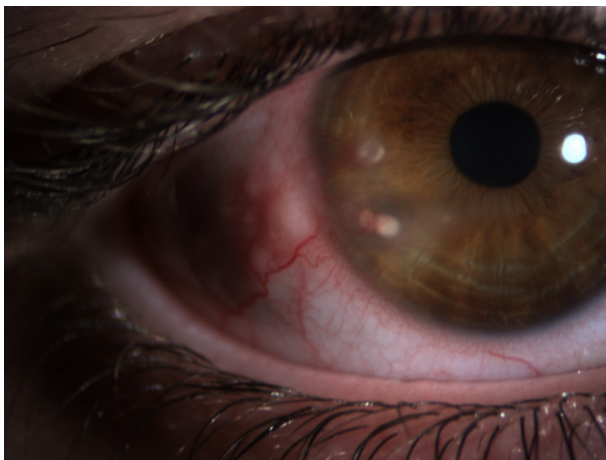
A 10-year-old white female was referred to our clinics presenting bilateral red eye, blurry vision and photophobia lasting for several months. She noticed progressive

worsening of symptoms, regardless of several courses of topical corticosteroids and antibiotics.

The patient had no relevant past systemic or ocular history, and had a family history of systemic lupus erythematosus (grandmother). Systemic clinical exam denoted body overweight (body mass index of 22, at 90<sup>th</sup> percentile) and facial acne, but was otherwise unremarkable.

Ocular examination revealed best visual acuity of 20/30 in the right eye and 20/40 in the left eye.

Intraocular pressure (IOP) was 18 mmHg in the right and left eye. Slit-lamp examination of the right eye revealed mild anterior blepharitis, conjunctival injection, conjunctival phlyctenae and peripheral temporal corneal infiltrates with overlying neovascularization (Figure 1). The left eye showed mild anterior blepharitis, temporal peripheral and pericentral corneal infiltrates and neovascularization.



**Figure 1:** Slit-lamp photograph at presentation reveals in the right eye conjunctival hyperemia and bulbar phlyctenae, infiltrates of peripheral temporal cornea at eight and nine clock hours with corneal neovascularization.

The primary diagnosis of PKC associated to staphylococcal blepharitis was assumed and etiological investigation was made. The stool parasite test was positive for *Giardia intestinalis*. All other exams, including tuberculin skin test and chest radiography were normal. Dermatological examination excluded other cutaneous diseases apart from acne vulgaris. Rheumatologic evaluation revealed unremarkable clinical examination and normal value ranges for rheumatoid factor, antinuclear antibodies, double-stranded DNA antibodies, antibodies to cytoplasmic components and antiphospholipid antibodies.

The patient was started on topical prednisolone acetate q6h and prednisolone ointment [7]. Additionally, blepharitis treatment was prescribed (eyelid hygiene, warm compresses and oral doxycycline 200 mg/day followed by 100 mg/day [1], [7]) as well as anti-parasitic therapy with metronidazol 250 mg t.i.d. for five days.

The patient responded well to the initial treatment with topical corticosteroids, but tapering this therapy resulted in reactivation of the corneal phlyctenae and exacerbation of the neovascularization.

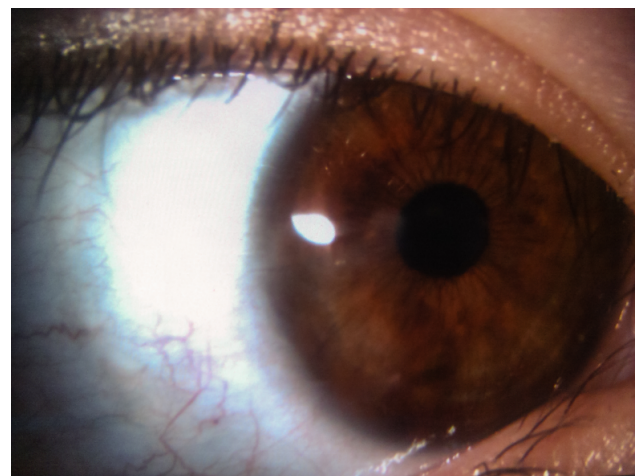
In view of several failed attempts of tapering the corticosteroids, topical 1% CsA-castor oil q.i.d was added to the

therapy, but this additional measure did not enable corticosteroid discontinuation either.

As flare-ups became more frequent and severe, local corticosteroids (subconjunctival dexametasone and metilprednisolone) and oral prednisolone (60 mg/day) were prescribed; however, all attempts of tapering the systemic medication led to flare-ups. Oral methotrexate 7.5 mg weekly with folate 1 mg/day was 20 prescribed for one year with the purpose of decreasing oral corticosteroids, but flare-ups persisted.

Despite intensive treatment, conjunctival and corneal phlyctenae with neovascularization and peripheral corneal thinning persisted, as well as occasional anterior chamber reaction in the right and left eyes. In some of the episodes, the neovascularization advanced centripetally, reaching the visual axis and leading to visual loss, which improved partially with regression of the neovessels, but frequently left pericentral corneal opacities with permanent decrease in vision.

Exhausted all the above mentioned treatments, we finally decided to resort to a more unconventional but eventually sight-saving therapy, and initiated infliximab at a dose of 5 mg/kg administered at six-week intervals in combination with methotrexate [4], [8]. The patient responded successfully to this combination and became asymptomatic in three months with resolution of phlyctenae and neovascularization.



**Figure 2:** Slit-lamp photograph of the right eye, 11 months after therapeutic combination of infliximab and methotrexate. A nubecula of temporal peripheral and pericentral cornea is noticeable with infiltrates and neovascularization resolution.

Eleven months after suspension of all corticosteroid treatment the patient remains asymptomatic, with complete resolution of the phlyctenae and neovascularization (Figure 2). No flare-ups were noticed in this time period and visual acuity remained stable (20/25 BE).

As a means of achieving an optimal follow-up for the possible side effects of infliximab, the patient currently has a multidisciplinary evaluation in the Departments of Ophthalmology and Rheumatology.

## Discussion

Phlyctenular keratoconjunctivitis is an allergic response to various systemic antigens. It usually presents in a mild to moderate form with conjunctival and/or corneal phlyctenae [1], [2], [7]. Generally, the mainstays of treatment of severe PKC are topical corticosteroids and etiological treatment. This case of a 10-year-old female, followed in the ophthalmology clinic for three years for an unusually severe form of bilateral phlyctenular keratoconjunctivitis was a therapeutic challenge.

Further investigation showed blepharitis and intestinal parasitosis. Both clinical conditions responded to treatment with subsequent improvement of the blepharitis and negative stool analysis for worm cysts. However, even after successful treatment of these underlying conditions, PKC flare-ups were frequent and led to a progressive decrease in visual acuity.

After long-term topical corticosteroid therapy, the attempt to combine other topical immunosuppressive agents such as CsA and local and systemic corticosteroids showed only mild benefits, as flare-ups became more frequent and severe. No ocular complications, such as elevated IOP or cataract, resulted from the use of corticosteroids. Topical CsA and tacrolimus have shown to be effective and safe in children with severe and refractory forms of PKC, the last being a more potent immunosuppressive agent [2], [6]. However, topical tacrolimus was not available as a therapeutic option in our institution.

The combination of an inconsistent clinical response, symptom recrudescence and worsening of ocular findings, such as corneal phlyctenae associated with corneal neovascularization, scarring and thinning, led us to consider the use of systemic biologic immunosuppressive therapy.

Although biologic therapy has been well documented as an effective therapy for refractory inflammatory diseases of the eye, such as recalcitrant uveitis [4], [8], to our knowledge this is the first PKC case treated with a biologic agent, namely infliximab.

The therapy with anti-TNF- $\alpha$  agents is associated with serious systemic complications, such as infections, implying special attention and clinical experience [9]. However, in this case, the significant risk of visual loss in a young patient, combined with an unsatisfactory response to all other agents, led us to propose this therapy.

## Conclusions

Not many cases of severe recurrent PKC have been described [6], but ocular morbidity associated with PKC and its impact on patients' quality of life is undeniable and cannot be underestimated.

Systemic immunosuppressive therapy with infliximab and methotrexate may be a resourceful alternative to control severe and refractory forms of the disease. In the described case this combination showed promising results,

deserving further attention as a valuable treatment approach for severe and refractory PKC.

## Notes

### Competing interests

The authors declare that they have no competing interests.

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### Corresponding author:

Joana Valério Sequeira Valadares, MD  
Centro Hospitalar Lisboa Norte, Hospital Santa Maria,  
Avenida Professor Egas Moniz, 1649-035 Lisboa, Portugal  
joanavaladares@gmail.com

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