

CASE REPORT

Rheumatoid Arthritis-Associated Corneal Perforation

Authors

Kashinatha Shenoy¹, Nadiya AlKhaurosi²

Affiliation

Department of Ophthalmology, College of Medicine and Health Sciences, Sultan Qaboos University Hospital, Muscat, Oman.

Correspondence

Kashinatha Shenoy

Email: kashinath_sullia@yahoo.co.in

Abstract

- 1) To describe the association between rheumatoid arthritis and corneal perforation.
- 2) To review the aetiology and management of rheumatoid arthritis -associated Peripheral ulcerative keratitis (PUK).

Patient and methods: A 35-year-old female presented with a five days history of decreased vision, pain, and watering and foreign body sensation in her left eye. She is a known case of Rheumatoid arthritis, which was quiescent at the time of presentation, and for which she is taking oral prednisolone, methotrexate, and etanercept and folic acid supplements. She never had any prior consultation with an ophthalmologist. The patients' visual outcomes and the development of any significant systemic complications were recorded. Slit-lamp examination in right eye showed mild meibomian gland dysfunction, central corneal thinning of about 60%, and also inferonasal thinning. Anterior chamber was of normal depth. Pupil was round and reacting, lens clear. Left eye had inferonasal corneal perforation, less than 2mm in maximum diameter, with iris prolapsed. There was no infiltration around the perforation and no corneal edema. Seidel test was positive in left eye. Corneal vascularization was noticed at 3'clock position. Anterior chamber was shallow with inferior iridocorneal touch. Pupil was peaked inferiorly, lens being clear. Patient was admitted to ward started oral Carbonic anhydrase inhibitors, T. acetazolamide 250mg, four times per day for five days and artificial tears hourly. Perforation was sealed with cyanoacrylate glue with bandage contact lens. Patient was discharged after week.

Conclusion.

PUK associated with rheumatoid arthritis often has a poor visual outcome and its appearance may herald the transformation of a patient's RA into the systemic vasculitic phase. RA-associated PUK should be managed with aggressive immunosuppression if the associated morbidity and mortality are to be avoided.

Keywords: Peripheral ulcerative keratitis (PUK), Rheumatoid arthritis (RA), cyanoacrylate glue.

Introduction

PUK has an incidence of 3 cases per million per year. Males and females are equally affected, age varies and is dependent on the associated systemic or local disorder. Bilateral disease may be present in 21% of patients.

Peripheral ulcerative keratitis is associated with many autoimmune disorders. Corneal ulcer can be the first manifestation of systemic disease and is referred to as PUK, it can quickly produce progressive necrosis of the corneal stroma, leading to perforation and blindness.¹ Pathophysiology of PUK as the name implicates involvement the peripheral cornea with distinct morphologic and immunologic characteristics that predispose it to inflammatory reactions. The peripheral cornea is very closer to limbal conjunctiva and derives part of its nutrient supply from the limbal capillary arcade, a source of immunocompetent cells, for example, macrophages, Langerhans cells, lymphocytes, and plasma cells.^{2, 3}

PUK has been associated with many autoimmune disorders, including, Rheumatoid arthritis (RA), which is present in 34 – 42% of PUK patients^{4, 5, and 6}. PUK may be the initial manifestation of Wegener granulomatosis (WG) also known as granulomatosis Angitis and polyarteritis nodosa (PAN). PUK is rare in patients with relapsing polychondritis (RP);

only 2 of 112 patients with RP were reported to develop PUK in a clinical review study^{7,8}. Systemic diseases that may cause immune complex deposition at the peripheral cornea and PUK such as collagen vascular disease, Inflammatory causes are usually associated with life-threatening autoimmune collagen vascular diseases and PUK might be the initial sign of a systemic disease. Systemic and ocular evaluation for underlying autoimmune diseases may include⁴, Complete Blood Count (CBC), Antinuclear Antibody (ANA), Anti-Neutrophil Cytoplasmic Antibody (ANCA), Rheumatoid Factor (RF), Anti-Cyclic Citrullinated Peptide (anti-CCP) Fluorescent Treponemal Antibody (FTA-Abs), Chest X-Ray (CXR) Purified Protein Derivative (PPD), Sacroiliac joint X-Ray, Hepatitis B Virus, Hepatitis C Virus, Ultrasound of the eye and Anterior Segment Optical Coherence Tomography to Monitor Disease Progression¹⁰.

Main complications are infection, corneal melting and perforation at the site ulcer. Visual prognosis is related to the severity of disease. If Patients with systemic disease have an increased mortality rate from vascular events. The mainstay in the treatment of peripheral ulcerative keratitis are to minimize inflammation, prevent super infection and promote healing of the ulcer and treating the underlying systemic vasculitic disease. Initiation of appropriate immunosuppressive

therapy with corticosteroids and cytotoxic agents are organ saving and life-saving.

Local treatment of peripheral ulcerative keratitis (PUK) is aimed at preventing or reducing corneal damage. Systemic therapy is aimed at controlling the underlying disease. The goal is reepithelialization of the epithelial defect to halt progressive corneal ulceration. Lubricating drops, gels, and ointments and antibiotic drops or ointments can be helpful in aiding epithelialization and prevention of infection. Topical steroid use is not recommended and should be used with caution in the treatment of patients with PUK associated with systemic disease because it may aggravate corneal melt due to collagen synthesis inhibition. Systemic collagenase inhibitors (tetracycline 250-mg tab qid or doxycycline 100-mg tab bid) may help slow the progression and oral vitamin C given at 500 mg four times a day to facilitate corneal healing.

Most of the studies have documented that patients with PUK who have associated systemic diseases have recurrences following localized temporizing treatment unless they are given adequate systemic immunosuppressive therapy. Immunosuppressive agents have been indicated for management of the following: PUK associated with potentially lethal systemic vasculitic syndromes, such as, RA, SLE, etc.

Cyclophosphamide is the drug of choice for almost all PUK associated with a connective tissue disorder. The intravenous route has been used with success in PUK associated with rheumatoid arthritis.¹⁸ Methotrexate (MTX), azathioprine, cyclosporine A, and chlorambucil have been found to be effective.⁶ High-dose oral prednisone may be started, while the chemotherapeutic agents take effect after 4-6 weeks.

The use of the tumor necrosis factor alpha (TNF-alpha) antagonist infliximab has been reported to be effective in rheumatoid arthritis-associated PUK cases refractory to the above conventional immunomodulatory therapy⁹. Adalimumab a human monoclonal antibody against tumor necrosis factor, has been used with success in combination with other immunosuppressives to treat RA-associated PUK¹¹.

Rituximab, a chimeric monoclonal antibody directed against the CD20 protein found in B cells, has been used in treatment-resistant PUK in GPA¹² and RA¹³, and was noted to have the highest success rate in achieving steroid-free remission in GPA-associated PUK²⁴.

Treatment for corneal perforation

Tissue adhesives, such as cyanoacrylate glue, are recommended for use in impending perforation and perforation size smaller than 1-2 mm.⁴

Application of a bandage contact lens prevents discomfort and dislodging of the adhesive⁴. Amniotic membrane transplantation has limited role in treating eyes with severe ischemia (eg, rheumatoid arthritis)²².

Tectonic procedures, including lamellar keratoplasty, penetrating keratoplasty, and corneoscleral patch grafts, are performed as needed to maintain the integrity of the globe when corneoscleral perforation is imminent or has occurred.

Case Report

A 35-year-old female presented with a five days' history of decreased vision, pain, and watering and foreign body sensation in her left eye. She is a known case of Rheumatoid arthritis, which was quiescent at the time of presentation, and for which she is taking oral prednisolone, methotrexate, and etanercept and

folic acid supplements. She never had any prior consultation with an ophthalmologist.

On examination she had visual acuity of 6/36 in right eye and hand movements in left eye. Slit-lamp examination in right eye showed mild meibomian gland dysfunction, central corneal thinning of about 60%, and also inferonasal thinning. Anterior chamber was of normal depth. Pupil was round and reacting, lens clear. Left eye had inferonasal corneal perforation, less than 2mm in maximum diameter, with iris prolapse. There was no infiltration around the perforation and no corneal edema. Seidel test was positive in left eye. Corneal vascularization was noticed at 3'clock position. Anterior chamber was shallow with inferior iridocorneal touch. Pupil was peaked inferiorly, lens being clear. [Figure 1]

Figure 1: Slit lamp photo showing shallow anterior chamber with inferior iridocorneal touch. Pupil was peaked inferiorly, lens being clear.



Diagnosis of rheumatoid arthritis-related corneal thinning in right eye and healed corneal perforation in left eye was laid out.

Treatment: Patient was admitted to ward started oral Carbonic anhydrase inhibitors T. acetazolamide 250mg, four times per day for five days and artificial tears hourly. Perforation was sealed with cyanoacrylate glue with bandage contact lens. Patient was discharged after one week.

Discussion

Peripheral ulcerative keratitis may be associated with various ocular and systemic infectious and noninfectious diseases. The most common disorders associated with PUK are systemic collagen vascular diseases, of which rheumatoid arthritis, accounting for 34% of noninfectious PUK cases^{4, 5, 6}. Other causes are, Wegener granulomatosis, relapsing polychondritis, and systemic lupus erythematosus.etc.²³. The management of corneal thinning due to connective tissue disease management is usually coordinated with a rheumatologist or internist. The treatment includes preservative free artificial tears, Cyanoacrylate adhesive applied to the ulcer bed to limit ulceration in cases of impending perforation, Topical antibiotics are used to prevent bacterial superinfection, systemic immunosuppressives (Steroids, Antimetabolites such as methotrexate, T cell

inhibitors such as cyclosporine, alkylating agents such as cyclophosphamide and biologic agents such as infliximab . Recently, biologic agents that serve as TNF- α antagonists by blocking its receptors have become more important in the treatment of cases refractory to conventional immunomodulatory therapy^{23, 24, 25}. Cyclophosphamide is the drug of choice for almost all PUK associated with a connective tissue disorder. The intravenous route has been used with success in PUK associated with rheumatoid arthritis.¹⁸ Methotrexate (MTX), azathioprine, cyclosporine A, and chlorambucil have been found to be effective⁶. High-dose oral prednisone may be started, while the chemotherapeutic agents take effect after 4-6 weeks.

The use of the tumor necrosis factor alpha (TNF-alpha) antagonist infliximab^{15, 17, 23} has been reported to be effective in rheumatoid arthritis-associated PUK cases refractory to the above conventional immunomodulatory therapy^{9, 23, 24, 25}. Adalimumab, a human monoclonal antibody against tumor necrosis factor, has been used with success in combination with other immunosuppressives to treat RA-associated PUK^{11, 14}. Rituximab, a chimeric monoclonal antibody directed against the CD20 protein found in B cells, has been used in treatment-resistant PUK in GPA^{12, 19, 20} and RA¹³, and was noted to have the highest success rate in achieving steroid-free remission

in GPA-associated PUK. Ebrahimiadib has been tried in some cases²¹. Tissue adhesives, such as cyanoacrylate glue, are recommended for use in impending perforation and perforation size smaller than 1-2 mm.⁴ Application of a bandage contact lens prevents discomfort and dislodging of the adhesive.⁴

Amniotic membrane transplantation has limited role in treating eyes with severe ischemia (eg, rheumatoid arthritis)²². The surgical options are Full thickness penetrating keratoplasty and resection of the conjunctiva adjacent to the area of peripheral ulcerative keratitis to limit inflammation originating from

the conjunctiva²³. Tectonic procedures, including lamellar keratoplasty, penetrating keratoplasty, and corneoscleral patch grafts, are performed as needed to maintain the integrity of the globe when corneoscleral perforation is imminent or has occurred.

Disclosure

The author reports no conflicts of interest in this work. Caption:

References.

1. Mondino BJ. Inflammatory diseases of the peripheral cornea. *Ophthalmology*. 1988 Apr. 95(4):463-72.
2. Shiuey Y, Foster CS. Peripheral ulcerative keratitis and collagen vascular disease. *Int Ophthalmol Clin*. 1998 Winter. 38(1):21-32.
3. Ladas JG, Mondino BJ. Systemic disorders associated with peripheral corneal ulceration. *Curr Opin Ophthalmol*. 2000;11:468-471.
4. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. *Surv Ophthalmol*. 1999 Mar-Apr. 43(5):379-96. .
5. Foster CS, Sainz de la Maza M. Immunological considerations of the sclera. Foster CS, ed. *The Sclera*. 1st ed. New York: Springer-Verlag; 1993:33-58.
6. Gregory JK, Foster CS. Peripheral ulcerative keratitis in the collagen vascular diseases. *Int Ophthalmol Clin*. 1996 Winter. 36(1):21-30.9
7. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. *Surv Ophthalmol*. 1999 Mar-Apr. 43(5):379- 13
8. Eiferman RA, Carothers DJ, Yankeelov JA Jr. Peripheral rheumatoid ulceration and evidence for conjunctival collagenase production. *Am J Ophthalmol*. 1979 May. 87(5):703-9.
9. Nolle B, Specks U, Ludemann J, et al. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener granulomatosis. *Ann Intern Med*. 1989 Jul 1. 111(1):28-40
10. Garg A, De Rojas J, Mathews P, Hazan A, Lin J, Trief D, et al. Using Anterior Segment Optical Coherence Tomography to Monitor Disease Progression in Peripheral Ulcerative Keratitis. *Case Rep Ophthalmol Med*. 2018. 2018:3705753.
11. Squirrel DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: a case series. *Rheumatology (Oxford)*. 1999 Dec. 38(12):1245-8. .
12. Sharma N, Sinha G, Shekhar H, Titiyal JS, Agarwal T, Chawla B, et al. Demographic profile, clinical features and outcome of peripheral ulcerative keratitis: a prospective study. *Br J Ophthalmol*. 2015 Nov. 99 (11):1503-8. .
13. Liegner JT, Yee RW, Wild JH. Topical cyclosporine therapy for ulcerative keratitis associated with rheumatoid arthritis. *Am J Ophthalmol*. 1990 May 15. 109(5):610-2.
14. abs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders:

- recommendations of an expert panel. *Am J Ophthalmol.* 2000 Oct. 130(4):492-513
15. Thomas JW, Pflugfelder SC. Therapy of progressive rheumatoid arthritis-associated corneal ulceration with infliximab. *Cornea.* 2005 Aug. 24(6):742-4
16. Sharma N, Sinha G, Shekhar H, Titiyal JS, Agarwal T, Chawla B, et al. Demographic profile, clinical features and outcome of peripheral ulcerative keratitis: a prospective study. *Br J Ophthalmol.* 2015 Nov. 99 (11):1503-8
17. Pham M, Chow CC, Badawi D, Tu EY. Use of infliximab in the treatment of peripheral ulcerative keratitis in Crohn disease. *Am J Ophthalmol.* 2011 Aug. 152(2):183-188.e2.
18. Korsten P, Bahlmann D, Patschan SA. Rapid healing of peripheral ulcerative keratitis in rheumatoid arthritis with prednisone, methotrexate and adalimumab combination therapy. *Rheumatology (Oxford).* 2017 Jul 1. 56 (7):1094.
19. Huerva V, Sanchez MC, Traveset A, Jurjo C, Ruiz A. Rituximab for peripheral ulcerative keratitis with Wegener granulomatosis. *Cornea.* 2010 Jun. 29(6):708-10.
20. Albert M, Beltrán E, Martínez-Costa L. [Rituximab in rheumatoid arthritis-associated peripheral ulcerative keratitis]. *Arch Soc Esp Oftalmol.* 2011 Apr. 86(4):118-20. .
21. Ebrahimiadib N, Modjtahedi BS, Roohipour R, Anesi SD, Foster CS. Successful Treatment Strategies in Granulomatosis With Polyangiitis-Associated Peripheral Ulcerative Keratitis. *Cornea.* 2016 Nov. 35 (11):1459-1465.
22. Lambiase A, Sacchetti M, Sgrulletta R, et al. Amniotic membrane transplantation associated with conjunctival peritomy in the management of Mooren's ulcer: a case report. *Eur J Ophthalmol.* 2005 Mar-Apr. 15(2):274-6.
23. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. *Ophthalmology.* 2008;115:1826–1832.
24. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol.* 2000;130:492–513.
25. Odorcic S, Keystone EC, Ma JJ. Infliximab for the treatment of refractory progressive sterile peripheral ulcerative keratitis associated with late corneal perforation: 3-year follow-up. *Cornea.* 2009;28:89–92.