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Peripheral ulcerative keratitis: Challenges in immunosuppressing an immunocompromised patient

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Introduction: Peripheral ulcerative keratitis (PUK) is an inflammatory condition affecting the peripheral cornea. Although rare, it causes significant morbidity in affected individuals. Several autoimmune disorders are associated with the development of PUK. In an immunocompromised patient, the use of standard treatments may increase the risk of infections.

Patient presentation: A 60-year-old HIV-positive female on long-term antiretroviral therapy, with well-controlled hypertension, presented with a 3-week history of a painful, red, left eye with epiphora. Polyarthritis, saddle nose deformity and a CD4 count of 342 were present and tuberculosis (TB) was suspected but only later confirmed by a positive urine lipoarabinomannan (LAM) test. This delayed the initiation of systemic immunosuppressive therapy, necessitating the concurrent treatment of both a severe autoimmune condition and an active infectious disease.

Management and outcome: Initial treatment included lubricants, topical steroid, topical ciprofloxacin drops and oral doxycycline. Because of the risk of pulmonary TB, systemic steroids were withheld pending the TB investigation results. In collaboration with rheumatology, high-dose oral prednisone was initiated. The right eye, ultimately required surgical intervention with conjunctival resection and amniotic membrane transplantation (AMT). The left eye, progressed and required a Gundersen flap procedure.

Conclusion: This case highlights the critical need for a multidisciplinary approach, the complexities of balancing immunosuppressive therapy with the risk of infection and the potential for significant visual morbidity despite aggressive intervention.

Contribution: This research contributes towards refining the diagnostic and therapeutic strategies for this challenging patient population.

Keywords: peripheral ulcerative keratitis; PUK; immunocompromised patients; immunosuppression; keratitis; autoimmune-related PUK.

Introduction

Peripheral ulcerative keratitis (PUK) is a rare (0.2 per million per year – 3.0 per million per year)[1] inflammatory condition, characterised by progressive thinning of the peripheral corneal stroma and an epithelial defect[2] affecting the peripheral cornea. It causes significant morbidity and may indicate underlying systemic disease. The aetiological factors contributing to PUK can be categorised as either local or systemic, further delineated as infectious or non-infectious.[3] Several autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus and granulomatosis with polyangiitis, are frequently associated with the development of PUK.[4] The standard therapeutic approach for autoimmune-related PUK involves the administration of systemic corticosteroids to achieve rapid control of the inflammatory process, followed by cytotoxic agents or biologic therapies to maintain sustained disease suppression.[3]

In immunocompromised patients, these agents can increase infection risk necessitating co-management with a rheumatologist.[3] Surgical treatment is usually reserved for severe corneal thinning or perforation[4] with various techniques available, including penetrating keratoplasty,[5] penetrating or lamellar grafts, amniotic membrane transplantation (AMT)[1] and superficial anterior lamellar keratoplasty,[6] with no definitive consensus regarding the optimal approach.

This case report aims to elucidate the diagnostic and therapeutic complexities in the management of PUK in an immunocompromised patient.

Ethical considerations

Ethical clearance was obtained from the University of the Witwatersrand's Human Research Ethics Committee (Medical) as well as Chris Hani Baragwanath Academic Hospital Medical Advisory Committee (reference number: R14/49; protocol number: M241095; clearance certificate number: M241095).

Patient presentation

A 60-year-old HIV-positive female on long-term antiretroviral therapy, with well-controlled hypertension, presented with a 3-week history of a painful, red left eye with epiphora. In the past year, she experienced painful joints in both hands and left ankle. Recent symptoms include coughing, drenching night sweats and weight loss. General examination revealed bilateral finger deformities and a saddle nose. Ocular examination showed a distance visual acuity of 6/9 in the right eye and 6/12 in the left. The right eye was unremarkable except for nuclear sclerosis. The left eye exhibited conjunctival injection, crescentic peripheral corneal ulceration staining with fluorescein, keratic precipitates and an anterior chamber reaction (2+ cells). Seidel test was negative, indicating no perforation. The left lens also showed nuclear sclerosis cataract. The vitreous was clear and retina flat with a cup to disc ratio of 0.3. The retinal vessels were of normal calibre, and a foveal light reflex was present.

A provisional diagnosis of PUK was made. A corneal scrape was performed to rule out an infective cause. Blood samples were collected for autoimmune and infectious workup, as well as CD4 count and HIV viral load. Given the presence of polyarthritis and saddle nose deformity, a rheumatological consultation was requested. Initial treatment included lubricants, topical steroid, topical ciprofloxacin drops and oral doxycycline. Because of possible pulmonary tuberculosis (TB), systemic steroids were withheld pending the TB investigation results.

Four weeks later, follow-up revealed a CD4 count of 342, lower than detectable viral load and a negative GeneXpert, but the chest X-ray was inconclusive. Unfortunately, urine lipoarabinomannan (LAM) testing was unavailable at this time. The autoimmune screen showed a normal rheumatoid factor of 19 IU/mL, but a positive anti-cyclic citrullinated peptide (CCP) antibody of 12.0 U/mL and positive anti-nuclear antibodies with a speckled pattern and a titre of 80. The corneal scrape showed no organisms on microscopy, and bacterial, fungal and viral cultures were all negative. Four weeks post initial presentation, the left eye had deteriorated, exhibiting 360-degree peripheral thinning exceeding 50% with persistent anterior uveitis. To control the inflammation, a left orbital floor steroid injection was administered. Rheumatology considered rheumatoid arthritis, sarcoidosis and psoriatic arthritis in their differential diagnosis. Despite the chest X-ray not completely ruling out pulmonary TB, they decided to start the patient on oral steroids to control the immune response, as it is an appropriate first-line treatment for all the differentials. The patient was prescribed oral prednisone 50 mg daily.

Eight weeks after initial presentation, the left eye continued to show 360 degrees of peripheral corneal ulceration with fluorescein staining and severe anterior uveitis. Therefore, despite the high dose of steroids given, the left eye showed no clinical improvement. The right eye developed nasal peripheral corneal thinning from 2 o'clock to 4 o'clock with fluorescein staining. At this stage, the visual acuity was unchanged at 6/9 in the right eye and 6/12 in the left. Urine LAM testing became available, and the patient tested positive, confirming TB. Because of the risk of immunomodulatory therapy exacerbating systemic TB, the patient was started on TB treatment. Rheumatology settled on a definitive diagnosis of seronegative spondyloarthropathy and commenced intravenous cyclophosphamide pulses.

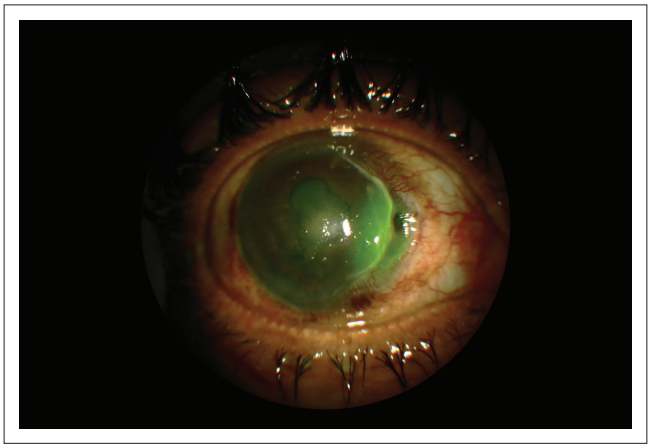
At 12 weeks, the left eye had developed posterior synechiae. The vision had deteriorated to 6/24 in the right eye and 6/36 in the left eye. The right eye had 6 clock hours of nasal peripheral corneal thinning with small staining areas. The left eye maintained 360 degrees peripheral corneal thinning but with minimal staining. Bilaterally, posterior blepharitis, conjunctival hyperaemia, diffuse keratic precipitates, flare and posterior synechiae were present. This indicated active uveitis despite the patient being on 60 mg oral prednisone daily and completing two intravenous cyclophosphamide pulses. Oral ibuprofen, topical tacrolimus and oral vitamin D supplementation were added. Because of ongoing active disease, rheumatology recommended the patient be admitted for intravenous methylprednisolone pulsing.

Over the following 2 weeks, the patient reported significant symptomatic improvement, with reduced conjunctival and anterior chamber inflammation in both eyes. This was attributed to the intravenous methylprednisolone pulse. A growing concern was the thinning of the right nasal limbal cornea, approximately 5% thickness. Because of the risk of impending perforation, the patient was admitted to the ophthalmology ward with a hard shield and closely monitored. The left cornea, while not severely thinned, developed 360 degrees of peripheral pannus expanding centripetally.

At 20 weeks, the patient demonstrated disease inactivity. Her treatment included oral steroids, a 3-day course of intravenous methylprednisolone, five intravenous cyclophosphamide pulses, oral doxycycline, oral omeprazole and topical medications (prednisolone, tacrolimus, lubricants, chloramphenicol, atropine). Bilateral conjunctival injection had markedly improved. Vision was 6/36 in the

right eye (improving to 6/12 with pinhole) and Hand Movements in the left eye because of corneal haze. The right cornea showed 6 clock hours of peripheral corneal neovascularisation, but was otherwise clear without perforation, however with severe thinning. The left cornea was centrally hazy with 12 clock hours of neovascularisation and no perforation. Anterior chambers were quiet with bilateral posterior synechiae. The patient was scheduled for right eye conjunctival resection and AMT under local anaesthesia, involving resecting the conjunctiva 2 mm posterior to the limbus at the area of corneal thinning, followed by suturing amniotic membrane to cover the conjunctival defect and the thinned cornea using 8/0 vicryl. A bandage contact lens was applied. Figure 1 and Figure 2 show the right eye before and after the conjunctival resection and AMT.

In Figure 1, conjunctival injection, severe thinning of the cornea at 3 o'clock, staining with fluorescein and corneal haze are visible. After conjunctival resection and AMT in Figure 2, the corneal clarity is greatly improved, with iris details more visible as well as a reduction in conjunctival hyperaemia.



Source: Photograph taken by Dr Jacobus Frederik Heukelman on 15 April 2024 at Chris Hani Baragwanath Hospital, Department of Ophthalmology. Used with permission. No unauthorised duplication allowed.

FIGURE 1: Right eye before conjunctival resection and amniotic membrane transplantation.

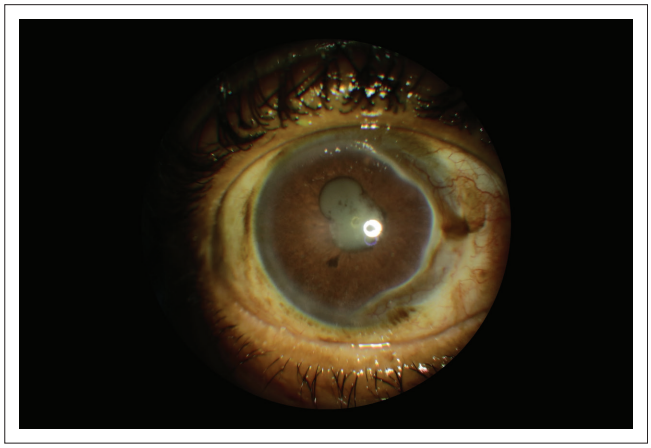


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FIGURE 2: Right eye after conjunctival resection and amniotic membrane transplantation.

Two weeks after surgery, the patient's right eye had improved, with no areas of corneal staining. Her left eye had, however, deteriorated, with completely opacified central cornea and three areas of severe corneal thinning, as well as 12 clock hours of peripheral neovascularisation. Visual acuity was 6/24 in the right eye and Light Perception in the left eye. The left eye presented a high risk of perforation with no visual prognosis. A left Gundersen flap was scheduled.

Figure 3 and Figure 4 show the left eye before and after the Gundersen flap procedure.

Before the Gundersen flap the eye showed severe conjunctival injection, corneal vascularisation and a central epithelial defect staining with fluorescein. After the Gundersen flap, the conjunctival injection is greatly improved, corneal clarity is decreased, but there are no epithelial defects.

A primary advantage of the Gundersen flap in the context of PUK is the potential for pain relief[7] in cases of severe corneal thinning or impending perforation because of covering the

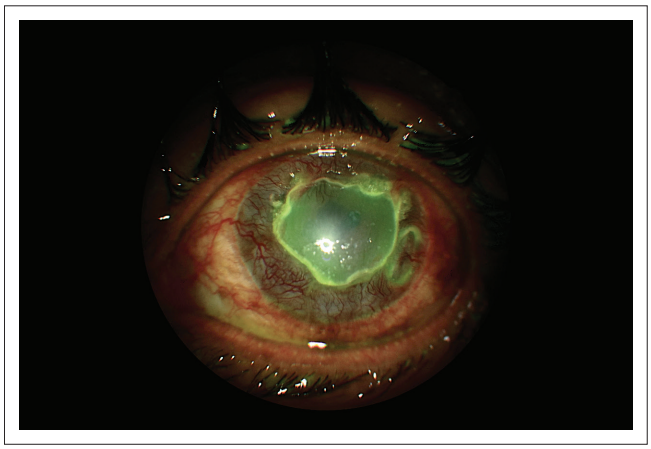

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FIGURE 3: Left eye before Gundersen flap.

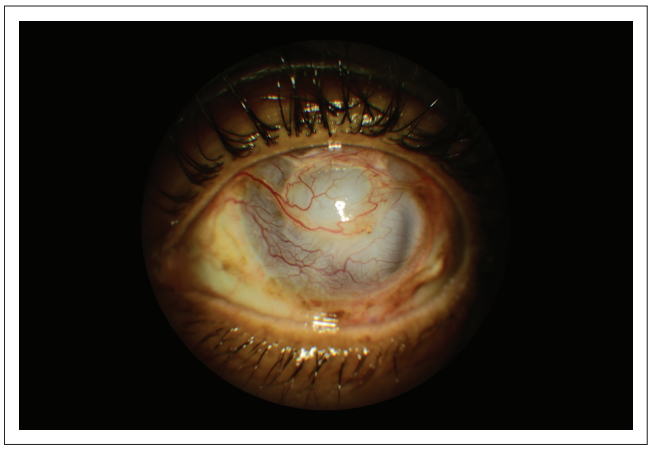

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FIGURE 4: Left eye after Gundersen flap.

ulcerated cornea with conjunctival tissue, reducing nerve exposure and inflammation. It also provides tectonic support, helping to maintain globe integrity and preventing perforation.

Discussion

Peripheral ulcerative keratitis carries a high burden of morbidity and, when associated with an underlying autoimmune cause, can increase the mortality rate.[8] However, throughout literature, there are several examples of corticosteroid therapy exacerbating existing TB infection or reactivating latent TB.[9,10] Immunosuppression in the form of corticosteroids should not form the basis of long-term treatment.[11] 'Long-term immunomodulatory therapy (IMT) is essential to prevent recurrences and manage the underlying process effectively'.[11]

This case underscores the significant diagnostic and therapeutic challenges in the management of PUK in an immunocompromised patient. Prioritising the exclusion of active infection before administering immunosuppressants highlights the dilemma in managing these complex cases. The decision-making process involves a continuous risk-benefit assessment, meticulously considering the potential for irreversible ocular damage versus the risk of exacerbating an underlying infection.

The initial diagnostic uncertainty, compounded by the patient's HIV status and the clinical suspicion of pulmonary TB, necessarily delayed the initiation of systemic immunosuppressive therapy for the treatment of autoimmune-related PUK.[12] Despite being immunocompromised, our patient required high-dose intravenous steroids for initial control, as well as immunomodulatory therapy in the form of cyclophosphamide. The subsequent confirmation of TB further complicated the management strategy, necessitating concurrent treatment of both a severe autoimmune condition and an active infectious disease. The necessary delay in initiating systemic immunosuppression because of the imperative to rule out active TB possibly contributed to the rapid and aggressive progression of the PUK.

Despite the eventual initiation of high-dose corticosteroids and the cytotoxic agent cyclophosphamide, the patient experienced progressive bilateral corneal thinning and neovascularisation. While the patient ultimately achieved disease inactivity, the right eye, although initially less severely affected, ultimately required surgical intervention with conjunctival resection and AMT, while the more severely affected left eye necessitated a Gundersen flap because of perforation risk and poor visual prognosis. This underscores the potential for significant visual morbidity associated with PUK, particularly in complex cases characterised by diagnostic and therapeutic challenges.

Conclusion

The management of PUK in immunocompromised patients with concurrent active or suspected infections presents a significant clinical challenge. This case highlights the critical need for a multidisciplinary approach, the complexities of balancing immunosuppressive therapy with the risk of infection and the potential for significant visual morbidity despite aggressive intervention. Further research is essential to refine diagnostic and therapeutic strategies for PUK in immunocompromised individuals.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

J.F.H. did the investigation, obtained ethical clearance and wrote up the case report. C.D.A. provided guidance in his capacity as supervisor and contributed to editing of the report.

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Data availability

The data that support the findings of this study are available from the corresponding author, J.F.H., upon reasonable request.

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