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A Vision- and Life-threatening Case of Peripheral Ulcerative Keratitis

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A Vision- and Life-threatening Case of Peripheral Ulcerative Keratitis

Abstract

Background: Peripheral ulcerative keratitis (PUK) is a rare but severe ocular manifestation most commonly associated with rheumatoid arthritis amongst other autoimmune diseases. Quick diagnosis and co-management with corneal specialist and rheumatologist are crucial to preserve vision and life. A rare case of PUK associated with rheumatoid arthritis (RA) is presented with updates on current understanding and co-management of this condition.

Case Report: A 76 year-old Caucasian male presented to the eye clinic on a Friday as a new patient, with a chief complaint of a red right eye started two weeks ago and was treated with erythromycin ointment, but it got worse with moderate pain so he was referred over from the urgent care clinic. His BCVA OD, OS was 20/80 PHNI and PH20/25, respectively. Anterior segment evaluation showed severe conjunctival chemosis and injection, a superior temporal circular infiltrate and an inferior temporal linear infiltrate across the cornea with moderate corneal edema. Chart review confirmed the patient has been treated for rheumatoid arthritis with hydroxychloroquine and leflunomide for several years. The patient was diagnosed with PUK with mild scleritis associated with (RA) and initially treated with tobradex topical drops OD qid. His rheumatologist was contacted for co-management, and the patient was to return to clinic after the weekend. On the follow up visit, the patient felt better but the linear infiltrate persisted so oral prednisone 60mg/day was started with ofloxacin qid instead of Tobradex qid. The condition continued to improve over the next few follow up however the linear thinning of the cornea was not fully resolved so the patient was referred to a local corneal specialist. His rheumatologist continued to manage his RA closely and the patient confirmed that he was doing better overall at the latest visit.

Conclusion: In cases of PUK with stromal thinning and scleritis, autoimmune diseases such as RA and systemic lupus erythema often are the underlying systemic cause. Prompt diagnosis and co-management with other specialists are essential to minimize irreversible vision loss and save lives.

Keywords

Peripheral ulcerative keratitis, scleritis, rheumatoid arthritis

Cover Page Footnote

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INTRODUCTION

Peripheral ulcerative keratitis (PUK) is a rare and severe ocular manifestation associated with autoimmune diseases that leads to peripheral corneal thinning and potential corneal perforation. PUK has been reported in patients with rheumatoid arthritis (RA), polyarteritis nodosa, inflammatory bowel disease, collagen vascular diseases such as systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (GPA) (Table 1).[1]

Systemic autoimmune vasculitic disease	Rheumatoid arthritis Wegener granulomatosis/ granulomatosis with polyangiitis Systemic lupus erythematosus Polyarteritis nodosa Sjogren Syndrome
Dermatological disorders	Acne rosacea Cicatricial pemphigoid Stevens-Johnson syndrom
Inflammatory bowel disease	Crohn disease
Local ocular immunity	Mooren ucer

Table 1: Major Autoimmune Diseases Causing Peripheral Ulcerative Keratitis

The most prevalent forms of autoimmune diseases are RA and SLE. PUK is most commonly associated with RA, followed by GPA. The pathophysiology of autoimmune diseases remains to be fully uncovered. This group of diseases affect most of the organs in the body. The eye, a specialized sensory organ, can be affected at any point throughout the course of these diseases. Some of the early signs of autoimmune diseases manifested first in the eye, including dry eye disease, episcleritis, scleritis, uveitis, and retinitis; therefore, optometrist may be the first clinician in the process of a systemic diagnosis. PUK, however, is a late and most destructive ocular manifestation of these systemic diseases.[1] We present a case report of PUK in a patient with a history of rheumatoid arthritis and other comorbidities including chronic obstructive lung disease and deep vein thrombosis. The patient passed away within five months of the initial ocular manifestations.

CASE REPORT

A 76-year-old Caucasian male presented with a history red eye OD that started 2 weeks ago. He saw an outside optometrist and was treated with erythromycin ointment for one week. The redness persisted with worsening ocular pain so he

went to an urgent care clinic for further evaluation. He was then referred to our eye clinic. His medical history consisted of multiple systemic problems including chronic obstructive lung disease, hyperlipidemia, deep vein thrombosis, diabetes, hypothyroidism, and rheumatoid arthritis. His active medication list included Symbicort, tiotropium, atorvastatin, aspirin, levothyroxine, hydroxychloroquine and leflunomide. His last comprehensive eye exam two months ago was unremarkable.

The patient complained of moderate ocular pain and was severely photophobic at initial presentation. Habitual visual acuity (VA) was 20/80 OD and 20/40-2 OS. His refractive error was -1.75-2.75x170 OD, -1.50-1.50x157 OS, and ADD+2.50. His pupils were equal and reactive to light without afferent pupillary defect.

Extraocular movement was full without restriction albeit moderate pain OD. Confrontation field was full to finger counting. Cover test was orthophoric. Slit lamp evaluation showed severe conjunctival injection and chemosis, a superior nasal circular infiltrate and an inferior temporal linear infiltrate across the cornea with moderate corneal edema (Fig. 1).

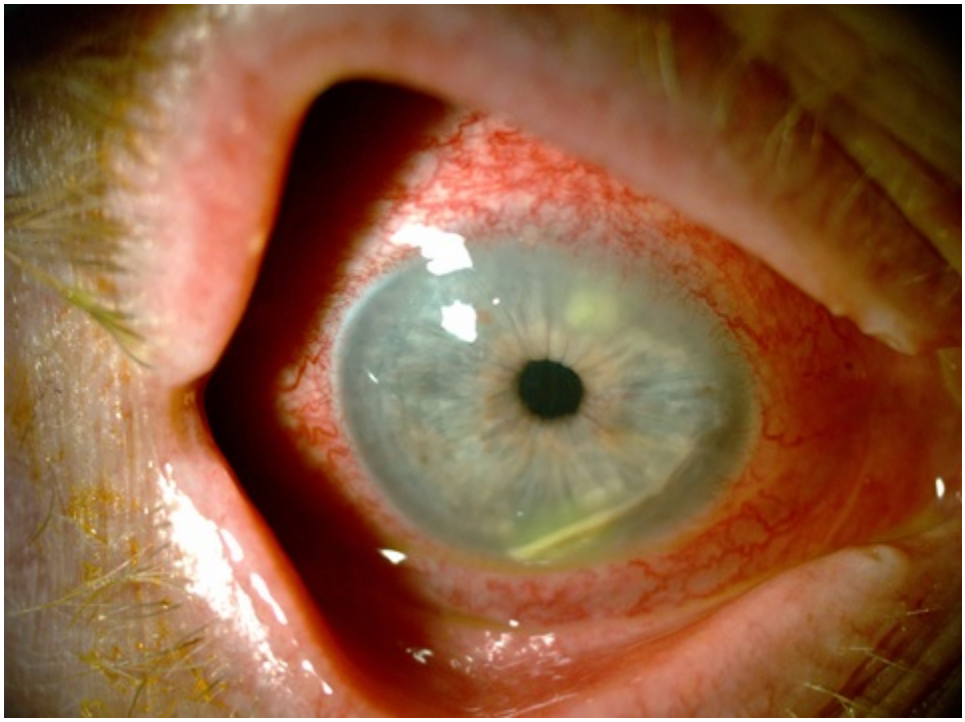

Figure 1: Anterior segment photo showed moderate scleritis, superior nasal circular infiltrate, inferior nasal linear infiltrate with corneal thinning OD at initial visit.

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Goldmann applanation tonometry revealed an intraocular pressure of 14 mmHg OU. Under the consultation of an ophthalmologist, the patient was diagnosed with PUK and moderate scleritis associated with RA and was initially treated with Tobradex (tobramycin-dexamethasone) qid OD. Chart review confirmed the patient has been treated for RA with hydroxychloroquine and leflunomide for several years. His rheumatologist was contacted for co-management, and the patient was to return to clinic in two days.

The patient felt better with Tobradex qid OD over the weekend, but his right eye still was viscous and sticky in the morning. His VA remained at 20/80 without improvement. The superior nasal circular infiltrate resolved, and the inferior temporal linear infiltrate across the cornea and scleritis were resolving, however peripheral corneal thinning persisted. After consultation with his rheumatologist, he was put on a pulse treatment of 60 mg prednisone p.o. daily with substitution of Tobradex qid for ofloxacin qid, and artificial tears qid. After two days of oral prednisone, the patient felt the same with little improvement, his eye was not sticky in the morning and the VA improved to 20/50+2 with less conjunctival injection, corneal edema and linear infiltrate. He was recommended to continue the course of treatment.

After a week of oral prednisone, his BCVA improved to 20/40-1, corneal infiltrate resolved but the peripheral cornea was thin, so he was referred to a corneal specialist for further management while continuing to take prednisone and ofloxacin. After a month of oral prednisone and awaiting for a corneal specialist consult, the patient felt that his eyes were not experiencing any pain or discomfort and doing quite well. His VA was stable at 20/40 OD and the eye has mild hyperemia nasally with the persistent linear peripheral corneal thinning (Fig. 2).

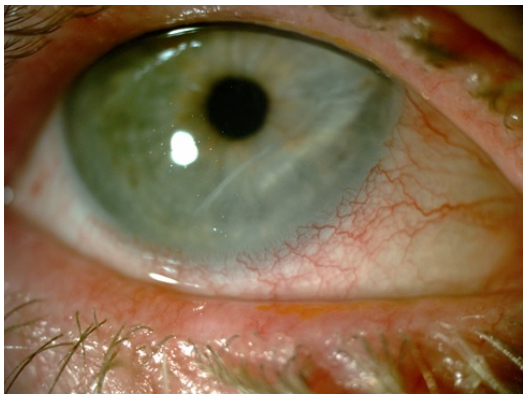

Figure 2: Anterior segment photo showed resolving scleritis, resolved superior nasal circular infiltrate and inferior nasal linear infiltrate, but linear corneal thinning persist OD after one month of treatment.

Oral prednisone was tapered to 40 mg/d until the next visit in three weeks. At that visit, he saw his rheumatologist two days prior and was scheduled to see the corneal specialist in two months. His rheumatologist took him off of leflunomide because he recently had pneumonia. He continued to take hydroxychloroquine 400 mg/d and prednisone 40 mg/d. He developed leg edema and elevated blood sugar over the past several weeks while taking high dose of prednisone. His internist was informed as a part of the co-management team. His eye felt better and habitual VA improved to 20/30-2 OD. Anterior segment optical coherence tomography (OCT) of the cornea confirmed persistent peripheral thinning (Fig. 3).

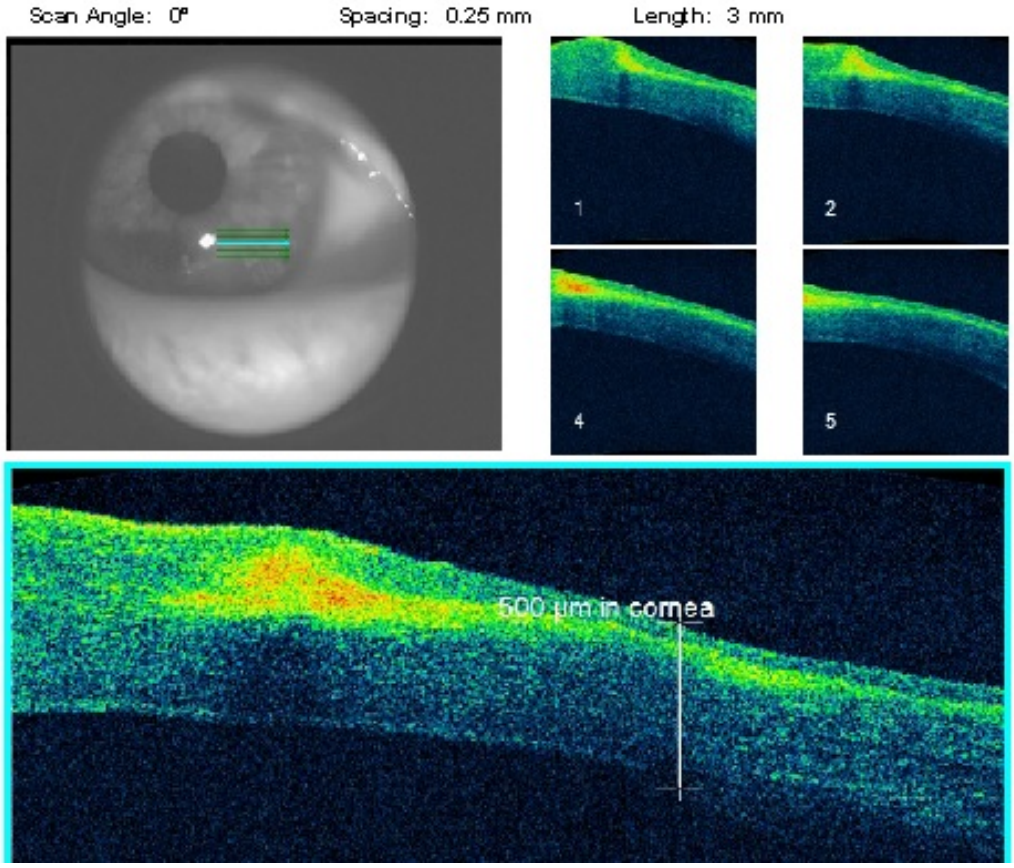

Figure 3: Anterior segment OCT confirmed paracentral corneal thinning to 500um OD.

Patient was to taper prednisone to 30 mg/d for 2 weeks, then 20 mg/d for 2 weeks and return to clinic in a month for follow up with dilated fundus exam to monitor for hydroxychloroquine maculopathy. Unfortunately, the patient passed away from respiratory complications associated with autoimmune disease before he could attend his appointment with the corneal specialist.

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DISCUSSION

Peripheral ulcerative keratitis is a manifestation of excessive corneal inflammatory reaction that leads to corneal tissue damage and subsequent curvilinear peripheral stromal thinning. It is often associated autoimmune diseases, with RA being the most common underlying cause. The incidence of PUK is estimated to be approximately 3 cases per million per year with equal prevalence in males and females.[1] A recent retrospective review of 18 patients with PUK from a multidisciplinary Uveitis Unit from 1996 to 2017 in Barcelona, Spain identified 8 patients with RA, 2 ANCA-vasculitis, 1 SLE and 1 Takayasu's arteritis. Three cases were idiopathic and the other three were infectious. The median age was 72 (range 33-85) and women accounted for majority of the cases. Half of the patients had associated scleritis and four (33%) patients suffered ocular perforation and required surgery.[2] This study supports the previous findings that RA accounted 34-42% of patients with PUK, followed by GPA and SLE.[3]

Patients usually present with ocular irritation, pain, redness, photophobia, and impaired vision. Important ocular manifestations include scleritis (especially, necrotizing scleritis), episcleritis, keratoconjunctivitis sicca, and anterior uveitis. The differential diagnosis for PUK is broad as it includes other inflammatory condition such as Mooren's ulcer, Terrien's marginal degeneration, Pellucid marginal degeneration, and other infectious or neoplastic causes.[1] Mooren's ulcer also presents with painful peripheral corneal thinning, but adjacent scleritis is not seen. Terrien's marginal degeneration differs from PUK in that it is a painless, noninflammatory disease causing peripheral corneal thinning without ulceration. Pellucid marginal degeneration causes inferior corneal thinning without inflammation and pain.[1] A blood work up is essential in identifying the probable systemic cause of PUK. Fortunately, the patient was in an integrative health care system at a VAMC, his blood work up as well as active medical problems were updated regularly and readily available. For clinicians in other settings, laboratory tests for potential autoimmune diseases may need to be ordered (Table 2) because PUK is unlikely to be idiopathic. Furthermore, 50% of PUK cases are associated with collagen vascular disease.[1]

Table 2

Laboratory test	**Indications**
Complete Blood Count (CBC)	Hematology
Complete Metabolic Profile (CMP)	Metabolism
Urinalysis with microscopic analysis (UA & micro)	Kidney elimination

Laboratory test	Indications
Erythrocyte Sedimentation Rate (Sed Rate)	Inflammation
C-Reactive Protein (CRP)	Inflammation
Antinuclear Antibody (ANA)	Systemic lupus erythematosus
Anti-Neutrophil Cytoplasmic Antibody (ANCA)	Granulomatosis with polyangiitis
Rheumatoid Factor (RF)	Rheumatoid arthritis, Sjorgren's syndrome
Anti-Cyclic Citrullinated Peptide (anti-CCP)	Rheumatoid arthritis
Fluorescent Treponemal Antibody (FTA-Abs)	Syphillis
Purified Protein Derivative (PPD)	Tuberculosis
Corneal Culture	Infection
Ultrasound of the eye	Neoplasm

Table 2: Recommended laboratory test to identify potential systemic cause of PUK.1

The pathogeneses of PUK associated with RA are not fully understood but cumulative evidence suggests that both T cells and antibodies are involved in the manifestation.[4] Peripheral cornea is well vascularized with abundant immune cells that can be activated abnormally in RA and other autoimmune diseases. The deposition of antigen-antibody complexes and subsequent inflammatory reactions induces macrophages and keratocytes to elevate the levels of proteolytic enzymes such as matrix metalloproteinases and collagenases that degrade corneal collagens and extracellular matrices leading to thinning and potential perforation.[5]

The goal in the treatment of RA is to control synovitis and prevent joint injury. All patients with active RA are treated with disease-modifying antirheumatic drugs (DMARDs) to prevent, arrest, or retard joint injury. Methotrexate (MTX), hydroxycholorquine (HCQ), sulfasalazine (SSZ) and leflunomide (LEF) are the conventional DMARDs often used as initial therapy with a preference for MTX. Nonsteroidal anti-inflammatory drugs (NSAIDs, 3200 mg of ibuprofen, 1000 mg naproxen, or 20 mg piroxicam per day) and/or glucocorticoids (5 to 10 mg/d) is added for initial symptomatic control of inflammation while awaiting the response to DMARD therapy.[6] Biologic DMARDs including etanercept, adalimumab, tofacitinib are alternative medications for patients who are unable or unwilling to take traditional DMARDs. For refractory cases that are not responsive to above treatments, infliximab or rituximab may be needed.[1] The management of acute PUK is to calm the inflammation by using topical corticosteroid with an adjunct

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broad-spectrum antibiotic to prevent infection because the cornea is compromised. Systemic corticosteroids are considered first-line therapy to control systemic inflammation. Topical cyclosporine-A can be considered because it can suppress damaging immunological response.[7] Anterior segment OCT can be used to monitor for progressive or resolving cornea thinning. When corneal perforation occurs, surgical procedures involving corneal glue, conjunctival flaps, amniotic membrane grafts and penetrating keratoplasty are necessary.[8]

Prior to the advent of efficacious DMARDs, the mortality rate of patients with RA-associated PUK was up to 50% because it may herald systemic vasculitis.[9] After the advent of DMARDs, the mortality rate of patients with RA-associated PUK is expected to be lower but there has not been a more recent study with updated estimates. Visual acuity is usually poor for patients with PUK, up to 2/3 of eyes with corneal melt (with or without perforation) had vision worse than 20/200.[10]

CONCLUSION

In conclusion, early diagnosis and proper management of PUK in patients with autoimmune diseases including RA is vital to preserving sight and saving life. A co-management team consisting of internist, rheumatologist, pharmacist and eye care providers including corneal specialists are crucial to manage the complexity of this disease and the adverse side effects posed by systemic therapies.

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