

Corneal melt:
A paradoxical adverse event to
interleukin-6 receptor blockage?

INTRODUCTION

In rheumatoid arthritis inflammatory involvement of the cornea and sclera is usually a sign of severe generalized rheumatic disease. Unless the disease is properly identified and intense systemic therapy is instituted promptly, the outcome for the afflicted eye and even the life of the patient is guarded. Intensive comanagement of the patient with rheumatologists using systemic and topical anti-inflammatory as well as immunomodulatory therapy is mandatory to ensure good visual and general outcome.

We describe a case of a 39 years old gentleman with known rheumatoid arthritis, who was well managed for his systemic disease by tocilizumab therapy since 12 months. However he was complaining of recent onset severe redness and pain in his eyes as well as reduced vision despite good general control of his disease.

CASE PRESENTATION

A 39 years old male of Egyptian descent was referred from the rheumatology service. He had been treated with methotrexate (MTX) 15mg/week and tocilizumab 500mg iv. every four weeks since 12 months for his rheumatoid arthritis, which had been diagnosed in 04/2005 and showed a marked involvement of shoulders, hands, knees and feet bilaterally.



Figure 1. Markedly afflicted joints of the left hand.

With the therapy he had noticed marked improvement in joint pain and motion range. However since two months he noted increased redness of both eyes with marked pain, and sensitivity to light especially in his left eye. He was referred from the rheumatology service.

On initial presentation in 03/2011 he presented with a corrected visual acuity of 20/30 in his right eye (RE), 20/100 in his left eye (LE). His conjunctiva and sclera was heavily inflamed in both eyes (OU) with marked granulomatous, centrally ulcerated episcleral lesions more pronounced in the right eye superiorly (Fig. 2, 3).

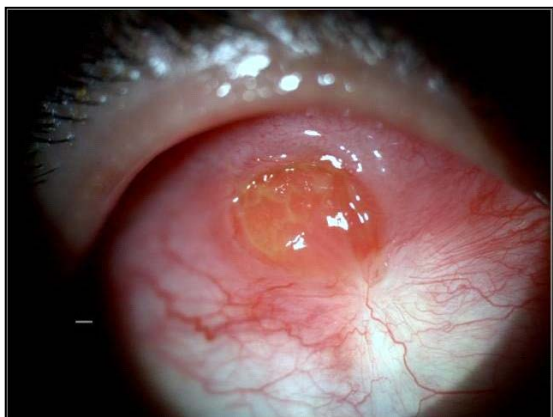


Figure 2. Granulomatous, ulcerated lesion RE.



Figure 3. Granulomatous, ulcerated lesion LE.

His right eye showed punctuate keratopathy, his left revealed a central, round, flat corneal erosion (Fig. 4). The anterior chambers were normal in both eyes. The fundus exam was unremarkable OU.

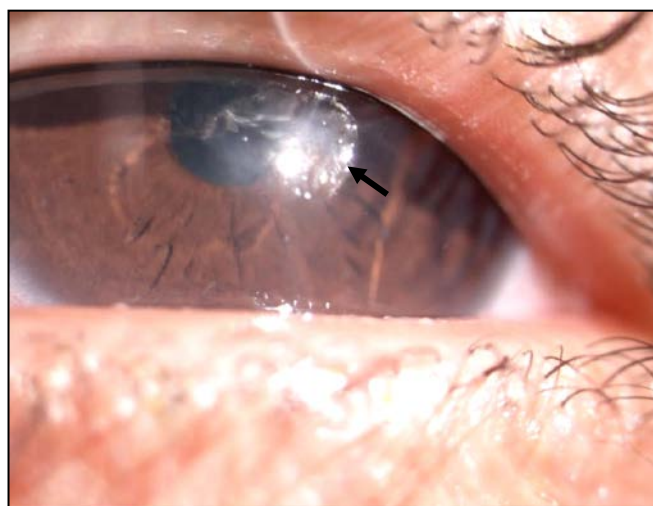


Figure 4. A central, round, flat corneal erosion left eye (arrow).

A conjunctival swab and blood work up was performed.

A biopsy was taken from the lesion of the right eye.

Topical therapy was started with prednisolone acetate eye drops 6 times/day, ofloxacin eye drops 4 times/day and copious use of non preserved hyaluronic acid artificial tears. Systemic prednisolone 60mg/die was added to the existing systemic therapy. His blood work up was unremarkable for inflammatory parameters as well as infectious diseases such as tuberculosis or syphilis. The conjunctival swab was negative for bacteria and chlamydia trachomatis. The biopsy revealed chronic granulomatous and active infiltrates characterized by eosinophil granulocytes, lymphocytes and plasma cells with some histiocyte aggregations.

Despite the systemic therapy of 60 mg prednisolone added to MTX and tocilizumab the granuloma in the right eye enlarged (Fig.5) and the corneal erosion in the left eye progressed to a central ulcer with beginning tissue melt in the ensuing 4 weeks.



Figure 5. The enlarged progressing granuloma in the right eye.

Locally serum eye drops were added hourly and azithromycin eye drops 4 times /day were used instead of ofloxacin eye drops. Since the situation did not change and further loss of corneal tissue due to uncontrolled inflammation was feared, the decision was made to perform an amnion membrane transplant in the left eye (Fig.6).

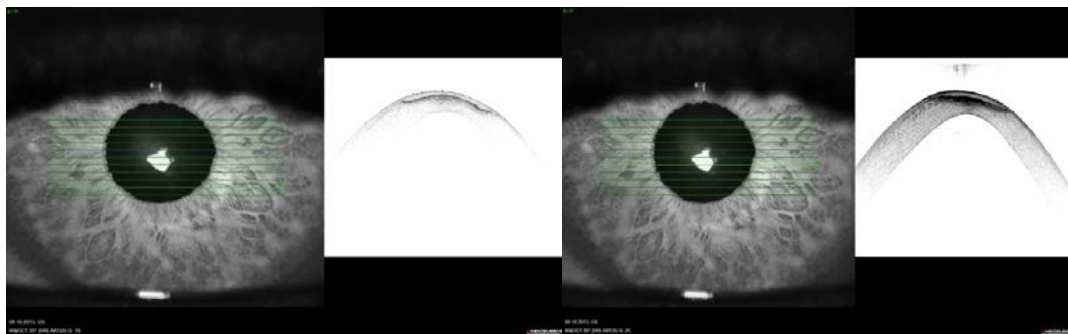


Figure 6. Anterior segment OCT of the left cornea after sandwich technique amnion membrane transplant, demonstrating corneal scar and central thinning with masking multilayered epithelium.

The sclera granulomas were unchanged. Together with the rheumatologists we decided six weeks after initial presentation to switch the systemic immunosuppressive therapy. The rheumatologists initiated a therapy with certolizumab pegol.

After two more weeks of intensified topical therapy with serum eye drops, prednisolone acetate eye drops 6 times /daily and moxifloxacin eye drops 4 times /daily as well as a therapeutic bandage contact lens the sclera granulomas slowly regressed (Fig.7) and the left cornea healed leaving a paracentral subepithelial scar.

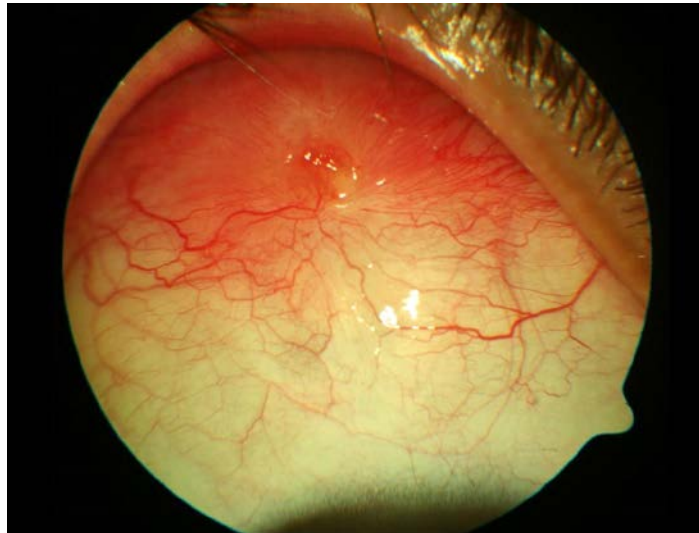


Figure 7. Granuloma right eye regressed after cessation of tocilizumab therapy.

From 7/11 to 9/14 the patient was treated by the rheumatologist with certolizumab pegol and by the ophthalmologists by frequent 0,3% non preserved hyaluronic acid eye drop application. Sometimes slight decompensation of the left corneal epithelium with corneal fluorescein punctate staining occurred which could be managed by contact lens application and dexamethasone unpreserved eye drops 2 times /daily, when flare ups occurred. His visual acuity remained stable at corrected 20/20 right eye and 20/50 left eye, with a beginning cataract in his left eye and the corneal subepithelial scar (Fig.8).



Figure 8. Residual corneal scarring in left eye after cessation of tocilizumab. Managed with artificial tears and rigid gas permeable contact lens.

In 10/14 the patient presents with increased sensitivity to light, beginning granulomatous episcleral lesions in both eyes (Fig.9) and a non healing central corneal erosion in his left eye. Additionally long strands of mucus were present in both eyes (Fig.10).



Figure 9. Recurrence of granuloma in right eye after reexposure to tocilizumab.



Fig 10: Left eye with bandage contact lens for non healing central erosion and pain management. Also note pathological mucus formation (arrow).

Topical therapy with bandage contact lens to the left eye and serum eye drops was started together with 6 x unpreserved dexamethasone eye drops OU. The situation slowly worsened over three weeks.

The patient then revealed that his new rheumatologist had started him on a new preparation of tocilizumab 162mg sc once a week since 3 months, thus reexposing him to the drug used in 2011 on initial presentation.

After consultation with the rheumatologist the systemic therapy was switched to abatacept 125mg sc plus methotrexate 15 mg every week and the granulomas slowly regressed over the ensuing 2 months.

The topical therapy was switched to 6 x hyaluronic acid OU and polycarboxymethylglucose sulfate matrix eye drops every other day OU in order to expedite corneal healing.

The patient presented last in September 2016 with a systemic medication of abatacept 125mg sc plus methotrexate 15 mg every week for his rheumatoid arthritis with acceptable results. Visual acuity was 20/20 RE and 20/60 LE. The eye exam showed mildly injected conjunctiva OU, regular cornea in his right eye (Fig. 10 a), a subepithelial central scar in his left eye (Fig.10 b) and calm anterior chamber OU. The fundus is unremarkable OU.



Figure 10a. RE with slightly dry eye symptoms but otherwise normal anterior segment. **10b.** LE after cessation of reexposure to tocilizumab with subepithelial irregular scar causing irregular astigmatism.

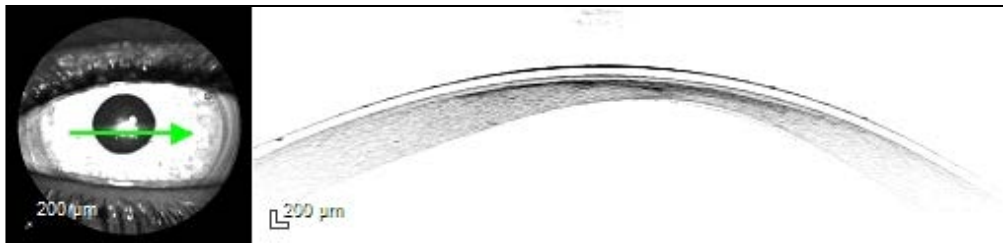


Fig 11. Anterior segment OCT of LE after cessation of reexposure to tocilizumab. Demonstrating considerable corneal thinning, subepithelial irregular scar causing irregular astigmatism and bandage contact lens.

Local therapy with non preserved 0,3% hyaluronic acid eye drops every hour and eventual use of a bandage contact lens when necessary in the left eye is continued. The patient is content and able to work.

DISCUSSION

We present a case of a man who was exposed to tocilizumab treatment for his rheumatoid arthritis twice, first as i.v. infusion once a month and on the second occasion sc injection 162mg every week. Tocilizumab is a humanized monoclonal antibody against the IL6 receptor. It is an immunosuppressive drug mainly used in rheumatoid arthritis. It is however also used in severe inflammatory diseases of the eye such as scleritis^[1] or uveitis^[2].

On each exposition our patient presented with severe bilateral granulomatous scleritis and central keratitis more pronounced in his left eye. The effect of tocilizumab on his joints was good. Despite intensive topical anti-inflammatory treatment, the scleral and corneal situation only got better when the tocilizumab was discontinued by the rheumatologists and the systemic medication switched to another biologic agent.

The advent of biological agents has dramatically changed the therapeutic approach to a variety of systemic immune-mediated diseases, such as chronic inflammatory rheumatic

diseases (rheumatoid arthritis and spondyloarthritis), plaque psoriasis and inflammatory bowel diseases (Crohn's disease and ulcerative colitis). Currently, five tumor necrosis factor α (TNF- α) blocking agents are available: three monoclonal antibodies (infliximab, adalimumab, golimumab), a p75 TNF- α soluble receptor (etanercept) and a Fab' fragment associated with a pegol molecule (certolizumab). With the improved understanding of the pathophysiology of immune-mediated diseases, new relevant therapeutic targets have been identified, leading to the development of new biological drugs. In this setting, anti-CD20 (rituximab), anti-interleukin (IL)-1 (anakinra), anti-IL-6 (tocilizumab) and a fusion protein inhibiting the costimulatory pathway (abatacept) have been developed for the treatment of rheumatoid arthritis.

Of course one would assume that these agents meant to treat the different sequelae of the disease would also positively affect the ocular involvements. So potentially two reasons could be the cause for the repeat granulomatous scleritis and non healing erosions leading to corneal melt in our patient.

First, the dosage of tocilizumab might be too low to influence the ocular involvement. This sometimes is the case in uveitis accompanying systemic inflammatory diseases. For example in uveitis patients treated with adalimumab, antibodies against adalimumab may form. This immunogenicity is more common in patients in whom uveitis is associated with a systemic disease^[3]. Therefore clinicians sometimes recommend higher dosages of adalimumab for the ocular involvement than required for the treatment of e.g. joint involvement.

Open-label studies and post hoc analysis of randomised controlled trials in patients with SpA indicate that anti-TNF- α agents may reduce the frequency of uveitis flares. On the other hand, anecdotal reports have suggested that uveitis can occur during anti-TNF- α therapy which might be due to undertherapy^[4].

Theoretically this could also have happened in the presented case, because after the switch to a more targeted and efficient therapy the scleral and corneal involvements resolved.

The **second explanation** is that, we might have seen a paradoxical adverse event. Paradoxical adverse events (PAE) are gaining more and more attention in rheumatology. If extraarticular tissue such as the eye is involved these events are called borderline PAEs.

In general, PAEs are described as isolated events and they are mainly reported with anti-TNF- α agents. This may be explained by the long-term use of anti-TNF- α agents compared to more recently introduced biological drugs. Certain PAEs such as uveitis, Crohns disease or sarcoidosis occur more frequently with the TNF- α soluble receptor (namely etanercept) as compared to monoclonal antibodies, suggesting the involvement of the differential immunological properties of these two classes of anti-TNF- α agents. Conversely, etanercept is used for more than 15 years compared to the more recently available anti-TNF- α monoclonal antibodies. The pre-existing condition that requires TNF- α inhibition is in general well controlled, indicating that the TNF- α agent is given at an adequate dosage or interval. However, some PAEs correspond to conditions that usually require a high dose regimen compared to the standard dose given for inflammatory rheumatic disease. For instance, adalimumab treatment in Crohns disease requires a loading dose at initiation. This could potentially explain certain PAEs observed with standard dose anti-TNF- α . The hypothesis of an imbalance in the cytokine milieu is advanced for most PAEs, especially for psoriasis, as well as a shift towards a Th1 cytokine profile or unopposed production of IFN- α ^[4].

IL-6 is a macrophage/monocyte-derived cytokine and plays a role in the promotion and maintenance of granulomatous inflammation through the activation of CD4+ T cells ^[5]. In patients with sarcoidosis, IL-6 is increased in bronchoalveolar fluid^[6] and in urine from patients with acute renal failure ^[7]. IL-6 blockers should have a protective role in sarcoidosis. However PAE have been described with tocilizumab in sarcoidosis^[8]. Other possible induced events have been reported with tocilizumab, such as eye inflammation including uveitis^[9], onset of psoriasis ^[10], and immune complex-mediated glomerulonephritis^[11].

Whether the biological agent associated with PAE onset should be maintained or not is a challenging issue that depends on a number of factors, namely: the type of PAE and its severity, the preexisting condition that initially required the biological agent, and the existence of alternative therapeutic options for the underlying disease.

In our case the successful therapy consisted in taking the patient off the tocilizumab which was suspected to produce the PAE plus local anti-inflammatory as well as surface reconstitution eye drops. Because of a switch in the person of the treating rheumatologist the exposure happened to the patient twice. Up to date he could be sufficiently managed with systemic abatacept.

The non healing corneal erosion and melt and the granulomas responded very well to topical therapy with tear substitutes, dexamethasone eye drops and polycarbomethylglucose sulfate matrix eye drops once the tocilizumab was halted.

This case illustrates once more that close comanagement and communication between treating rheumatologist and ophthalmologist is important for the management of the patient.

CONCLUSION

Patients suffering from systemic inflammatory disease may present with various ocular involvement. The disease itself as well as side effects of the necessary systemic medication may progress during the course of the disease. In order to treat the patients adequately close cooperation between rheumatologist and ophthalmologists is mandatory. This is the case especially in patients with severe disease and those receiving relatively new therapies, for which not all side effects might be known yet. This was the case in our patient who was exposed twice to the IL-6 receptor antagonist tocilizumab and on both occasions experienced scleral granulomas, non healing corneal erosions and corneal melt, a condition which has not yet been described. After cessation of the tocilizumab the lesions healed with subepithelial corneal scar formation with the help of topical dexamethasone, hyaluronic acid, polycarbomethylglucose sulfate matrix eye drops and a bandage contact lens.

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