Etiology, clinical profile, and treatment outcome of peripheral ulcerative keratitis

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Abstract:

PURPOSE: To assess the etiology, clinical features, and treatment outcome in patients with peripheral ulcerative keratitis (PUK).

METHODS: In this retrospective, observational study, forty-eight eyes of 32 consecutive patients with PUK were included. Demographic profile, etiology, clinical features, treatment history, and outcome were documented.

RESULTS: Of the 32 patients, 19 (59%) were male and the mean age at presentation was 54.72 ± 14.92 years. Sixty-eight percent of patients were from rural backgrounds. Half of the patients had bilateral involvement. Fifty percent of patients presented after 4 weeks of the onset of symptoms. Of 48 eyes at presentation, 11 had mild disease, 9 had moderate disease and 28 had severe disease. At presentation, best-corrected visual acuity <3/60 was found in 26 (54%) eyes. Mooren’s ulcer (40% eyes) was the most common etiology for PUK. Rheumatoid factor was positive in 8 of 32 patients (25%). Of 32 patients, 19 (59%) required systemic immunosuppression for the control of disease activity. Surgical intervention to maintain anatomical integrity was required in 27 (56%) eyes. No significant change in vision was seen in pretreatment and posttreatment groups. Four eyes failed to heal after 4 weeks of initiation of treatment due to noncompliance of the patient. None of our patients died during follow-up.

CONCLUSION: PUK is an indicator of occult systemic autoimmune disease. Mooren’s ulcer is the most common cause of PUK. Prompt and adequate immunosuppression is not only eye saving but also lifesaving for patients with PUK of autoimmune origin.

Keywords: Collagen vascular disease, immunosuppression, Mooren’s ulcer, peripheral ulcerative keratitis, rheumatoid arthritis

INTRODUCTION

Peripheral ulcerative keratitis (PUK) is a potentially devastating disorder.[1,2] No age is immune for PUK.[3] Perception of the peripheral cornea as a peerless discernable anatomical region has emerged recently in ophthalmic practice due to the immunologic differences from the central cornea.[4] Immunologic machinery required to generate the immune response is present in the peripheral cornea relating to its proximity to the conjunctiva.[5] Collagen vascular diseases may be associated with PUK with or without scleritis. PUK is associated with collagen vascular diseases in almost 50% of cases with rheumatoid arthritis (RA) accounting for 34% of cases.[4] The development of PUK in the setting of connective tissue disorder is a reflection of potentially lethal systemic vasculitis.[6] The treatment protocol of PUK is based on the etiology.[1] Surgical intervention is primarily indicated in severe cases threatening anatomical integrity. Associated systemic conditions if left unaddressed may carry...
grave prognosis for the eye and may turn out to be life-threatening.[7]

This retrospective study was accomplished to evaluate the diverse etiology, clinical features, and treatment outcome with different modalities in patients with PUK attending a tertiary eye care hospital.

**Methods**

This retrospective, observational study included 48 eyes of 32 consecutive patients with PUK who presented to a tertiary care eye hospital of Western India between July 2018 and July 2020. The study protocol was approved by the Institutional Review Board which followed the tenets of the Declaration of Helsinki. All patients of PUK with follow-up of minimum of 6 months were included in the study. Patients with other ocular comorbidities were excluded from the study.

The patient was diagnosed to have PUK if there was the presence of crescent-shaped destructive inflammation within 2 mm of limbus associated with epithelial defect, stromal lysis, and surrounding conjunctival inflammation. Demographic details of patients were noted.

Documentation of detailed history regarding the duration of complaints, laterality, associated systemic illness, and previous treatment was done. Details of ocular examination including visual acuity, slit-lamp examination including the number of quadrants and depth of corneal involvement, presence of an epithelial defect, degree of corneal thinning, associated anterior chamber inflammation, and dilated fundus examination using 90D lens on slit lamp was noted. Fluorescein staining was done at presentation and at all follow-up visits.

PUK severity was graded into mild, moderate, and severe depending on quadrant and depth of corneal involvement. One quadrant of corneal involvement with ulceration of anterior stroma was considered mild disease. Two quadrants of corneal involvement with anterior stromal ulceration or any quadrant of corneal involvement with mid stromal ulceration was considered as moderate disease. Any quadrant of corneal involvement with impending perforation or presence of perforation was considered severe disease. Findings of detailed systemic examination done by rheumatologist and physician were noted. Ocular investigations included clinical photography for documentation and B-scan to rule out any posterior segment pathology.

Systemic investigations included complete hemogram, erythrocyte sedimentation rate, renal function test, liver function test, HIV, Hepatitis B surface antigen, rheumatoid factor, anti-neutrophilic antibody, anti-neutrophilic cytoplasmic antibody (ANCA), and anti-Cyclic Citrullinated Peptides (anti-CCP). Radiologic investigations like X-ray chest PA view were done to search for cavitation and calcific lesion in the lung or mediastinal region and X-ray sacroiliac joint was performed to rule out changes of sacro-illitis. Furthermore, special radiological investigation like computed tomography chest was done in cases with high index of suspicion.

According to the severity of disease and etiology, these cases were managed medically or surgically. Surgical treatment was required in cases with impending perforation, presence of perforation, or failure of medical therapy. Patients with staphylococcal marginal keratitis received oral doxycycline 100 mg twice daily for 21 days along with topical steroids and antibiotics. In patients with herpes simplex PUK, oral acyclovir 400 mg five times a day along with topical steroids was given.

Topical lubricants were given to aid healing of epithelial defects and cycloplegics were given as adjunctive to relieve ciliary spasm. Topical steroids were given in all cases where microbial infection was ruled out and there was no perforation. Patients with autoimmune disease or with Mooren’s ulcer were started on topical and systemic immunosuppressive therapy based on the severity of the disease. In mild cases, only topical steroids were given. In moderate cases, topical steroids along with oral steroids were given. Severe cases required topical steroids along with systemic immunosuppressive therapy either in the form of intravenous methylprednisolone pulse therapy or cyclophosphamide pulse therapy or oral methotrexate or oral azathioprine or mycophenolate mofetil.

Patients on systemic immunosuppressive therapy underwent detailed systemic evaluation by a physician or rheumatologist before the initiation of therapy and counseled for the importance and side effects of long-term immunosuppressive therapy. While on treatment, liver function tests, renal function tests, and blood counts were monitored. Along with oral steroids, patients received oral Ranitidine 150 mg twice a day as prophylaxis for peptic ulcers. Oral calcium supplements 500 mg twice daily were given as prophylaxis for osteoporosis.

At each follow-up visit, visual acuity and slit-lamp examination were done to look for the activity of the disease or signs of resolution or recurrence. Healing was defined as nonprogression of ulcer and filling of the ulcer crater with no fluorescein staining. Topical steroids were tapered over two to 3 weeks and then stopped if there were signs of resolution.

The surgical intervention included tissue adhesive (cyanoacrylate) glue with bandage contact lens (TABCL), amniotic membrane grafting (AMG) with fibrin glue/sutures, conjunctival resection, tenon’s patch graft, and penetrating keratoplasty (PK).

Conjunctival resection was done in at least two clock hours on each side of the ulcer and 4 mm posterior to the limbus along with cautereization of the bleeder. In patients with small (<3 mm) perforation or impending perforation TABCL or AMG or tenon’s patch graft was done. For larger perforations (≥3 mm), patch graft or PK was done. Conjunctival peritomy adjacent to the ulcer was done to look for the extent of perforation and scleral involvement. The anterior chamber was formed and prolapsed iris was either repositioned or excised depending upon the duration. Margins of the ulcer were...
Kochhar, et al.: Etiology, clinical profile, and treatment outcome of peripheral ulcerative keratitis

Results

The study analyzed 48 eyes of 32 patients who presented with PUK. Out of 32 patients, 19 (59%) were male and 13 (41%) were female. The mean age at presentation was 54.72 ± 14.92 years. Twenty-two (68%) out of 32 patients were from the rural area.

Only 4 (12%) patients presented within 2 weeks of the onset of symptoms. Twelve (38%) patients presented between 2 and 4 weeks and 16 (50%) patients presented after 4 weeks of the onset of symptoms. Sixteen (50%) patients had bilateral eye involvement with PUK. Eleven (23%) eyes had mild disease, 9 (19%) eyes had moderate disease and 28 (58%) eyes had severe form of the disease. Out of 48 eyes, only 7 (15%) eyes had best-corrected visual acuity (BCVA) ≥6/18 at presentation, while 15 (31%) eyes had BCVA <6/18 to ≥6/60 and 26 (54%) had BCVA <3/60 at presentation [Table 1]. Perforation at presentation was found in 12 (25%) of 48 eyes. At presentation, perforation was present in 44% of eyes with severe disease.

The most common etiology of PUK in our study was Mooren’s ulcer seen in 19 (40%) eyes followed by collagen vascular disease (27%) i.e., RA in 9 (19%) eyes and Granulomatosis with polyangiitis (GPA) in 4 (8%) eyes [Table 2]. Positive rheumatoid factor was the most common abnormal serology found in 8 (25%) patients.

Corneal scraping was negative in all cases. All 48 eyes received topical steroids according to the severity of disease. Due to uncontrolled disease, for 33 (68%) eyes oral steroid was added and for 19 (39%) eyes intravenous methylprednisolone (IVMPS) was added to the treatment regimen. Methotrexate was added to the treatment regimen for treatment of 5 (10%) eyes, mycophenolate mofetil for 1 (2%) eye, azathioprine for 1 (2%) eye, and intravenous cyclophosphamide for 14 (29%) eyes. Oral acyclovir was added to the regimen for 3 (6%) eyes and oral doxycycline for 4 (8%) eyes.

Surgical intervention was required in 27 (56%) eyes to maintain anatomical integrity. Cyanoacrylate glue with Bandage Contact Lens (BCL) was done in 8 (17%) eyes, conjunctival resection with AMG was done in 13 (27%) eyes, tenon’s patch graft was done in 1 (2%) eyes and PK was done in 5 (10%) eyes [Table 3]. One (2%) eye had recurrence, 9 (19%) eyes were lost to follow-up and in 4 (8%) eyes ulcer failed to heal after 6 weeks of treatment due to noncompliance.

Posttreatment BCVA was ≥6/18 in 7 (15%) patients, <6/18 to ≥6/60 in 17 (35%) patients, <6/60 to ≥3/60 in 2 (4%) patients, and <3/60 in 22 (46%) patients. There was no statistical difference between pre and posttreatment BCVA between mild, moderate, and severe disease [Table 4].

Discussion

This retrospective observational study included 48 eyes of 32 patients with PUK. The demographic data of our study

Table 1: Best-corrected visual acuity of patients presenting with peripheral ulcerative keratitis

| BCVA       | Mild disease | Moderate disease | Severe disease |
|------------|--------------|-----------------|---------------|
| ≥6/18      | 2            | 2               | 3             |
| <6/18      | 7            | 0               | 8             |
| <6/60‑3/60 | 0            | 0               | 0             |
| <3/60      | 2            | 7               | 17            |

BCVA: Best-corrected visual acuity

Table 2: Etiology of patients presenting with peripheral ulcerative keratitis

| Etiology                                    | Number of patients | Number of eyes |
|---------------------------------------------|--------------------|----------------|
| Mooren’s ulcer                              | 11                 | 19             |
| Idiopathic                                  | 7                  | 9              |
| Rheumatoid arthritis                        | 6                  | 9              |
| Granulomatosis with polyangiitis            | 2                  | 4              |
| Mebormand gland dysfunction                 | 3                  | 4              |
| Herpes simplex viral keratitis              | 3                  | 3              |

Table 3: Patients with peripheral ulcerative keratitis requiring surgical intervention

|                     | TABCL | AMG  | Tenon’s patch graft | PK  |
|---------------------|-------|------|---------------------|-----|
| Mild disease        | 0     | 0    | 0                   | 0   |
| Moderate disease    | 0     | 3    | 0                   | 0   |
| Severe disease      | 8     | 10   | 1                   | 5   |

TABCL: Tissue adhesive with bandage contact lens, AMG: Amniotic membrane grafting, PK: Penetrating keratoplasty

Table 4: Comparison of visual outcome between mild, moderate, and severe cases of peripheral ulcerative keratitis

|                | Mean BCVA pretreatment | Mean BCVA posttreatment | P   |
|----------------|------------------------|-------------------------|-----|
| Mild           | 0.8±0.29               | 0.7±0.32                | 0.09|
| Moderate       | 0.9±0.25               | 0.9±0.16                | 0.17|
| Severe         | 0.9±0.23               | 0.8±0.24                | 0.14|

BCVA: Best-corrected visual acuity

Statistical analysis

Statistical analysis was performed using SPSS software (version 20.0, SPSS Inc. Armonk, NY, USA: IBM corp.). Quantitative data were analyzed using Student’s t-test. P < 0.05 was considered statistically significant.
resembled the study carried out by Sharma et al.\[1\] In our study, most of the patients belonged to the elderly age group with a mean age of 54.72 ± 14.92 years. The age range of patients was between 23 and 82 years. PUK was more common in men (59%). Female preponderance is seen in PUK patients with collagen vascular diseases like Wegener’s granulomatosis and RA.\[8\] Mooren’s ulcer is more common in males\[8,10\] and our study also showed that males outnumbered females. Most of our patients were from rural backgrounds (68%).

Our study differed in terms of laterality, with the equal number of unilateral and bilateral cases. In contrast, most of the parallel studies showed a greater number of cases with unilateral involvement.\[1,11\]

Twenty-eight (88%) patients presented after 2 weeks of the onset of symptoms and had severe disease at presentation. Lack of awareness regarding the severity of disease, reduction in symptoms on treatment with topical steroids by local ophthalmologist or economical constraints can be attributed for late presentation.

PUK represents the final avenue common to many diseases. Disease spectrum presenting as PUK includes Mooren’s ulcer, staphylococcal marginal keratitis, HSV marginal keratitis, idiopathic ulcer, and collagen vascular diseases like RA and Wegener’s granulomatosis.\[11\] Mooren’s ulcer is a local autoimmune disease with no associated systemic features. The diagnosis is clinical, evident from the classical crescent-shaped peripheral corneal ulcer with undermined peripheral edge and overhanging central border progressing centrally in the absence of scleral involvement.\[2,5]\n
A study carried by Sharma et al.\[1\] found Mooren’s ulcer (31.5%) to be the most common etiology for PUK alike our study with 40% eyes with Mooren’s ulcer. Collagen vascular diseases are the greatest masqueraders and often PUK can be the presenting sign of underlying collagen vascular disease.\[2,7\] Collagen vascular (27% eyes) disease was the second most common cause of PUK in our study with RA accounting for 19% of cases. A study by Squirrell et al.\[9\] also suggested RA as the most common collagen vascular disease in patients with PUK.

GPA formerly known as Wegener’s granulomatosis occurs in two forms: Classical and limited form. Ocular manifestations are present in both forms.\[8,16\] GPA rarely manifests with the classical triad of vasculitis, necrosis, and granulomatous inflammation, so the diagnosis is based on the combination of clinical examination, serology (ANCA), and radiological signs.\[6,7\] Inflammatory response in RA and GPA is different, as RA is having indolent course while GPA is having the fulminant course. Corneal melt in RA usually occurs late with long-standing disease but in GPA corneal melt can occur early.\[2,7\] Regardless of the underlying condition, corneal melt is an alarming sign. In systemic autoimmune disease, it indicates the massive and exuberant inflammatory response of the body and is substantially associated with increased mortality and morbidity in these patients.\[8,12\]

Multiple and varied etiologies of PUK necessitate detailed systemic evaluation for appropriate treatment that includes both medical and surgical approaches. No fixed recipe is sufficient enough in establishing a diagnosis. From our study of 32 cases, there appears to have no short cuts for the difficult task of deciding diagnostic workup. The lethal consequence of missing the diagnosis in necrotizing vasculitis necessitates for performing a battery of investigations that have a high likelihood of detection of these serious cases.\[4]\n
In our study, out of 32 patients, 8 (25%) had positive RA factor, five (16%) had positive anti-CCP and ANCA was positive in 2 (6%) patients. ANCA may not be positive in all cases, especially with the limited form of GPA, where clinical signs stand as essential diagnostic tool.\[12,13\] Furthermore, both the patients with GPA in our study had radiographic features suggestive of lung involvement, which was supportive to the diagnosis.

As the name suggests, PUK is a condition of the peripheral cornea. The central cornea is spared in most cases hence the severity of PUK cannot be correlated with vision in these patients. Reduced vision could be attributed to irregular scarring after healing of PUK or in cases with perforation. Furthermore, different modalities of surgical treatment based on case scenarios for the treatment of perforation can be a confounding factor for visual recovery.

The eye acts as a barometer for occult potentially lethal systemic diseases. The treatment strategy is based on etiology. Aggressive management using local and systemic immunosuppressive agents is indicated in cases which are potentially fatal or highly destructive for the eyes.\[2,6\] Furthermore, patients with bilateral Mooren’s ulcer, the course of ulceration is inexorable without systemic immunosuppressive therapy.\[14\] Communication and urgent referral to rheumatologist comfortable with initiating cytotoxic agent is important.

Topical steroid, antibiotic and lubricating eye drops were started in all cases depending on the severity of PUK. Out of 32 patients, three (9%) received systemic doxycycline for treatment of Meibomian gland dysfunction, three (9%) received systemic acyclovir and systemic immunosuppression was initiated in 19 (59%) patients. Six (19%) patients of RA, two (6%) patients of GPA, eight (25%) patients of Mooren’s, and three (9%) patients of idiopathic PUK received systemic immunosuppressive therapy.

Currently, a combination of systemic corticosteroids and a cytotoxic agent are the preferred treatment strategy for the control of the systemic disease. Cyclophosphamide is the standard of care for patients having GPA and PUK.\[7,13\] Both the patients with GPA in our study had fungal lung infections. The diagnosis of fungal infection was made by examination of bronchial aspiration lavage fluid using Galactomannan Aspergillus Test. Cyclophosphamide therapy was deferred in view of fungal infection. Both these patients received systemic antifungal therapy followed by pulsed dose of IV MPS. Healing
occurred in one case but the other patient was not compliant with treatment and was then lost to follow up.

In total out of 32 patients, eight (25%) patients received pulsed doses of cyclophosphamide therapy. Hematuria was not an evident finding in patients receiving cyclophosphamide in our series. Most studies did not encounter any significant increase in the incidence of infection or other complications associated with immunosuppressive therapy. Recurrence of PUK was noted in one patient with the moderate disease which was successfully treated with pulse dose of cyclophosphamide.

Conjunctival resection is critical as it has both diagnostic and therapeutic roles. Demonstration of inflammatory mediators in the resected conjunctiva is censorious for the commencement of immunosuppressive therapy. Conjunctival resection transiently ameliorates the disease by the removal of immunocompetent cells capable of liberating proteolytic enzymes and chemotactic factors. Conjunctival resection alone may fail to heal Mooren’s ulcer and tissue adhesive or amniotic membrane (AM) may be required for tectonic support. In addition to anti-inflammatory and tectonic support, AM is immune-privileged by the expression of immune factors like HLA-G and Fas ligand. However, AM gets absorbed relatively faster in inflamed eyes. Cyanoacrylate glue is another alternative to AM grafting which provides better tectonic support to thin corneas. In our study, three (6%) eyes with moderate PUK and ten (21%) eyes with severe PUK underwent conjunctival resection with AM grafting. Eight (17%) eyes with severe disease required TABCL.

In cases with impending perforation or frank perforation TABCL, tenon’s patch graft or PK can be done depending on the size of perforation. One (2%) eye with severe disease underwent tenon’s patch graft and in 5 (10%) eyes PK was done. There are high chances of recurrences of PUK in graft and hence patients should be kept in close follow up after surgery. None of our patients had recurrence of PUK in graft. All patients undergoing surgery should have a quiet eye. In the case of patients requiring emergency surgical procedures, there is a definite role of perioperative intravenous steroids. Multiple recurrences may necessitate evisceration in some patients. None of our patients underwent evisceration.

In summary, PUK can be an indicator for occult systemic autoimmune disease. Mooren’s ulcer is the most common cause for PUK. Surgical treatment is ancillary to systemic immunosuppressive therapy. Prompt and adequate immunosuppression is not only eye saving but also lifesaving for patients with PUK of autoimmune origin.

**Conclusion**

PUK can be an indicator for occult systemic autoimmune disease. Mooren’s ulcer is the most common cause for PUK. Surgical treatment is ancillary to systemic immunosuppressive therapy. Prompt and adequate immunosuppression is not only eye saving but also lifesaving for patients with PUK of autoimmune origin.

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**Conflicts of interest**

There are no conflicts of interest.

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