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CASE REPORT

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Rheumatoid arthritis-associated corneal ulceration complicated by bacterial infection

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Abstract We report two cases of rheumatoid ocular disease complicated by infection of methicillin-sensitive *Staphylococcus aureus* (MSSA) in one case, and methicillin-resistant *Staphylococcus aureus* (MRSA) in the other. In both cases, punctal occlusion and immunosuppressive therapy were presumed to be major risk factors of the infections. In addition, the characteristic feature was corneal melting, which is probably accelerated by infection. To avoid infectious progression and melting, potent antibiotics followed by immunosuppressive therapy were necessary.

Key words Corneal melting · Immunosuppression · Infection · Methicillin-resistant *Staphylococcus aureus* (MRSA) · Rheumatoid arthritis (RA)

Introduction

Extra-articular problems in rheumatoid arthritis (RA) occur in approximately 25% of patients and may involve the heart, lung, skin, and, rarely, the central nervous system.[1] Ocular involvement tends to occur in patients in more advanced stages of the disease, especially those with subcutaneous nodules, vasculitis, or cardiac involvement.[2,3] The ocular manifestations of RA, in order of descending frequency, include keratoconjunctivitis sicca (dry eye syndrome), scleritis, and sterile corneal ulceration. Sterile corneal ulceration can occur in either the central or peripheral cornea, with a paucity of ocular symptoms. This ulceration tends to occur more frequently in the peripheral area because of easier access of inflammatory cells in the peripheral cornea than the central cornea, which ordinarily lacks blood vessels and lymphatics. These manifestations are usually not severe; however, a small percentage of patients with RA present with severe ocular inflammation that may be associated with systemic and potentially lethal vasculitis. The melting tends to occur as a late feature in those with RA, on average some 20 years after diagnosis, and it may lead to corneal perforation.[3–6]

The recommended systemic medical management for RA patients with ocular complications includes nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids,[7,8] and systemic immunosuppressive chemotherapy.[8–10] In addition, the management of keratoconjunctivitis sicca is very important, and includes the use of preservative-free artificial tear eye drops and sodium hyaluronate eye drops, dry eye spectacles, and punctal occlusion.

In this article, two cases of rheumatoid corneal ulceration complicated by infection are presented. These cases indicate that immunosuppressant drugs against RA and insufficient tear turnover possibly increase the risk of infection, and also suggest that corneal infection probably accelerates corneal melting.

Case reports

Case 1

A 59-year-old woman was diagnosed with RA at the age of 29, with a 27-year history, at the first examination in Osaka University Hospital. From that time, she was treated with oral methotrexate (MTX). In 1988, permanent punctal occlusion by sutures was performed for secondary Sjögren's syndrome. Sodium hyaluronate eye drops and ofloxacin

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ophthalmic ointment had been prescribed since then without any noteworthy ocular symptoms.

She complained of conjunctival injection and discharge in the left eye at the beginning of October 1999. On October 13, 1999, she was referred to Osaka University Hospital because of complaints of conjunctival injection and discharge. At the first examination, the best-corrected visual acuity (BCVA) was 20/30 in the right eye (OD). Best-corrected visual acuity in the left eye (OS) was limited to counting fingers.

Slit-lamp examination in the left eye demonstrated mucopurulent conjunctivitis, notable ciliary injection, scattered shallow peripheral corneal ulcers and infiltrates, a wide-ranging corneal epithelial defect in the central region, many keratic precipitates, and corneal edema (Fig. 1A,B). Although definite corneal infectious foci with dense infiltrates were not observed on her central cornea, some of these findings were indicative of infection, at least in her conjunctiva. Peripheral corneal ulcer and infiltration were presumed to be related to RA, but not to infection. However, at this time it was difficult to discern definitely which findings were due to RA and which ones were due to infection. There were no notable ocular findings in the right eye.

We initiated ofloxacin eye drops (six times daily), cefmenoxime hydrochloride eye drops (six times daily), ofloxacin ophthalmic ointment (twice daily), atropine sulfate eye drops (once in the morning), and faropenem sodium (200 mg orally three times daily). The next day, corneal opacity and edema improved, but the left central cornea experienced a perforation with a flat anterior chamber (Fig. 1C). Considering the thickness of the cornea on the first day, this indicated that the corneal melting rapidly progressed in the course of only one day. Cultures from both the cornea and discharge were positive for methicillin-sensitive *Staphylococcus aureus* (MSSA). Based on antimicrobial sensitivity testing, we continued ofloxacin, and started a drip infusion of imipenem cilastatin (1 g, twice daily). To help reformation of the anterior chamber, a trial of a bandage soft contact lens was performed and oral acetazolamide administration was also started.

With this regimen, the infectious findings faded notably. Injection and infiltration decreased remarkably, the perforation wound sealed, and the anterior chamber was reformed. Therefore, imipenem–cilastatin was reduced, and fluorometholone ophthalmic suspension was administered. Although infectious symptoms became still less apparent, newly peripheral corneal thinning was progressive. Consequently, imipenem–cilastatin was discontinued and fluorometholone was changed to betamethasone ophthalmic solution to reduce inflammation more thoroughly, resulting in a stable condition. Her current BCVA is 20/20 OD and 20/50 OS (Fig. 1D).

Case 2

In Osaka University Hospital on November 12, 1997, a 55-year-old woman, with a 33-year history of RA necessitating prednisolone for 20 years (5 mg twice daily), underwent deep lamellar keratoplasty for a corneal perforation in her left eye related to RA. Although the perforation site was sealed, deep-layer corneal opacity and nuclear cataract remained. On January 6, 2000, she successfully underwent penetrating keratoplasty and extracapsular cataract extraction with intraocular lens insertion in her left eye. Following this operation, betamethasone eye drops were resumed.

The patient's condition after the operation was generally stable. Severe punctate epithelial erosion due to keratoconjunctivitis sicca, however, disturbed her vision despite the instillation of preservative-free artificial tears, and subsequently punctal plugs were inserted to block both tear ducts in the left eye. This resulted in eventual improvement.

Two months after the insertion of the plugs, however, she complained of bulbar conjunctival injection and blurred vision in the left eye, and visited our department on March 27, 2000. Slit-lamp examination in the left eye demonstrated obvious infectious findings; suture abscess at the 3 o'clock position, entire corneal edema, keratic precipitates, cells in the anterior chamber, and slight hypopyon (Fig. 2A). Therefore, cultures from her cornea and from the suture abscess were obtained and sent for analysis. Cefoselis sulfate drip infusion (1 g, twice daily), ofloxacin eye drops (every hour while awake), ofloxacin ophthalmic ointment (before sleep), cefmenoxime hydrochloride eye drops (every hour while awake), and atropine sulfate eye drops (once in the morning) were prescribed, while betamethasone eye drops were discontinued.

Cultures from both the cornea and the suture were positive for methicillin-resistant *Staphylococcus aureus* (MRSA). Based on the result of the antimicrobial sensitivity test, all the antibiotics prescribed above were discontinued, atropine sulfate eye drops (once in the morning) were continued, and vancomycin hydrochloride drip infusion (1 g twice daily) and tobramycin eye drops (every hour while awake) were started. With this regimen, signs and symptoms improved promptly (Fig. 2B); however, rapid progression of thinning at the site of infection was noted (Fig. 2C). Betamethasone eye drops were started again to avoid further melting and the induction of graft rejection. The systemic dose of immunosuppressant was not altered in the course of treating this infection. Despite the thinning remaining at the 3 o'clock position, she is at a stable stage with ofloxacin eye drops, fluorometholone eye drops, and artificial tears. Her current BCVA is 20/20 OD and 20/25 OS.

Discussion

Jabs suggested that rheumatoid corneal ulceration could be classified as either noninflammatory or necrotizing in nature. Noninflammatory melts are usually associated with Sjögren's syndrome[11,12] and may respond to local treatment with soft contact lens application.[11] Necrotizing disease with

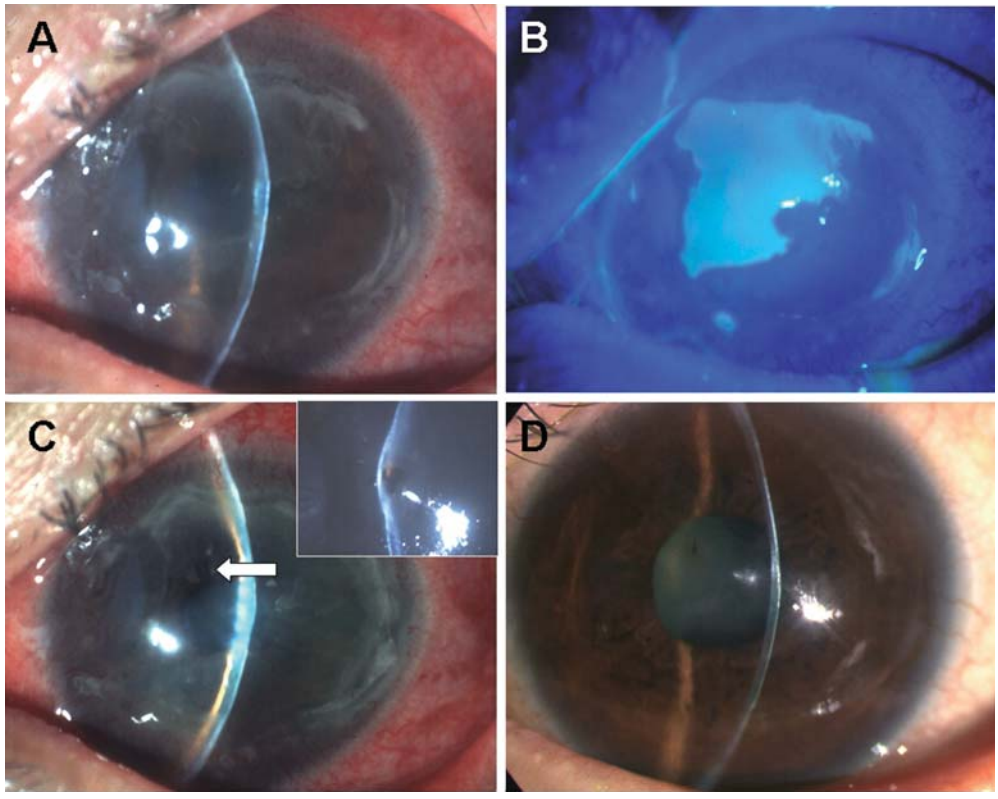

Fig. 1A–D. Slit-lamp photographs of Case 1. **A** At the first examination (October 13, 1999), mucopurulent conjunctivitis, notable ciliary injection, scattered shallow peripheral corneal ulcers and infiltrates, and central corneal edema with keratic precipitates are noted. **B** Wide-ranging central corneal epithelial defect at the first examination (October 13, 1999), **C** Corneal perforation in the left central cornea 1 day after the first examination. (October 14, 1999). The *arrow* indicates perforation site. *Inset*: Higher magnification of perforation site indicates notable corneal melting. **D** Stable corneal condition with notable corneal thinning after the treatment (August 31, 2001)

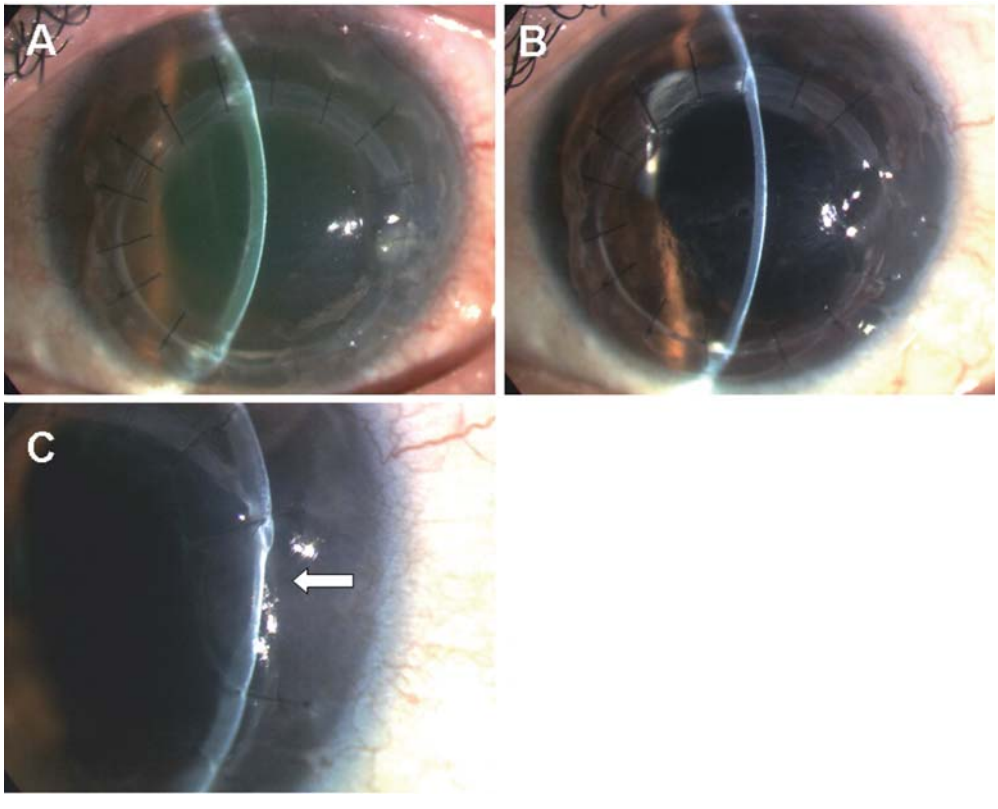

Fig. 2A–C. Slit-lamp photographs of Case 2. **A** Suture abscess at 3 o'clock position with graft edema (March 27, 2000). **B** Clear graft without injection and anterior chamber reaction after the treatment (April 3, 2000). **C** Remaining corneal thinning at 3 o'clock position after the treatment (November 6, 2000). The *arrow* indicates corneal thinning

stromal infiltrates that develop under an intact epithelium and progress to corneal ulceration is not necessarily associated with keratoconjunctivitis sicca,[11,13] and therapy can be extremely difficult.[4] In actual cases of corneal ulceration in RA patients, however, definite classification of causes is difficult, and many potential factors including systemic immune-mediated inflammation, an unstable corneal epithelium due to keratoconjunctivitis sicca, and infections of the ocular surface trigger the process of corneal thinning/perforation.

In Case 1, paracentral corneal perforation occurred within 1 day, despite there being no definite infectious foci on the perforated site the day before. In Case 2, a successfully treated small infectious focus caused corneal thinning after a short period of active infection. These findings indicate that infections are closely related to corneal melting in RA patients. First of all, infection allows many inflammatory cells access to the cornea even in the central portion, which is an inflammatory cell-free area under usual conditions. Moreover, the toxins and proteases produced by bacteria may accelerate the melting process in RA patients. It is noteworthy that *Staphylococcus* is known as a microbe that produces numerous toxins and enzymes.[14,15] In addition, infection further increases the ratio of matrix metalloproteinases to tissue inhibitors of metalloproteinases.[16,17] This increase is working in RA even in sterile conditions.[18,19] Finally, it is further speculated that bacteria such as *Staphylococcus* are related to corneal melting even in apparently sterile cases, because there are usually normal flora in conjunctiva, and a constant appearance of various bacteria, including drug-resistant ones, in the conjunctiva of immunosuppressed RA patients.

As for the susceptibility to infection in RA, there are various important factors. Most RA patients are under immunosuppressive therapy. The incidence of infection naturally increases in proportion to the dose and the length of immunosuppression. Long hospitalization is an additional factor of infection, especially by drug-resistant microorganisms such as MRSA. Tear insufficiency in RA patients is the other major factor for corneal infection, because in addition to the unstable epithelium due to dry eye, protective factors in tear fluid are not supplied. For dry eye, the techniques include punctal plugs (Case 2) and sutures (Case 1) resulting in watery eyes; however, tear turnover is not improved, but rather suppressed after punctal occlusion.[20,21] In these two patients, the clearance of infectious agents on the ocular surface was presumed to be profoundly disturbed, which resulted in destructive infection.

We must be aware of the increased risk of secondary ocular microbial infection in RA patients administered systemic immunosuppressants. Appropriate culturing and scraping should be performed in suspicious cases, especially in patients with Sjögren's syndrome, which is seen most frequently in RA-associated ocular problems.

Generally, infectious corneal ulceration occurs in the central area as a circular infiltration, accompanied by many anterior chamber cells. In contrast, typical rheumatoid-associated infiltration occurs in the peripheral cornea parallel to the limbus with few anterior chamber cells. This, however, is not always the case. In practice, there may be many confusing and indistinguishable cases. Also in our Case 1, the only clue by which we could tell whether the symptoms were due to RA or infection was the patient's good response to antibiotics.

The therapy for infection usually contradicts the immunosuppressive therapy; therefore, we must start the treatment with potent antibiotics with waning immunosuppression, at least locally. We tackled the infection aggressively using antibiotics at first, and subsequently reinforced the immunosuppressive therapy to avoid undesirable inflammation and melting.

In summary, care must be taken to keep patients from becoming infected when treating RA-associated ocular diseases. In particular, punctal occlusion and immunosuppressive therapy are presumed to be major risk factors of corneal infection in RA patients. When we encounter infection-suspicious cases, potent antibiotic measures should first be taken to avoid the progression of the infection and, after the subsidence of infection, the therapy should be shifted to an immunosuppressive one. Even with this regimen, it is difficult to avoid the development of corneal thinning, because infection probably accelerates corneal melting in RA patients.

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