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Rheumatoid Arthritis-Associated Corneal Ulceration with Superimposed Infection by Methicillin-Resistant *Staphylococcus aureus*: A Complicated Type of Corneal Melt

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 70
Final Diagnosis: Rheumatoid arthritis-associated corneal ulcer
Symptoms: Blurring of vision
Medication: Vancomycin • etanercept • adalimumab
Clinical Procedure: Anterior lamellar keratoplasty
Specialty: Rheumatology

Objective: Unusual clinical course





Background: Severe extra-articular manifestations of rheumatoid arthritis usually occur in advanced stages of the disease. In particular, ocular involvement may lead to inflammatory corneal ulceration, in which therapy is challenging owing to its association with systemic vasculitis. Close collaboration between ophthalmologists and rheumatologists is paramount in providing the best treatment approach in this sight-threatening condition.

Case Report: We present a case of seropositive rheumatoid arthritis associated with corneal melting in the absence of other typical clinical manifestations of rheumatoid arthritis flare. The rheumatoid arthritis-associated corneal ulcer was complicated in our case by concomitant infection with methicillin-resistant *Staphylococcus aureus*, which was treated with intravenous vancomycin after an initial antimicrobial ophthalmic solution proved not to be making adequate improvement in the corneal healing. The recurrent corneal melting appeared to be aggravated by the ophthalmic infection while on immunosuppressive regimen.

Conclusions: In patients on biologic agents, intravenous antibiotics must be considered in addition to ophthalmic eye solution in controlling the infectious process. Excluding concomitant ophthalmic infection is equally important before initiation of high-dose steroid and immunosuppressive regimens.

MeSH Keywords: Arthritis, Rheumatoid • Corneal Ulcer • Scleritis • Staphylococcal Infections

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/891127>

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Background

Rheumatoid arthritis (RA) is a symmetric, inflammatory, polyarthritides of unknown etiology. Although the central pathology is within the synovium of diarthrodial joints, extra-articular manifestations occur in about 40% of RA patients with positive rheumatoid factor (RF). The ocular complications of RA include scleritis, which is particularly important because slight inflammatory changes may cause severe interference with vision. Rarely, extra-articular manifestations can be severe and not respond to immunosuppressive therapy. Immunosuppressive therapy in itself poses a major risk for infections.

We report a case of RA with severe recurrent scleritis with corneal ulceration, which did not respond to immunosuppressive therapy because of superimposed bacterial infection.

Case Report

A 70-year-old female with history of RA, achieved clinical remission with etanercept, which she self-discontinued. Five months later, she developed blurring of vision and pain in the left eye accompanied with burning sensation and watery discharge. Ophthalmology evaluation was consistent with corneal perforation at 11 o'clock position in the left eye secondary to corneal melt attributed to RA. She underwent anterior lamellar keratoplasty on the left eye using a 3-mm donor corneal graft and was treated with intravenous corticosteroids (CS) – methylprednisolone 1 mg/kg/day. Conjunctival aspirate, ocular discharge, and corneal tissue cultures grew methicillin-resistant *Staphylococcus aureus* (MRSA). The patient was started on topical vancomycin along with intravenous CS, which was later changed to oral CS, and 2 weeks later etanercept 50 mg SQ weekly was restarted. On follow-up in the eye clinic 8 days later, she was found to have dehiscence of the inferior sutures along with corneal dehiscence and graft failure. Evaluation was also suggestive of the graft having epithelial defects, positive Seidel test with shallow anterior chamber, thinning, and a small area of leakage. Based on corneal graft culture, the patient was also found to have concomitant MRSA infection, which was sensitive to vancomycin, linezolid, tetracycline, and trimethoprim/sulfamethoxazole. She was readmitted and restarted on intravenous CS, vancomycin eye drops, and intravenous vancomycin 1 g IVPB every 12 h. She thereafter underwent repeat graft revision and anterior lamellar keratoplasty. Intravenous CS was switched to oral CS and etanercept was switched to adalimumab 40 mg SQ every 2 weeks in an attempt to control the eye inflammation.

After 2 weeks, she was re-admitted with septic shock due to left lower extremity cellulitis and nosocomial pneumonia complicated by acute renal failure requiring hemodialysis. Initial

blood cultures grew *Morganella morganii*, which was sensitive to amikacin, ceftazidime, imipenem/cilastatin, gentamicin, ceftriaxone, and tobramycin. Endotracheal aspirate culture grew *Pseudomonas*, extended-spectrum beta-lactamase (ESBL)-resistant *Klebsiella pneumoniae*, and multi-drug resistant (MDR) *Acinetobacter baumannii*, while repeat blood cultures were positive for ESBL *Klebsiella pneumoniae* and urine cultures grew *Candida albicans*. She was treated initially with intravenous ampicillin/sulbactam for the lower extremity cellulitis, which was later changed to intravenous imipenem/cilastatin and intravenous fluconazole. Metronidazole and vancomycin were initiated enterally because she also developed antibiotic-associated diarrhea. Intravenous gentamicin and aztreonam were also added and administered at renal dosing parameters for additional therapeutic coverage for the *Morganella*-associated sepsis and based on other culture results. The patient subsequently developed severe hypoxic respiratory failure secondary to acute respiratory distress syndrome (ARDS) due to the underlying septic shock and died in the ICU. Just prior to her last admission, she was seen in the eye clinic and her corneal graft was found to be intact and healing well.

Discussion

The predominant ocular manifestations of RA include dry eyes in the form of Sjögren's syndrome, scleritis, and corneal ulceration, which may lead to blindness [1]. The pathogenesis of RA-associated corneal ulcer is attributed to a local imbalance between levels of a specific collagenase (MMP-1) and its tissue inhibitor (TIMP-1), causing the rapid keratolysis [2]. Furthermore, it has been suggested that corneal ulceration heralds the presence of active vasculitis locally and systemically requiring aggressive immunosuppression [3]. Systemic steroids are the mainstay of treatment in the acute management of corneal ulceration, but in severe cases combination immunosuppression is required such as TNF- α inhibitors.

This case illustrates a rare extra-articular presentation of RA manifesting only with corneal ulcer in the absence of clinically active flares of joint inflammation. The rheumatoid-associated corneal ulcer was complicated in our patient with concomitant MRSA infection. When corneal dehiscence occurred again, we decided to start intravenous vancomycin after revision of corneal graft, because corneal melt can be rapidly progressive and can lead to endophthalmitis if undertreated. The patient received only 1 dose of adalimumab, because biologic agents have been shown to be effective for ulcerative keratitis.

A previous case of rheumatoid corneal ulceration complicated by infection with MRSA has suggested that corneal infection can accelerate the corneal melting. This occurs by three

postulated mechanisms brought about by the infection: (1) inflammatory cells migrate to the central portion of the cornea, which is usually devoid of inflammatory cells; (2) bacterial toxins and proteases may hasten the melting process; and (3) increased ratio of matrix metalloproteinases-to-tissue inhibitors of metalloproteinases [4].

Our patient had a long history of seropositive RA and presented with corneal melting, but her RA was well-controlled with the immunosuppressive regimen. The onset of corneal melting could represent either RA progression or development of severe eye infection while on immunosuppressive regimen. Our patient had increased clinical risk factors for the development of ocular complications – immune compromised state, presence of concomitant bacterial eye infection, and the RA with seropositive markers (RF and anti-CCP), which have been shown to represent higher risk of worse inflammatory ocular disease [5].

Although immunosuppressive therapy is a major risk factor of corneal infection in RA patients [4], previous reports have suggested that autoimmune corneal melting is an indication for systemic immunosuppression to avoid morbidity and mortality [2,6].

In a retrospective study done to compare the effect of tumor necrosis factor inhibition in managing RA manifestations, it was reported that there is a higher clinical efficacy in treating joint inflammation (100%) compared to inflammatory eye disease (38%), suggesting differences in the pathogenesis in these 2 inflammatory sites. The differential effect of TNF inhibitors implies that immunosuppressive therapy for one target

site might not work for another organ involvement, even in the same individual [7].

Graft survival is highly influenced by adequate control of immune-mediated corneal melting and prevention of superimposed corneal surface infection. A retrospective review on rheumatoid arthritis-associated corneal perforations by Bernauer et al. reported that 80% of early (within the first 6 months) graft failures were attributed to recurrent corneal melting following penetrating keratoplasty. This suggests the need for an aggressive immunosuppressive regimen in the postoperative state. However, it was also observed that concomitant corneal infection was responsible for most graft failures after 6 months [8].

Conclusions

We reported a rare case of extra-articular manifestation of RA in the form of corneal ulcer, complicated by MRSA infection in the absence of active disease flare, with systemic and articular features. In patients with RA on immunosuppressive therapy presenting with corneal ulcer, superimposed bacterial infection should be treated aggressively with intravenous antibiotics and not just topical antibiotics. It is equally important to exclude possible underlying infection, which must be treated appropriately before starting the immunosuppressive regimen.

Statement

All authors have no conflicts of interest. There were no funding sources to declare.

References:

1. Illiou C, Anthis N, Tsifetaki N et al: Clinical images: Corneal melt in a woman with longstanding rheumatoid arthritis. *Arthritis Rheum*, 2012; 64(1): 253
2. Squirell DM, Winfield J, Amos RS: Peripheral ulcerative keratitis corneal melt and rheumatoid arthritis: a case series. *Rheumatology*, 1999; 38(12): 1245–48
3. Stylianides A, Jones MN, Stewart RM et al: Rheumatoid Arthritis-Associated Corneal Ulceration: Mortality and Graft Survival. *Ophthalmology*, 2013; 120: 682–86
4. Ide T, Matsuda H, Nishida K et al: Rheumatoid arthritis-associated corneal ulceration complicated by bacterial infection. *Mod Rheumatol*, 2005; 15: 454–58
5. Itty S, Pulido JS, Bakri SJ et al: Anti-cyclic citrullinated peptide, rheumatoid factor, and ocular symptoms typical of Rheumatoid arthritis. *Trans Am Ophthalmol Soc*, 2008; 106: 75–83
6. Perez VL, Azar DT, Foster CS: Sterile corneal melting and necrotizing scleritis after cataract surgery in patients with rheumatoid arthritis and collagen vascular disease. *Semin Ophthalmol*, 2002; 17(3–4): 124–30
7. Smith JR, Levinson RD, Holland GN: Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Care Res*, 2001; 45: 252–57
8. Bernauer W, Ficker LA, Watson PG et al: The management of corneal perforations associated with rheumatoid arthritis. *Ophthalmology*, 1995; 102: 1325–37