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CORNEA (K HOUSER, SECTION EDITOR)

Peripheral Ulcerative Keratitis: Management

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Abstract

Purpose of Review This study aimed to discuss an updated, evidence-supported, stepwise approach to the diagnosis and treatment of peripheral ulcerative keratitis (PUK).

Recent Findings PUK conventionally describes a rapidly progressive, crescent-shaped, peripheral, and inflammatory corneal melt. Undertreated PUK may lead to vision loss and premature mortality. A comprehensive approach includes diagnosis, short-term treatment, long-term treatment, and surgical considerations. Diagnosis is based on clinical findings. Next, the clinician should pursue an underlying etiology with a meticulous workup, including careful consideration of microbial keratitis. Common causes are rheumatoid arthritis, microbial keratitis, systemic necrotizing vasculitis (such as granulomatosis with polyangiitis), and collagen vascular disease (such as systemic lupus erythematosus). For short-term management of noninfectious PUK, therapy involves intensive anti-inflammatory therapy with corticosteroids. Adjunctive therapies such as conjunctival resection, amnionic membrane transplantation, and topical cyclosporine are also discussed. Recurrence commonly occurs, sometimes months to years later. Recurrence is a major source of premature vision loss. Additionally, smoldering disease activity seems to confer a risk of early mortality. Therefore, we recommend starting or escalating immunomodulatory therapy patients in most patients with sight-threatening, steroid-responsive, noninfectious PUK, especially (but not limited to) those with systemic features or a corneal graft.

Summary PUK is a sight-threatening condition that requires a short-term and long-term view of the disease. Multidisciplinary collaboration with other physicians is crucial to achieve optimal outcomes.

Keywords Peripheral ulcerative keratitis · Rheumatoid arthritis · Vasculitis · Immunosuppressive · Immunomodulatory

Peripheral ulcerative keratitis (PUK) is a rare clinical phenotype that generally describes a rapidly progressive, peripheral corneal melt due to corneal inflammation [1, 2]. Many local and systemic inflammatory conditions cause it, especially uncontrolled systemic autoimmunity due to rheumatoid arthritis (RA) or systemic necrotizing vasculitis (SNV). PUK is sight-threatening. When due to undertreated systemic disease, it should be considered life-threatening. Because of its rarity, clinical treatment is guided by case series, retrospective reports, and expert opinions. Nevertheless, recent advances have been made in its diagnosis and management.

Different underlying causes of PUK likely have different underlying mechanisms [3]. For RA-associated or SNV-associated PUK, an early event involves immune complexes at the terminal ends of limbal vessels, which elicit an immune response. Innate immune cells (i.e., neutrophils and macrophages) drive early keratolysis. Additionally site-specific T cells and antibody-producing B cells populate the peripheral cornea and the limbal conjunctiva. This repository of immunologic memory may lead to recurrent bouts of inflammation. Occlusive vasculitis is often observed, with the degree of ischemia correlating to the severity of disease [4, 5]. PUK's association with prior corneal surgery, trauma, local infection, or systemic infection also suggests that immune sensitization plays a role, via either molecular mimicry or direct exposure of corneal antigens.

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Diagnosis

No diagnostic criteria exist for PUK. Conventionally, PUK implies a rapidly progressive, crescent-shaped, inflammatory, and peripheral corneal melt. Active disease demonstrates an epithelial defect, engorgement of limbal vessels, and a white blood cell infiltrate in the corneal stroma ("peripheral whitening"). These features separate it from conditions that are indolent (e.g., Fuchs superficial marginal keratitis), non-peripheral (e.g. paracentral rheumatoid ulceration) [6], or non-inflammatory (e.g. pellucid marginal degeneration), though some overlap may exist.

PUK may be unilateral or bilateral. Associated keratoconjunctivitis sicca, scleritis, and iridocyclitis are common. Scleritis, especially when necrotizing, increases the likelihood of local necrotizing vasculitis and systemic disease [7, 8]. In the USA and UK, RA is the most common cause of PUK [8–13]. The classic patient is a 50- to 80-year-old woman with longstanding, seropositive, erosive RA. Inflammatory arthritis is often inactive [14]. Consequently, these patients may be on little or no immunosuppression at the onset of PUK. In Africa and India, Mooren's ulcer is a more common cause of PUK. Mooren's ulcer is a specific subtype of PUK defined by its clinical presentation—intense pain, lack of scleritis and systemic disease association, and circumferential progression. The classic patient is a 30- to 60-year-old man who may be a smoker [15–17].

Finding an Underlying Cause

Because PUK is the final common pathway for diverse insults, one must search for an underlying cause. Broadly, the two common causes are systemic autoimmunity and microbial keratitis. Autoimmunity typically requires high doses of steroids and immunomodulatory therapy, whereas infections may worsen with these same treatments.

As such, microbial keratitis requires careful consideration. In the setting of risk factors (trauma, contact lenses, steroids, immunosuppression, recent eye surgery, or prior herpetic disease), corneal scrapings for bacteria, fungus, acanthamoeba, mycobacteria, and viruses are mandatory. Infectious keratitis commonly occurs in the periphery. For example, up to 50% of Moraxella ulcers begin peripherally [18, 19]. Even when clinical suspicion is low (e.g., longstanding RA), scrapings should be considered for many reasons. Minor insults (e.g., cataract surgery [20–23], refractive surgery [24], or typically non-pathogenic infections [25]) can trigger an exaggerated inflammatory response in a predisposed individual. A microbial superinfection may occur over a primary rheumatoid melt. Patients with rheumatologic disease are often immunosuppressed. And finally, herpesviral keratitis occurs spontaneously and may present similarly [26–30]. The literature is replete with cases of infectious keratitis initially diagnosed as autoimmune PUK. Thus, our practice is to culture all patients with PUK.

Simultaneously, one should consider underlying autoimmunity, which usually falls under one of three categories: (1) rheumatoid arthritis (RA); (2) systemic necrotizing vasculitis (SNV), especially granulomatosis with polyangiitis (GPA); and (3) collagen vascular diseases (CVD), especially systemic lupus erythematosus (SLE) and relapsing polychondritis (RP). Systemic necrotizing vasculitis is an umbrella term for the many systemic vasculitides not caused by RA and may include conditions such as polyarteritis nodosa, cryoglobulinemia, and leukocytoclastic vasculitis. For the ophthalmologist, joint pains (for RA), sinus and lung issues (GPA), genitourinary issues (GPA), mouth ulcers (SLE), foot drop (SNV), ear and nose abnormalities (RP), and skin rashes (SNV, SLE, and others) should prompt a referral to a specialist who can diagnose and manage these issues.

Basic ancillary testing includes a complete blood count, a comprehensive metabolic panel, erythrocyte sedimentation rate, C-reactive protein, a urinalysis, and a chest x-ray. In this author's experience, urinalysis and chest x-ray are often overlooked by ophthalmologists. For PUK, these are critically important because lung and urinary abnormalities are important signs of SNV. Specific antibodies for RA (rheumatoid factor (RF), anti-citrullinated cyclic antibodies (anti-CCP)), SNV (anti-myeloperoxidase or p-ANCA; anti-proteinase 3 or c-ANCA), and SLE (anti-nuclear antibody) should be obtained. Of note, anti-CCP may be more sensitive than RF for RA, so both should be obtained. A treponemal specific test [31] and a tuberculosis test should also be obtained. Depending on the clinical scenario, additional testing may include HIV [32–36], hepatitis panel [37–41], cryoglobulin screen [39, 41, 42], anti-SSA/SSB, and complement levels. Finally, the clinician should consider a biopsy since this may be the best way to diagnose SNV. Common sites include the skin, lungs, and kidney. Although high dose steroids negatively affect biopsy yield, treatment should not be delayed. Expedited referral and multi-disciplinary communication are key.

If initial evaluation is negative, the differential expands to include other causes of PUK. Ocular surface disease can cause peripheral keratitis. Conditions include cicatricial pemphigoid [23], trichiasis, keratoconjunctivitis sicca, rosacea blepharitis, dermatologic causes like hidradenitis supparativa [43], poorly fitting contact lenses, and exposure keratopathy. Other items on the differential include culture-negative infectious keratitis, leukemia [44–46], indolent systemic infections (e.g., bartonella) [47], Vitamin A deficiency

[48], inflammatory bowel disease, anti-myelin oligodendrocyte disease [49, 50], sarcoidosis [51–53], and autoimmune hepatitis [40]. Recent case reports have focused on new descriptions of medication-associated PUK, such as rituximab [54], tocilizumab [55], dupilumab [56], COVID vaccine [57], checkpoint inhibitors [58, 59], and miltefosine [60].

A large minority of PUK cases are idiopathic or undifferentiated. Mooren's ulcer describes undifferentiated PUK without scleritis that generally presents with intense pain and an overhanging edge at the central aspect of the ulcer. It represents the most common form of PUK in many parts of the world and responds to anti-inflammatory therapy [16].

Treatment

The four goals of treating PUK are to (1) arrest keratolysis, (2) heal the epithelium, (3) prevent recurrences, and (4) prevent premature morbidity and mortality due to systemic disease. Different underlying causes require different therapies. For example, local infection may only require topical antimicrobials. GPA, by contrast, requires intensive immunomodulatory therapy. Treatment of microbial keratitis has been described elsewhere [61]. This review will focus on management of PUK due to other causes.

Corticosteroids

Aggressive corticosteroid therapy is the cornerstone of initial, short-term management when suspicion for infection is low. Oral Prednisone 1–1.5 mg/kg/day (up to 60 mg daily) in the AM with food and tapered over months is standard initial therapy, especially if there is an associated systemic condition or scleritis. Other forms of corticosteroids may be appropriate on a case-by-case basis. In the 1980s, hourly prednisolone acetate 1% was described the first rung in a stepladder approach to Mooren's ulcer [62, 63]. Indeed, a recent study using a modified version of this approach with conjunctival resection demonstrated good initial rates of resolution (47/62 patients). Nevertheless, recurrence rates remained high (26/62) [64]. Patients should be monitored closely, as topical steroids may exacerbate occult infections and delay epithelial healing. Monotherapy of PUK with topical steroids is controversial [2]. For severe melts, bilateral melts, or impending perforation, a loading dose with "pulsed" intravenous methylprednisolone (500–1000 mg daily for 1–3 consecutive days) may be appropriate. Patients should be screened for diabetes mellitus, hypertension, psychiatric disorders, endocrine disorders, fractures, and infections prior to receiving systemic corticosteroids, and their medical physician should be notified.

Adjunctive Therapies for Short-Term Management

Multimodal adjunctive therapy is often employed, especially in the early stages of disease. It is difficult to know whether and which interventions change the course of disease since they are usually used in combination. A thin cornea, epithelial defect, and immunosuppression carry a non-trivial risk of anthropogenic perforation or superinfection when patients touch the area around their faces. Thus, all therapies require justification.

Adjunctive eye drops are commonly used. Frequent, preservative-free, topical lubricants can help treat associated keratoconjunctivitis sicca. Topical antibiotics may prevent a bacterial superinfection in the setting of a sterile epithelial defect. Judicious use of topical corticosteroids, as discussed above, speeds resolution of inflammatory keratitis and treats associated iridocyclitis. Cycloplegia is recommended if there is a robust anterior chamber reaction. Topical cyclosporine (CsA) 1% or 2% may reduce keratitis. CsA has a favorable long-term safety profile compared to topical corticosteroids. Topical cyclosporine seems particularly effective in surgically induced necrotizing keratitis and paracentral rheumatoid ulceration, both of which have reports of success with CsA monotherapy [6, 21, 65].

Invasive interventions also have a role. One study reported that monotherapy with amniotic membrane transplantation successfully resolved the acute process in 16/18 eyes with Mooren's ulcer [66]. Nevertheless, reports with long-term follow caution that recurrence rates remain high [67, 68]. Similarly, conjunctival resection has long played a role in the management of PUK, especially Mooren's ulcer [69]. In theory, resection reduces inflammatory mediators coming from conjunctival vessels to the peripheral cornea. Indeed, numerous reports show that conjunctival resection as monotherapy or with topical corticosteroids can heal PUK and Mooren's ulcer during the initial episode [64, 70, 71]. Much like amniotic membrane transplantation; however, it does not consistently induce remission [64, 72].

Other options have anecdotal reports of efficacy, but they are limited by cost and accessibility. Blood-derived tear products (serum tears, platelet rich plasma, or plasma rich in growth factors) demonstrate possible efficacy in other inflammatory ocular surface diseases such as dry eye disease and persistent epithelial defects [73]. There are case reports of efficacy as a component of multimodal adjunctive therapy in PUK [74, 75]. Blood-derived tears are essentially a growth medium and should be used in caution in suspected infections without antimicrobial coverage. Adjunctive oral therapies may also be used. Animal studies show oral ascorbic acid slows keratolysis [76]. Oral tetracyclines or oral macrolides serve a dual role in reducing matrix metalloproteinases and reducing blepharitis [77, 78]. These agents are particularly effective if rosacea or meibomitis is contributing

to surface inflammation. Topical medroxyprogesterone, topical collagenase, low-dose povidone iodine, and oral collagenase inhibitors may serve an ancillary role [1, 79].

Some medications should be avoided in PUK. Topical non-steroidal anti-inflammatory drugs (NSAIDs) may paradoxically accelerate a corneal melt. Oral NSAIDs and oral steroids together pose an unacceptably high risk of peptic ulcer disease. Low potency formulations of cyclosporine (e.g., Cyclosporine 0.05%, Cyclosporine 0.09%, Cyclosporine 0.1%) are inappropriate for sight-threatening PUK. Subconjunctival depot of triamcinolone acetonide is usually avoided due a theoretical risk of accelerating necrosis.

Immunomodulatory Therapy

Noninfectious PUK should be considered an indication to start or escalate immunomodulatory therapy (IMT). Studies consistently demonstrate that outcomes improve with IMT compared to corticosteroid monotherapy [80, 81]. In 1984, Foster et al. described a non-randomized study comparing glucocorticoids to glucocorticoids + IMT. The mortality rate of patients on glucocorticoid therapy alone was 54%, whereas the mortality rate of patients on IMT was 5% [82]. Other studies echo this finding, including a recent study from 2020 that showed a mean estimated survival of 10.7 years of patients without IMT compared to 24.7 years with IMT [83]. On an eye level, IMT also improves outcomes. Without IMT, the success of corneal transplantation is dismal [65, 84]. A study from 1995 reported an 11% rate of success of grafts without IMT [85]. IMT also protects against recurrent disease, which is a major cause of long-term visual disability. For example, that same study described that of 25 graft failures, 20 occurred due to recurrent disease up to 6 months later.

Notably, many of these studies included all patients with PUK, not just those due to a named autoimmune disease. Our practice is to immunosuppress most patients with steroid-responsive, presumed noninfectious PUK even if a rheumatologic workup does not reveal a frank underlying cause. As mentioned above, inflammatory arthritis may be inactive at the time of a PUK episode. Thus, it is the responsibility of the ophthalmologist to communicate the sight-threatening and life-threatening nature of PUK to the rheumatologist, who may not find any other reason to immunosuppress the patient.

IMT typically takes 1–3 months to reach full efficacy. Therefore, IMT should not be considered a substitute for corticosteroids in the short-term. Rather, it should be thought of as long-term therapy to prevent recurrences and avoid the unacceptable safety profile of large cumulative doses of systemic corticosteroids. IMT is often started alongside corticosteroids to allow the clinician to safely taper off steroids without recurrence. It also serves an ancillary role for short-term therapy. Both high-dose corticosteroids and IMT should be managed with a provider experienced in using these agents, as they require careful monitoring for adverse events.

It is unclear how long patients must remain on IMT before they remit. One study with long-term follow up after conjunctival resection demonstrated recurrence-free survival rate of 42.5% at 1 year which dropped to 21.3% after 2 years. [72]. This is consistent with our clinical experience that recurrent disease may occur years after the initial episode. Our recommendation is a minimum of 2 years of quiescence prior to trialing a taper off IMT. Some patients with severe damage may benefit from indefinite IMT since the consequences of another flare would be blinding.

The choice of IMT depends on disease severity and underlying cause. Generally, the clinician can use similar IMT to that of scleritis. For mild or early disease, a trial of antimetabolite therapy is appropriate. Our preferred agents include methotrexate 25 mg weekly or mycophenolate mofetil 3 g daily. A study from the UK described patients with RA-associated PUK in which 69/70 patients received non-biologic IMT (antimetabolites, T-cell inhibitors, or cyclophosphamide). It demonstrated perforation in 8/58 patients and a 15% 10-year mortality rate, which were better outcomes than previous reports [10]. Inadequate response to antimetabolites should prompt biologic therapy. For PUK due to RA, early initiation with anti-TNF agents (adalimumab or infliximab) should be considered, as these agents have a strong track record in both RA and inflammatory eye diseases. If there is not a clear response, we have a low threshold to escalate to rituximab.

Rituximab may be particularly effective for PUK. A retrospective study of 34 PUK patients requiring biologic treatment described first-line success in 7/7 cases with rituximab, 10/16 with adalimumab, and 3/8 with infliximab [86]. A non-randomized study found that rituximab was more effective than cyclophosphamide for GPA-associated PUK [87]. A non-comparative study of RA patients found that 7/8 did not recur with rituximab maintenance dosing [88], and another found success in 6/6 eyes with refractory Mooren's ulcer [89]. Rituximab is first-line therapy for systemic GPA [90, 91]. Similarly, rituximab but not anti-TNF agents, work for systemic lupus erythematosus. Therefore, we typically recommend rituximab as first-line treatments in GPA-associated, SNV-associated, SLE-associated, and severe PUK. Historically, cyclophosphamide has been the drug of choice for severe cases of PUK, and it deserves consideration. Cyclophosphamide carries a risk of bladder toxicity, sterility, and cancer.

Newer US FDA-approved agents for RA or SLE show scattered anecdotal success, but there is less evidence for their efficacy in PUK. These include antimetabolites (leflunomide), anti-TNF agents (golimumab, certolizumab),

anti-Il-6 agents (tocilizumab, sarilumab), anti-Il-1 agents (anakinra), anti-B cell agents (belimumab), and Janus kinase inhibitors (tofacitinib, upadacitinib, baricitinib). Other IMT agents such as azathioprine and cyclosporine have historically demonstrated efficacy. Of note, oral NSAIDs, hydroxychloroquine, sulfasalazine, and etanercept are not generally recommended for PUK.

Surgery for Perforation

Surgery is indicated for perforation [92]. A general approach involves corneal tissue adhesive and bandage contact lens for small perforations (less than 2–3 mm) and corneal transplantation with a full-thickness patch graft for larger perforations. Large-diameter corneal grafts are the standard method when diffuse central and peripheral support is required. Perioperative immunosuppression and/or conjunctival resection, as discussed above, are adjunctive measure that may improve outcomes.

All of these methods are limited by a high risk of rejection and a risk of glaucoma due to destruction of the corneoscleral angle [93]. One retrospective review of RA-associated corneal ulceration from 1999 to 2006 found a 5-year graft survival rate of 48% [84]. In a study of 704 penetrating keratoplasties, PUK was reported to be single biggest risk factor for graft rejection [94]. Furthermore, surgery is limited by a worldwide scarcity of corneal tissue and inconsistent visual outcomes due to astigmatism.

As such, investigators have explored alternate methods for tectonic support. As early as the 1970s, peripheral anterior lamellar keratoplasty has been a popular technique due to a theoretically lower risk of rejection [4, 95–97]. This technique is technically challenging. Recently, endothelial keratoplasty has been described as a viable technique to achieve tectonic support [98, 99]. For situations requiring central and peripheral support, lamellar keratoplasty using a peripheral "tuck" into a mid-thickness scleral pocket has been described as a way of avoiding the corneoscleral angle [100]. Many regions have limited access to donor corneal tissue. Therefore, some surgeons advocate for alternate graft materials, including multilayered amnion, autologous tenons, and acelluar porcine stroma [101–105].

Conclusion

Peripheral ulcerative keratitis is a sight-threatening condition that requires aggressive therapy. Initially, a meticulous history, exam, and workup are required. The clinician should determine whether an infection, systemic autoimmunity, anatomic abnormalities, or other inflammatory conditions are the etiology of the inflammation. For noninfectious PUK due to presumptive autoimmunity, aggressive anti-inflammatory therapy with corticosteroids is recommended for short-term management and immunomodulatory therapy should be considered for long-term management to prevent recurrences, induce remission, and prolong the patient's life.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent No human or animal studies were associated with preparation of this manuscript.

References

1. Gupta Y, Kishore A, Kumari P, Balakrishnan N, Lomi N, Gupta N, Vanathi M, Tandon R. Peripheral ulcerative keratitis. Surv Ophthalmol. 2021;66:977–98.
2. Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin North Am. 2007;33:835–54 (vii).
3. Dana MR, Qian Y, Hamrah P. Twenty-five-year panorama of corneal immunology: emerging concepts in the immunopathogenesis of microbial keratitis, peripheral ulcerative keratitis, and corneal transplant rejection. Cornea. 2000;19:625–43.
4. Watson PG. Anterior segment fluorescein angiography in the surgery of immunologically induced corneal and scleral destructive disorders. Ophthalmology. 1987;94:1452–64.
5. Watson PG. Vascular changes in peripheral corneal destructive disease. Eye (Lond). 1990;4(Pt 1):65–73.
6. Kervick GN, Pflugfelder SC, Haimovici R, Brown H, Tozman E, Yee R. Paracentral rheumatoid corneal ulceration. Clinical features and cyclosporine therapy. Ophthalmology. 1992;99:80–8.
7. Tauber J. Sainz de la Maza M, Hoang-Xuan T, Foster CS: An analysis of therapeutic decision making regarding immunosuppressive chemotherapy for peripheral ulcerative keratitis. Cornea. 1990;9:66–73.
8. Sainz de la Maza M, Foster CS, Jabbur NS, Baltatzis S. Ocular characteristics and disease associations in scleritis-associated peripheral keratopathy. Arch Ophthalmol. 2002;120:15–9.
9. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv Ophthalmol. 1999;43:379–96.
10. Knox Cartwright NE, Tole DM, Georgoudis P, Cook SD. Peripheral ulcerative keratitis and corneal melt: a 10-year single center review with historical comparison. Cornea. 2014;33:27–31.
11. Malik R, Culinane AB, Tole DM, Cook SD. Rheumatoid keratolysis: a series of 40 eyes. Eur J Ophthalmol. 2006;16:791–7.
12. Timlin HM, Hall HN, Foot B, Koay P. Corneal perforation from peripheral ulcerative keratopathy in patients with rheumatoid arthritis: epidemiological findings of the British Ophthalmological Surveillance Unit. Br J Ophthalmol. 2018;102:1298–302.
13. McKibbin M, Isaacs JD, Morrell AJ. Incidence of corneal melting in association with systemic disease in the Yorkshire Region, 1995–7. Br J Ophthalmol. 1999;83:941–3.
14. Squirrell DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: a case series. Rheumatology (Oxford). 1999;38:1245–8.
15. Fasina O, Ogundipe A, Ezichi E. Mooren'S ulcer in ibadan, southwest Nigeria. J West Afr Coll Surg. 2013;3:102–19.
16. Sharma N, Sinha G, Shekhar H, Titiyal JS, Agarwal T, Chawla B, Tandon R, Vajpayee RB. Demographic profile, clinical features and outcome of peripheral ulcerative keratitis: a prospective study. Br J Ophthalmol. 2015;99:1503–8.

17. Srinivasan M, Zegans ME, Zelefsky JR, Kundu A, Lietman T, Whitcher JP, Cunningham ET Jr. Clinical characteristics of Mooren's ulcer in South India. Br J Ophthalmol. 2007;91:570–5.
18. Asbell P, Stenson S. Ulcerative keratitis. Survey of 30 years' laboratory experience. Arch Ophthalmol. 1982;100:77–80.
19. Baum J, Fedukowicz HB, Jordan A. A survey of Moraxella corneal ulcers in a derelict population. Am J Ophthalmol. 1980;90:476–80.
20. O'Donoghue E, Lightman S, Tuft S, Watson P. Surgically induced necrotising sclerokeratitis (SINS)—precipitating factors and response to treatment. Br J Ophthalmol. 1992;76:17–21.
21. Diaz-Valle D. Benitez del Castillo JM, Castillo A, Sayagues O, Banares A, Garcia-Sanchez J: Immunologic and clinical evaluation of postsurgical necrotizing sclerocorneal ulceration. Cornea. 1998;17:371–5.
22. Akpek EK, Demetriades AM, Gottsch JD. Peripheral ulcerative keratitis after clear corneal cataract extraction(1). J Cataract Refract Surg. 2000;26:1424–7.
23. Kiire CA, Srinivasan S, Inglis A. Peripheral ulcerative keratitis after cataract surgery in a patient with ocular cicatricial pemphigoid. Cornea. 2011;30:1176–8.
24. Burkholder BM, Kuo IC. Peripheral ulcerative keratitis following laser in situ keratomileusis. Case Rep Ophthalmol. 2016;7:9–15.
25. Pokharel A, Subedi S, Bajracharya M. Peripheral ulcerative keratitis triggered by bacterial conjunctivitis. Nepal J Ophthalmol. 2010;2:71–3.
26. Zaher SS, Sandinha T, Roberts F, Ramaesh K. Herpes simplex keratitis misdiagnosed as rheumatoid arthritis-related peripheral ulcerative keratitis. Cornea. 2005;24:1015–7.
27. Praidou A, Androudi S, Kanonidou E, Konidaris V, Alexandridis A, Brazitikos P. Bilateral herpes simplex keratitis presenting as peripheral ulcerative keratitis. Cornea. 2012;31:570–1.
28. Chranioti A, Malamas A, Metallidis S, Mataftsi A, Chalvatzis N, Ziakas N. Bilateral Herpes Simplex virus-related peripheral ulcerative keratitis leading to corneal perforation in a patient with primary Herpes Simplex virus infection. J Ophthalmic Vis Res. 2019;14:93–6.
29. Neves RA, Rodriguez A, Power WJ, Muccioli C, Lane L, Belfort R Jr, Foster CS. Herpes zoster peripheral ulcerative keratitis in patients with the acquired immunodeficiency syndrome. Cornea. 1996;15:446–50.
30. Gupta N, Sachdev R, Sinha R, Titiyal JS, Tandon R. Herpes zoster ophthalmicus: disease spectrum in young adults. Middle East Afr J Ophthalmol. 2011;18:178–82.
31. Vignesh AP, Srinivasan R, Vijitha S. Ocular syphilis masquerading as bilateral peripheral ulcerative keratitis. Taiwan J Ophthalmol. 2016;6:204–5.
32. Gharai S, Venkatesh P, Tandon R, Garg S. Peripheral ulcerative keratitis and central retinal vein occlusion as the initial manifestation of HIV infection. Ocul Immunol Inflamm. 2007;15:407–9.
33. Soni ND, Ingole AB, Murade SM. An unusual case of peripheral ulcerative keratitis as a presenting feature in an otherwise healthy patient with undiagnosed human immunodeficiency virus infection and low CD4 counts. Indian J Ophthalmol. 2013;61:138–9.
34. Tavassoli S, Gunn D, Tole D, Darcy K. Peripheral ulcerative keratitis with corneal melt as the primary presentation in a case of human immunodeficiency virus. BMJ Case Rep. 2019;12.
35. Radhakrishnan N, Smit D, Venkatesh Prajna N. S RR: Corneal involvement in HIV-infected individuals. Ocul Immunol Inflamm. 2021;29:1177–82.
36. Jiamjunkupt T, Sasiprapha N, Changpradub D, Choontanom R, Sansanayudh W. Rare manifestation of ocular immune reconstitution inflammatory syndrome from mycobacterium scrofulaceum infection in a patient with AIDS. Int J Mycobacteriol. 2021;10:202–5.
37. Pluznik D, Butrus SI. Hepatitis C-associated peripheral corneal ulceration: rapid response to intravenous steroids. Cornea. 2001;20:888–9.
38. Wenkel H, Krist D, Korn K. Detection of hepatitis C virus RNA in tear film of a patient with recurrent peripheral corneal ulcers. Klin Monbl Augenheilkd. 2001;218:459–62.
39. Kedhar SR, Belair ML, Jun AS, Sulkowski M, Thorne JE. Scleritis and peripheral ulcerative keratitis with hepatitis C virus-related cryoglobulinemia. Arch Ophthalmol. 2007;125:852–3.
40. Eshraghi H, Mahtabfar A, Dastjerdi MH. A case of peripheral ulcerative keratitis associated with autoimmune hepatitis. Case Rep Med. 2017;2017:3939413.
41. Wei DW, Pagnoux C, Chan CC. Peripheral ulcerative keratitis secondary to chronic hepatitis B infection. Cornea. 2017;36:515–7.
42. Aiello F, Congliaro P, Malaspina C, Gallo Afflitto G, Nucci C. Peripheral ulcerative keratitis as the primary clinical manifestation of type 2 cryoglobulinemia. Can J Ophthalmol. 2021;56:e148–50.
43. Saygin D, Syed AU, Lowder CY, Srivastava S, Maya JJ, Hajj-Ali RA. Characteristics of inflammatory eye disease associated with hidradenitis suppurativa. Eur J Rheumatol. 2018;5:165–8.
44. Chawla B, Agarwal P, Tandon R, Titiyal JS. Peripheral ulcerative keratitis with bilateral optic nerve involvement as an initial presentation of acute lymphocytic leukemia in an adult. Int Ophthalmol. 2009;29:53–5.
45. Morjaria R, Barge T, Mordant D, Elston J. Peripheral ulcerative keratitis as a complication of acute myeloid leukaemia. BMJ Case Rep. 2014; 2014.
46. Lim LT, Ramamurthi S, Collins CE, Mantry S. Peripheral ulcerative keratitis associated with multiple myeloma. Ann Acad Med Singap. 2011;40:550–1.
47. Prasher P, Di Pascuale M, Cavanagh HD. Bilateral chronic peripheral ulcerative keratitis secondary to cat-scratch disease. Eye Contact Lens. 2008;34:191–3.
48. Lange AP, Moloney G, Sheldon CA, Sasaki S, Holland SP. Bilateral corneal ulceration caused by vitamin a deficiency in eosinophilic gastroenteropathy. Case Rep Ophthalmol. 2011;2:302–6.
49. Ramanathan S, Fraser C, Curnow SR, Ghaly M, Leventer RJ, Lechner-Scott J, Henderson A, Reddel S, Dale RC, Brilot F. Uveitis and optic perineuritis in the context of myelin oligodendrocyte glycoprotein antibody seropositivity. Eur J Neurol. 2019;26:1137-e1175.
50. Vosoughi AR, Ling J, Tam KT, Blackwood J, Micieli JA. Ophthalmic manifestations of myelin oligodendrocyte glycoprotein-IgG-associated disorder other than optic neuritis: a systematic review. Br J Ophthalmol. 2021;105:1591–8.
51. Siracuse-Lee D, Saffra N. Peripheral ulcerative keratitis in sarcoidosis: a case report. Cornea. 2006;25:618–20.
52. Harthan JS, Reeder RE. Peripheral ulcerative keratitis in association with sarcoidosis. Cont Lens Anterior Eye. 2013;36:313–7.
53. Cordoba A, Mejia LF, Gonzalez N, Gil JC. Unusual corneal sarcoidosis manifestations. Ocul Immunol Inflamm. 2022; 1–5.
54. Mehta K, Gujjar AP, Babu K. Peripheral ulcerative keratitis in a young lady with systemic lupus erythematosus post rituximab infusion—a case report. Ocul Immunol Inflamm. 2022; 1–3.
55. Cohen F, Gabison EE, Stephan S, Belkhir R, Nocturne G, Best AL, Haigh O, Barreau E, Labetoulle M, Seror R, et al. Peripheral ulcerative keratitis in rheumatoid arthritis patients taking tocilizumab: paradoxical manifestation or insufficient efficacy? Rheumatology (Oxford). 2021;60:5413–8.
56. Far PM, Quinn MP, Johnson D. Bilateral peripheral ulcerative keratitis associated with Dupilumab. Ophthalmology. 2022;129:561.

57. Penbe A. Peripheral ulcerative keratitis secondary to the inactive COVID-19 vaccine-CoronaVac. Ocul Immunol Inflamm. 2022; 1–5.
58. Parker JS, Feagin W, Wang C, Heersink M, Parker JS. Corneal ulceration associated with Nivolumab use. Am J Ophthalmol Case Rep. 2019;14:26–7.
59. Antoun J, Titah C, Cochereau I. Ocular and orbital side-effects of checkpoint inhibitors: a review article. Curr Opin Oncol. 2016;28:288–94.
60. Kusumesh R, Ambasta A, Arya LK, Mohan N, Sinha BP, Ravidas V. Keratitis occurring in patients treated with miltefosine for post-kala-azar dermal leishmaniasis. Br J Ophthalmol. 2021;105:1497–503.
61. Austin A, Lietman T, Rose-Nussbaumer J. Update on the management of infectious keratitis. Ophthalmology. 2017;124:1678–89.
62. Brown SI, Mondino BJ. Therapy of Mooren's ulcer. Am J Ophthalmol. 1984;98:1–6.
63. Sangwan VS, Zafirakis P, Foster CS. Mooren's ulcer: current concepts in management. Indian J Ophthalmol. 1997;45:7–17.
64. Ashar JN, Mathur A, Sangwan VS. Immunosuppression for Mooren's ulcer: evaluation of the stepladder approach–topical, oral and intravenous immunosuppressive agents. Br J Ophthalmol. 2013;97:1391–4.
65. Pleyer U, Bertelmann E, Rieck P, Hartmann C. Outcome of penetrating keratoplasty in rheumatoid arthritis. Ophthalmologica. 2002;216:249–55.
66. Ngan ND, Chau HT. Amniotic membrane transplantation for Mooren's ulcer. Clin Exp Ophthalmol. 2011;39:386–92.
67. Chen KH, Hsu WM, Liang CK. Relapsing Mooren's ulcer after amniotic membrane transplantation combined with conjunctival autografting. Ophthalmology. 2004;111:792–5.
68. Schallenberg M, Westekemper H, Steuhl KP, Meller D. Amniotic membrane transplantation ineffective as additional therapy in patients with aggressive Mooren's ulcer. BMC Ophthalmol. 2013;13:81.
69. Eiferman RA, Carothers DJ, Yankeelov JA Jr. Peripheral rheumatoid ulceration and evidence for conjunctival collagenase production. Am J Ophthalmol. 1979;87:703–9.
70. Genvert G, Sakauye CM, Arentsen JJ. Treatment of marginal corneal ulcers with cryotherapy and conjunctival recession or resection. Cornea. 1984;3:256–61.
71. Feder RS, Krachmer JH. Conjunctival resection for the treatment of the rheumatoid corneal ulceration. Ophthalmology. 1984;91:111–5.
72. Lal I, Shivanagari SB, Ali MH, Vazirani J. Efficacy of conjunctival resection with cyanoacrylate glue application in preventing recurrences of Mooren's ulcer. Br J Ophthalmol. 2016;100:971–5.
73. Shtein RM, Shen JF, Kuo AN, Hammersmith KM, Li JY, Weikert MP. Autologous serum-based eye drops for treatment of ocular surface disease: a report by the American Academy of Ophthalmology. Ophthalmology. 2020;127:128–33.
74. Mavrakanas NA, Kiel R, Dosso AA. Autologous serum application in the treatment of Mooren's ulcer. Klin Monbl Augenheilkd. 2007;224:300–2.
75. Katz EA, Sunshine S, Mun C, Sarwar M, Surenkhuu B, Pradeep A, Jain S. Combinatorial therapy with immunosuppressive, immunomodulatory and tear substitute eyedrops ("Triple Play") in Recalcitrant Immunological Ocular Surface Diseases. Ocul Surf. 2022;23:1–11.
76. Chen J, Lan J, Liu D, Backman LJ, Zhang W, Zhou Q, Danielson P. Ascorbic acid promotes the stemness of corneal epithelial stem/progenitor cells and accelerates epithelial wound healing in the cornea. Stem Cells Transl Med. 2017;6:1356–65.
77. Riley GP, Harrall RL, Watson PG, Cawston TE, Hazleman BL. Collagenase (MMP-1) and TIMP-1 in destructive corneal disease associated with rheumatoid arthritis. Eye (Lond). 1995;9(Pt 6):703–18.
78. Smith VA, Hoh HB, Easty DL. Role of ocular matrix metalloproteinases in peripheral ulcerative keratitis. Br J Ophthalmol. 1999;83:1376–83.
79. Bordin P. Low-Concentration (0.66%) Povidone Iodine treatment of a corneal ulcer in a rheumatoid arthritis patient. Am J Case Rep. 2021;22:e928748.
80. Saripalli L, Harrington TM, Notz RG, Torretti D. Corneal melt in rheumatic disorders: effect of disease-modifying antirheumatic drugs on morbidity. J Clin Rheumatol. 2005;11:134–9.
81. Petrushkin HJ, Stanford M, Fortune F, Jawad A. Improving morbidity and mortality in peripheral ulcerative keratitis associated with rheumatoid arthritis. Clin Exp Rheumatol. 2016;34:S18-19.
82. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis. Effects of systemic immunosuppression. Ophthalmology. 1984;91:1253–63.
83. Ogra S, Sims JL, McGhee CNJ, Niederer RL. Ocular complications and mortality in peripheral ulcerative keratitis and necrotising scleritis: the role of systemic immunosuppression. Clin Exp Ophthalmol. 2020;48:434–41.
84. Stylianides A, Jones MN, Stewart RM, Murphy CC, Goodson NJ, Kaye SB. Rheumatoid arthritis-associated corneal ulceration: mortality and graft survival. Ophthalmology. 2013;120:682–6.
85. Bernauer W, Ficker LA, Watson PG, Dart JK. The management of corneal perforations associated with rheumatoid arthritis. An analysis of 32 eyes. Ophthalmology. 1995;102:1325–37.
86. Dominguez-Casas LC, Sanchez-Bilbao L, Calvo-Rio V, Maiz O, Blanco A, Beltran E, Martinez-Costa L, Demetrio-Pablo R, Del Buergo MA, Rubio-Romero E, et al. Biologic therapy in severe and refractory peripheral ulcerative keratitis (PUK). Multicenter study of 34 patients. Semin Arthritis Rheum. 2020;50:608–15.
87. Ebrahimiadib N, Modjtahedi BS, Roohipoor R, Anesi SD, Foster CS. successful treatment strategies in granulomatosis with polyangiitis-associated peripheral ulcerative keratitis. Cornea. 2016;35:1459–65.
88. Bonnet I, Rousseau A, Duraffour P, Pouchot J, Nguyen CD, Gabison E, Seror R, Marotte H, Mariette X, Nocturne G. Efficacy and safety of rituximab in peripheral ulcerative keratitis associated with rheumatoid arthritis. RMD Open. 2021; 7.
89. Guindolet D, Reynaud C, Clavel G, Belange G, Benmahmed M, Doan S, Hayem G, Cochereau I, Gabison EE. Management of severe and refractory Mooren's ulcers with rituximab. Br J Ophthalmol. 2017;101:418–22.
90. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–32.
91. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, Maurier F, Decaux O, Ninet J, Gobert P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371:1771–80.
92. Lohchab M, Prakash G, Arora T, Maharana P, Jhanji V, Sharma N, Vajpayee RB. Surgical management of peripheral corneal thinning disorders. Surv Ophthalmol. 2019;64:67–78.
93. Skeens HM, Holland EJ. Large-diameter penetrating keratoplasty: indications and outcomes. Cornea. 2010;29:296–301.
94. Reinprayoon U, Srihatrai P, Satitpitakul V, Puangsricharern V, Wungcharoen T, Kasetsuwan N. Survival outcome and prognostic factors of corneal transplantation: a 15-year retrospective cohort study at King Chulalongkorn Memorial Hospital. Clin Ophthalmol. 2021;15:4189–99.
95. Raizman MB. Sainz de la Maza M, Foster CS: Tectonic keratoplasty for peripheral ulcerative keratitis. Cornea. 1991;10:312–6.

96. Bessant DA, Dart JK. Lamellar keratoplasty in the management of inflammatory corneal ulceration and perforation. Eye (Lond). 1994;8(Pt 1):22–8.
97. Yokoyama K, Nakamura R, Otsuka T, Kimoto K, Kubota T. Deep anterior lamellar keratoplasty and peripheral lamellar keratoplasty for a case of severe peripheral ulcerative keratitis. Case Rep Ophthalmol. 2022;13:9–16.
98. Trese M, Schimmel O, Gupta C. Extensive autoimmune keratolysis with subsequent corneal perforation managed with tectonic endothelial keratoplasty. Am J Ophthalmol Case Rep. 2021;21:101031.
99. Roberts HW, Gunasekera CD, Law EM, Seifelnasr M, Giannaccare G, Busin M, Myerscough J. Sutureless tectonic mini-Descemet's stripping automated endothelial keratoplasty ("mini-DSAEK") for the management of corneal perforations. Eur J Ophthalmol. 2022;32:2133–40.
100. Kaushal S, Jhanji V, Sharma N, Tandon R, Titiyal JS, Vajpayee RB. "Tuck in" lamellar keratoplasty (TILK) for corneal ectasias involving corneal periphery. Br J Ophthalmol. 2008;92:286–90.
101. Rodriguez-Ares MT, Tourino R, Lopez-Valladares MJ, Gude F. Multilayer amniotic membrane transplantation in the treatment of corneal perforations. Cornea. 2004;23:577–83.
102. Chen Y, Zhang L, Liu Z, Liu Q, Gao M. Efficacy of lamellar keratoplasty with acellular porcine corneal stroma in treatment for infectious central and peripheral corneal ulcers. Ther Clin Risk Manag. 2021;17:623–34.
103. Solomon A, Meller D, Prabhasawat P, John T, Espana EM, Steuhl KP, Tseng SC. Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. Ophthalmology. 2002;109:694–703.
104. Yildiz EH, Nurozler AB, Ozkan Aksoy N, Altiparmak UE, Onat M, Karaguzel H. Amniotic membrane transplantation: indications and results. Eur J Ophthalmol. 2008;18:685–90.
105. Anitha V, Ghorpade A, Ravindran M. A modified Tenons sling annular graft for advanced peripheral ulcerative keratitis with an hourglass cornea. Indian J Ophthalmol. 2022;70:655–7.

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