Rheumatoid corneal melt: autoimmunity or infection?

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The effect of immunosuppression may mask the typical signs of infective keratitis, potentially resulting in a devastating delay in diagnosis.

Case report

A woman with type 2 diabetes, rheumatoid arthritis and secondary Sjögren’s syndrome developed severe corneal ulceration (keratitis) on two separate occasions three years apart while taking systemic immunosuppression for her rheumatoid arthritis. Her ocular history included Sjögren’s syndrome-related dry eyes for which she used non-preserved ocular lubricants, together with recurrent episodes of marginal keratitis treated successfully with topical steroids and prophylactic antibiotics on an outpatient basis. The early management strategies for each of the severe clinical episodes are presented and the clinical outcomes for both eyes, discussed.

Clinical episode 1: left eye

The patient originally presented acutely aged 44 years, to a dedicated ophthalmology accident and emergency department with pain and blurred vision in her left eye. She was found to have an area of crescentic-shaped corneal thinning associated with an epithelial defect, peripheral corneal vascularization and cellular infiltration of the normally clear cornea, consistent with a diagnosis of presumed autoimmune peripheral ulcerative keratitis. Despite emergency admission and initial treatment with intensive one-hourly non-preserved topical Dexamethasone 0.1% day and night, together with a single infusion of i.v. methylprednisolone and maintenance of her existing DMARD regime of Methotrexate 12.5 mg weekly, the corneal infiltration and ulceration rapidly progressed. After revising the diagnosis to rheumatoid peripheral ulcerative keratitis (corneal melt) with secondary microbial keratitis, appropriate microbiological sampling (corneal ‘scrape’) with direct inoculation onto agar plates was undertaken and broad spectrum topical antibiotics (intensive non-preserved topical Gentamicin 0.3% and Cefuroxime 5% [each 1 hourly]) were initiated. Unfortunately, a fulminant and refractory infected peripheral ulcerative keratitis ensued accompanied by severe destruction of the left eye, corneal perforation and endophthalmitis (Figure 1a). The microbial agent was confirmed as \textit{Streptococcus pneumoniae} which was isolated from both corneal sampling and a subsequent vitreous (intraocular) biopsy. The eye was eventually eviscerated (removed) just 10 days after her original presentation, and the orbit rehabilitated with an orbital implant and cosmetic ocular prosthesis.

Clinical episode 2: right eye

Three years later, the patient presented acutely again to the inflammatory eye diseases clinic for management of her Sjögren’s syndrome dry eye problems with non-preserved topical lubricants (Carboxymethylcellulose 1%, Sodium hyaluronate 0.18% each 6x/day), and the regional rheumatology service for her rheumatoid arthritis.

The patient was subsequently cared for in a tertiary inflammatory eye diseases clinic for management of her Sjögren’s syndrome dry eye problems with non-preserved topical lubricants (Carboxymethylcellulose 1%, Sodium hyaluronate 0.18% each 6x/day), and the regional rheumatology service for her rheumatoid arthritis.
6/18 and she was found to have an identical peripheral infero-temporal crescentric area of keratitis with minimal associated corneal infiltration, but significant corneal melt with up to 70% thinning (Figures 1b and 1c). She was afebrile and systemically well. With a working diagnosis of a microbial keratitis secondary to an autoimmune peripheral ulcerative keratitis precipitated by severe Sjögren’s syndrome dry eye and immunosuppression, she underwent corneal ‘scrapes’ for microbiological analysis and rapid diagnostics. The patient was admitted and commenced on intensive broad-spectrum topical antibiotics (Ofloxacin 0.3%, Cefuroxime 5% each 1 hourly) in addition to oral Ciprofloxacin 750 mg b. d. (administered as prophylaxis against systemic dissemination of infection), Doxycycline (a metalloproteinase inhibitor) and ascorbic acid (collagenase inhibitor). Haematological screening confirmed a normal total white blood cell count (5.0 x 10⁹/L) with borderline low lymphocytes (1.12 x 10⁹/L [normal:1–4.5 x 10⁹/L]) and normal neutrophils (3.11 x 10⁹/L [normal:1.7–7.5 x 10⁹/L]). All other investigations including her vasculitic markers, glucose, urinalysis, chest radiography and blood cultures were normal. Due to the high risk of perforation and previous left evisceration, the patient was given a single pulse of i.v. Methylprednisolone 1g, 24 hours after initiation of topical bactericidal antibiotics to sterilize.

Microscopy demonstrated Gram-negative cocci, confirmed after 48 h culture as Neisseria meningitides with likely sensitivities to penicillin. Her treatment was adjusted accordingly (replacement of Cefuroxime with non-preserved Penicillin 5% every hour); and due to the notifiable nature of the disease, advice from the Public Health Consultant was to trace and prophylactically treat all nearest contacts with a single dose of oral Ciprofloxacin 500 mg. Despite her vulnerability to disseminated meningococcal disease, the patient remained afebrile and systemically well. Within one week, there was significant improvement in the keratitis, permitting a gradual reduction of topical antibiotics and withdrawal of oral Ciprofloxacin after seven days. Non-preserved topical Prednisolone 0.5% qds was introduced cautiously at day 12 to reduce damage by the local inflammatory response. She was discharged home 13 days after admission. All topical treatment was withdrawn over the ensuing three months other than her existing non-preserved tear-film substitutes. Over the subsequent 12 months there was no recurrence of ocular inflammation with her visual acuity recovering to 6/12 (Figure 2). No further infusions of Rituximab were given in view of the ocular complication and that her rheumatoid arthritis did not respond optimally to Rituximab.

Discussion

This case highlights a number of diagnostic and management challenges. Local and systemic
immunosuppression masks the typical signs of overt corneal infection such as frank corneal abscess, epithelial defect and hypopyon. It is, therefore, important to have a high index of suspicion of an infective component in immunosuppressed patients presenting with a breakdown of the corneal epithelium. In this mildly lymphopenic patient, the exclusion of a systemic source of sepsis was aggressively pursued when she presented with problems with her second eye. The major dilemma pending microbiological confirmation of infection was whether the keratitis was: (1) pure autoimmune peripheral ulcerative keratitis; (2) peripheral ulcerative keratitis with a secondary infection; or (3) infective keratitis alone. Incorrect diagnosis and treatment can result in potentially blinding complications as exemplified by the loss of the patient’s first eye: this was treated as a peripheral ulcerative keratitis alone with topical and intravenous steroids without suspicion of a concomitant infection. The consequence was devastating ocular tissue destruction and eventual complete loss of the eye (Figure 1a).

We recommend that in all cases of acute peripheral ulcerative keratitis, appropriate ocular microbiological sampling (by the receiving ophthalmologist) is undertaken before commencing 24 h of intensive topical antibiotics day and night to initiate microbial sterilization of the cornea, followed by the introduction of 1–3 pulses of i.v. Methylprednisolone to treat an autoimmune component, supplemented by lubrication to facilitate epithelial migration across the ocular surface and healing. Systemic Doxycycline and ascorbic acid should also be administered to reduce the risk of perforation and promote corneal stromal-matrix remodelling by inhibiting metallo-matrix proteases, collagenases, and scavenging free radicals.

Methotrexate is a ‘broad-spectrum’ steroid sparing disease modifying agent which is a folic acid analogue that interferes with thymidine synthesis and, therefore, with DNA synthesis and cell division. It has little effect in resting cells but has pronounced effect on rapidly proliferating cells, affecting both B and T cells, and can inhibit both humoral and cellular responses. By contrast, Rituximab is a monoclonal antibody directed against the CD20 molecule expressed on B-cells, and is now an established therapy in rheumatoid arthritis following at least two failed DMARDS including at least one anti-TNF agent. Its action is thought to include suppression of antigen presentation and antibody/cytokine production. B-cell depletion is rapid and may persist for up to 6 months. Adverse effects include infusion reactions and an increased risk of serious infections. In two large randomized control trials, pneumonia, bronchitis, epiglottitis, gastroenteritis, pyelonephritis, cat-bite infection, influenza, fever of unknown aetiology, and denovo hepatitis B were reported. Although these studies did not identify an increased risk of opportunistic infections, there have been subsequent reports of a number of unusual infections most notably Pneumocystis pneumonia.

To our knowledge this is the second report of meningococcal opportunistic infection occurring after the use of Rituximab. N. meningitidis is a Gram-negative diplococcus, which is a familiar cause of bacterial meningitis and overwhelming sepsis (meningococcaemia) with a mortality of up to 30%. N. meningitidis colonises the nasopharynx in 8–25% of the normal population and is spread by airborne droplets resulting in a subclinical infection with only a minority of individuals developing metastatic spread including meningitis, sepsis or occasionally endogenous endophthalmitis. The risk of the disease is greater in children, those with complement deficiencies and in the immunosuppressed (the previous report in the context of Rituximab).
involved a splenectomised individual\(^6\)). In the case discussed here the use of Rituximab will have rendered the patient more susceptible to meningococcal infection due to iatrogenic host B-cell depletion. Meningococcal conjunctivitis (including ophthalmia neonatorum) is uncommon in both infants and adults,\(^9,10\) and may present as primary or secondary to systemic disease.\(^11\) The isolation of \(N.\) meningitidis as the causative agent for keratitis is rare, but can complicate meningococcal conjunctivitis in 15% patients.\(^9\) The potential for sight-threatening and life-threatening intraocular or systemic invasion necessitates prompt and aggressive treatment with systemic antibiotics.\(^10\) In the UK, both of these sequelae require notification under the Public Health (Infectious Diseases) Regulations 1988.

These episodes of peripheral ulcerative keratitis with superimposed infection sequentially affecting both eyes of the same patient, demonstrate the challenges of recognizing microbial keratitis in the immunosuppressed and underlines the need for all specialists to remain vigilant to the possibility of atypical infections, particularly in the context of the newer biological therapies. This is also the first reported case of an opportunistic meningococcal keratitis associated with Rituximab use.

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