Clinical Study of Peripheral Ulcerative Keratitis

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ABSTRACT

BACKGROUND

Peripheral Ulcerative Keratitis (PUK) is a group of destructive, inflammatory disorders involving the peripheral cornea (3.5 mm – 4 mm) from the visual axis. It is associated with epithelial defect, stromal necrosis, and thinning leading to perforation and blindness. Invasion of microbial organism, immune complex deposition, trauma serves as an inflammatory stimulus in the peripheral cornea causing Peripheral Ulcerative Keratitis (PUK). PUK is rare. It is more common in people with collagen vascular disease. The combination of clinical data, and test results can lead to better diagnosis. Early diagnosis helps in preventing PUK related complications.

METHODS

44 Eyes of 30 patients with PUK, who attended OPD of the Department of Ophthalmology at MKCG Medical College, Berhampur, in the state of Odisha, India were taken up for study. Their demographic profile & complaints were noted. A detailed history was taken, and a systemic evaluation with complete ocular examination was done along with microbiological and serological analysis.

RESULTS

The study showed that the prevalence of PUK is about 2.3 per 10000. (This study included both noninfectious and infectious causes). The age group commonly affected was middle aged individuals above the age of 30. Pain was more common in cases of Mooren's ulcer and corneal phlycten. Unilateral involvement was found to be more common than bilateral. In this study, 72% of cases presenting with inflammatory peripheral corneal disease was of noninfectious etiology. The commonest noninfectious cause of PUK was catarrhal infiltrates associated with blepharitis in elderly age group. Collagen vascular diseases (RA & WG) presenting with PUK were more commonly seen in females.

CONCLUSIONS

PUK is a destructive, inflammatory disorder involving the peripheral cornea. The predominant cause of inflammation is an auto immune process which is either due to systemic or local factors. Infections do play a role in its etiopathogenesis. A detailed serological and microbiological assay is required before commencing treatment with anti-inflammatory and immunomodulator medications.

KEYWORDS

Peripheral Ulcerative Keratitis (PUK), Marginal Keratitis (MK), Rheumatoid Arthritis (RA), Wegener's Granulomatosis (WG), Relapsing Polychondritis (RP), Polyarteritis Nodosa (PAN)

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BACKGROUND

Peripheral corneal ulcers (PUK) represent a distinct clinical entity. Being anatomically and physiologically distinct from its central counterpart, the peripheral cornea is predisposed to three main classes of disorders which do not normally affect the central cornea. Firstly- the peripheral cornea encompasses histological character of conjunctiva, episcleral and sclera. Conditions like hypersensitivity reaction, infection, mass lesion, degenerative conditions may secondarily spread to involve the limbus and peripheral cornea. Secondly- the presence of limbal vasculature, subconjunctival lymphatics allows for limited diffusion of small molecules (immunoglobulin and complement components) into the cornea.[1] Thus antigen antibody complex formed in the cornea, tear, aqueous humour, limbal vessel activate the complement pathways (both classical and alternative pathways) with recruitment of inflammatory cells in the peripheral cornea releasing lytic enzymes causing stromal degradation of the peripheral cornea leading to a distinct clinical disease - peripheral ulcerative keratitis. Finally, there are several conditions such as the non-inflammatory peripheral degeneration (Pellucid Marginal Degeneration, Terrien's Marginal Degeneration) which primarily affect the peripheral cornea without associated ocular and systemic changes.[2]

PUK is a group of potentially destructive inflammatory disorders affecting the peripheral cornea characterized by an epithelial defect, stromal necrosis, thinning, progressing centripetally and circumferentially threating the clarity of visual axis and integrity of the globe.

Aetiological Classification of PUK

Infectious – Bacterial, fungal, Viral (herpes simplex and herpes zoster) and Chlamydia.

Non-infectious – These are of two types.

Micro ulcerative – Drug allergy, catarrhal infiltrate, phlyctenule, Rosacea.

Macro ulcerative –

1. Secondary to Systemic vasculitis / Collagen vascular disease like RA, PAN, WG, SLE.
2. Mooren's ulcer.

PUK is uncommon. At least 50% of all non-infectious causes of PUK have associated Collagen Vascular Disease. Rheumatoid Arthritis (RA) is the most common systemic disease associated with collagen vascular disease. PUK may be the initial manifestation of Wegener's Granulomatosis (WG) and polyarteritis Nodosa (PAN). PUK is rare in patients with Relapsing polychondritis (RP); PUK also has been reported to be associated with systemic lupus Erythematosus (SLE), although this is uncommon. Mooren's ulcer is a local autoimmune disease associated with PUK. No good data is available on racial predilection for PUK. In collagen vascular disorders (especially RA), females are more commonly affected than males) PUK caused by Mooren's ulcer is more common in males.

Clinical presentation varies and is dependent on the associated systemic or local disorder. PUK is frequently the only manifestation of an occult systemic disease (either Mooren's like ulcer/Wegener's granulomatosis). Thus, a through history is very important and should include chief complaint, characteristics of present illness, past medical history, family history and a meticulous review of system. Early diagnosis of PUK helps to give appropriate treatment and prevent its associated vision and life-threatening complications

We wanted to study the demographic profile, clinical presentation and possible aetiology of patients presenting with peripheral corneal ulcer at MKCGMCH Berhampur Odisha, India.

METHODS

The study was carried out in the Department of Ophthalmology and medicine at M.K.C.G. Medical College & Hospital, Berhampur, Odisha, India, from August 2004 to September 2006. Thirty patients were included in the clinical study of PUK. The patients enrolled were from Ophthalmology OPD, referrals from Medicine indoor, ENT and Skin OPDs. Ethical approval was taken. An informed consent was taken from the patient willing to participate in the study. They were evaluated thoroughly on a preplanned proforma and investigated accordingly.

Name, age, sex, symptoms like dimness of vision, pain, photophobia, redness, watering with duration, any history of trauma to the eye was noted. Past history of any eye disease and History of any significant systemic disorders with treatment history, use of topical eye drops if any with duration. General and systemic examination was done. Visual Acuity, Intra Ocular pressure Measurement (Schiotz Tonometer), a detailed slit lamp examination (both anterior segment and posterior segment) with Schirmer's Test and Staining with a) Fluorescein and b) Rose Bengal.

Microbiological Test

Direct microscopy for bacteria (Gram stain) & fungi (KOH preparation) and culture on blood agar.

Laboratory Test

1. Blood test - Complete blood count, Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Mantoux test, Rheumatoid Factor
2. Chest X-Ray/ X-Ray of Para nasal sinuses.
3. Urine Analysis.

Exclusion Criteria

Patient presenting with non-inflammatory corneal thinning (Pellucid and Terrien's marginal degeneration) were

excluded from the study. Peripheral ulcers secondary to mass lesion or malignancy were excluded. Patient presenting with Shield's ulcer were also excluded. Central corneal ulcers with peripheral involvement were excluded.

RESULTS

The main outcome measures were sociodemographic profile, clinical features, diagnosis and possible aetiology. 30 cases of PUK were identified over duration of 2 years. Incidence of PUK is about 2.3 per 10000. (Including cases of noninfectious and infectious cause). The incidence of PUK in the setting of Collagen vascular disease was calculated as 3 cases per million per year.[3] Noninfectious causes of PUK are common in middle aged individuals. (30-50 years). PUK associated with infectious causes are more common in elderly individuals with existing predisposing factors (Dacryocystitis and lid abnormalities). Male: Female ratio was 13:17 in this study. In the age group >30 years, No of females were 13 and males were 9. Noninfectious etiology is commonest cause of PUK is female, whereas infectious etiology is common in males (working class, senior individuals suffering from systemic disease like hypertension, cerebrovascular accidents and low socioeconomic status).

Commonest presentation was photophobia, watering and redness. In phlyctenulosis corneal involvement results in the classical symptom of extreme photophobia. Mooren's ulcer patient complained of photophobia, tearing, redness but pain was typically the outstanding features. Marginal keratitis associated with Blepharoconjunctivitis had the commonest bilateral presentation in this study. PUK associated with autoimmune disease and peripheral corneal ulcers due to infection had unilateral presentation (in my study). All 3 cases with PUK and collagen vascular disease had unilateral involvement (this finding correlated with the study conducted by Wood & Kafuman).[4]

Signs	No. of Cases
Blepharoconjunctivitis	8
Uveitis	3
Scleritis	2
Episcleritis	1
Dry Eye Schirmer's Test (<5 MM)	4
Corneal Perforation & Iris Prolapse	1
Lagophthalmos	2
Entropion with Pseudo trichiasis	1
Dacryocystitis	1
Senile Ectropion	2
Foreign Body – Inferior Cornea/ Superior Tarsals	2
Decreased Corneal Sensation	2

Table 1. Ocular Associations with PUK (Table 1)

Meibomian gland dysfunction/Blepharoconjunctivitis is the commonest ocular association with inflammatory peripheral corneal disease (erythema and edema of lid margin with telangiectasia are distinctive feature). Presence of hard scales or collarets in the base of eyelash suggest long standing staphylococcal blepharitis. Untreated cases/recurrent cases result in catarrhal infiltrate and Phlyctens (limbal and corneal). In this study Keratoconjunctivitis sicca was associated with 2 cases of Rheumatoid Arthritis and 2 cases of Mooren's like ulcer. Keratoconjunctivitis sicca (dry eye disease) is the commonest ocular manifestation in collagen vascular disease. KCS is clinically evident in 15%-25% of patient with Rheumatoid Arthritis. Scleritis (anterior) was associated with RA and WG (36% -66% of cases with PUK have associated scleritis).[4,5] Approximately 50% of patients with scleritis have an associated underlying systemic disease.[6] Adjacent scleritis was present in Wegener's granulomatosis. Uveitis was commonly associated with infections (herpetic and bacterial) or Mooren's ulcer.[7] Ocular factors (lid abnormalities, dacryocystitis, nonsurgical trauma (foreign body), prolong use of topical NSAIDS for episcleritis caused inferior corneal thinning with superadded infection presented with peripheral corneal ulcer.

	No. of Cases
Dermatological (Rosacea)/ Atopic Dermatitis	2
Joint Pain	3
Blood Stained Pus Like Nasal Discharge	1
Bell's Palsy with Poor Bells Phenomenon	1
Cerebral Vascular Accident – CVA due to Hypertension	2
Urinary Tract Infection	1
Bloody Dysentery	1
Tuberculosis	1

Table 2. Systemic Associations with PUK

Systemic association (this study includes RA, WG, rosacea, atopic dermatitis, stroke, Bell's palsy & tuberculosis,) with PUK accounting for 33.33% of the total PUK cases. In this study RA accounts for a 11.11% of the total noninfectious cases (RA is the most common systemic association accounting for 34-66% of the non-infectious cases of PUK.[4,5] In RA PUK occurs late in the disease course. PUK associated with WG precluded the diagnosis in 1 outpatient. Rosacea and Atopic dermatitis are associated with catarrhal infiltrates /phlyctens. Systemic chlamydial (genitourinary) infections are associated with infectious PUK. 2 cases presenting with PUK and nonspecific results in laboratory investigation were categorized as Mooren's like ulcer.

Investigation	No. of Cases
Differential staining with gram stain	9 cases positive
Culture with blood agar	Cluster arrangement of cocci in 8 cases Chain arrangement in i case
Wet mount KOH preparation (fungus)	hyphae in 1 case

Table 3. Outcome of Microbiological Investigations

1 case suffered stroke presented with neurotrophic ulcer and superimposed infection was KOH positive. Bacteria (particularly gram-positive cocci) is the commonest pathogen in infectious cause of PUK.[8] The most common bacterial organisms infecting peripheral cornea are *Staphylococcus aureus, Streptococcus pneumoniae, Moraxella, pseudomonas, Hemophilus influenza*. Fungal hyphae were observed in 1 case of peripheral corneal ulcers. Fungal keratitis should always be suspected in patients who have altered host defense related to keratoconjunctivitis sicca, Lagophthalmos (suggested by Wagoner et al). 1 case was diagnosed to suffer from marginal herpetic keratitis with uveitis. A patient presented with dendritic ulcer near the

limbus showing peripheral corneal infiltrates and epithelial staining with loss of corneal sensation and a past history of herpes simplex infection.

Abnormal Lab Findings in Patients

Table 4 shows abnormal laboratory finding in PUK. 1 case of corneal phlycten showed nodules in hilar area with positive Tuberculin skin test suggesting Tuberculosis to be a cause of phlyctenules and 1 case showed fluffy granulomatous infiltrates in x-ray chest with abnormal urine finding (red blood cell cast and proteinuria) directing diagnosis in Wegener's granulomatosis. X ray joints were abnormal in 2 cases of Rheumatoid arthritis. Urine analysis of a young male patient showed plenty of pus cells, chronic conjunctivitis and history of recurrent UTI suggesting chlamydial infection. In my study Noninfectious causes of PUK accounts for 71.87%. Table 5 suggests that marginal keratitis/catarrhal infiltrate associated with blepharitis is the commonest cause of non-infectious PUK.

Investigation	No. of Cases and Findings
Raised ESR	Raised in 5 cases
RA Factor	Positive in 2 cases
CRP	high in 5 cases
X Ray of Small Joints	2 (periarticular soft tissue swelling, narrowing of joint space, peri articular osteopenia)
X Ray of Chest	1 (nodules in hilar areas suggestive of healed primary tubercular lesion) 1 (fluffy granulomatous infiltration suggestive of WG)
Urine Analysis	1 (RBC casts and proteinuria- in WG) 1 (plenty of pus cells- nonspecific)
X Ray of Para Nasal Sinuses	1 – sinus opacification and mucosal thickening.
Tuberculin Skin Test	1

Table 4. Laboratory Investigations

Noninfectious Causes	No. of Cases	Infectious Causes	No. of Cases
Rheumatoid arthritis	2	Gram positive cocci	9
Mooren's ulcer	1	Chlamydia	1
Mooren's like ulcer	2	Marginal herpes simplex keratitis	1
Catarrhal infiltrate	8	Fungal	1
Phlycten	4		
Wegener's Granulomatosis	1		

Table 5. Aetiology of PUK

DISCUSSION

PUK is a destructive, inflammatory disorder affecting the peripheral cornea clinically presenting with a crescent shaped destructive lesion of the juxta limbal corneal stroma with an overlying epithelial defect and vascularization/ congestion. The predilection for the periphery is believed secondary to its close proximity to the conjunctival vessels which supply the inflammatory mediators to the peripheral cornea. This condition may be triggered by surgical and nonsurgical trauma or may arise spontaneously.[5]

Macro Ulcerative Form of (Noninfectious) PUK

Macro ulcerative form of noninfectious PUK is commonly associated with CVD/ Systemic Vasculitis Approximately 50% 0f all noninfectious PUK cases have an associated collagen vascular disease.[4] The commonest association is with Rheumatoid arthritis followed by Wegener's granulomatosis.[9] Rheumatoid arthritis accounted for 34% of non-infectious PUK (Tauber et al). PUK associated with Rheumatoid arthritis may present with multiple peripheral corneal ulcer and anterior necrotizing scleritis or may cause non inflammatory corneal melts and perforation. PUK in RA generally appears late in the disease course and usually signals worsening of the systemic disease[10] One study found a mean of 19.6 years between the diagnosis and the onset of PUK.[3]

Scleromalacia perforans typically occurs in females with long standing Rheumatoid arthritis.[11] Secondary Sjogren's syndrome occurs in 34% of patients of Rheumatoid arthritis. PUK develops earlier in Wegener's granulomatosis, often presenting within 6 months of the diagnosis or precluding the diagnosis.[3] Patients with Wegener's granulomatosis presented with PUK as the initial manifestation of their occult Wegener granulomatosis (Foster CS study). Wegener granulomatosis with associated PUK always had involvement of adjacent sclera. (necrotizing scleritis).[12] Other Collagen vascular disease associations are Systemic lupus erythematosus (SLE), Relapsing polychondritis, Polyarthritis nodosa, Churg – Struss. Acquiring knowledge about the common manifestation of these process can be helpful, for example a history of weight loss, polyarthritis of small joints are commonly associated with Rheumatoid arthritis or a history of blood stained pus like discharge with nasal stuffiness, prolong cough or an associated inflammatory bowel disorder suggest Wegener's granulomatosis.

Mooren's Ulcer or Chronic Serpiginous Ulcer or Ulcer Rodens[13] is a macro ulcerative type of, non-infectious peripheral ulcerative keratitis. Mooren's ulcer is a diagnosis of exclusion. It is by definition, idiopathic occurring in complete absence of any diagnostic systemic disease or any ocular infection. It is strictly a PUK with no associated Scleritis.[14] Prior corneal surgery, corneal trauma and corneal infection are believed to be associated risk factors for Mooren's ulcer (suggested by Srinivasan et al).

Figure 1. Mooren's Ulcer after Cataract Surgery (Extracapsular Cataract Extraction)

Diagnostic criteria for Mooren's ulcer (Foster (1985)) include-

1. Crescent shaped peripheral ulcer
2. Undermining central ulcer with overhanging lip
3. Intra stromal yellowish white infiltrate in the spreading ulcer edge.
4. Circumferential and central progression of the ulcer.
5. Re epithelialized vascularized thinned corneal scar in the way of advancing ulcer and

6. Absence of scleral involvement.

Mooren's like ulcer clinically resembles Mooren's ulcer but are believed to be a manifestation of an occult systemic disease.

Micro Ulcerative Form of (Noninfectious PUK)
Catarrhal Infiltrates / Marginal Keratitis

Catarrhal/ marginal keratitis is micro ulcerative form of PUK usually occurs in middle aged individuals with a concomitant blepharo conjunctivitis. Catarrhal infiltrates and ulcers probably represent the most common form of peripheral corneal disorders. (Robin et al) clinically presenting as unilateral / bilateral small infiltrates in superficial stroma where lids touch the corneal periphery separated from the limbus by a clear corneal zone. Rosacea and Atopic dermatitis are dermatologic disorders associated with meibomian gland dysfunction.

Figure 2. Sub Epithelial Infiltrates with Superficial Punctate Keratitis and Ulcerative Blepharitis (Re)

Phlyctens are micro ulcerative form of PUK .It can present a significant diagnostic challenge. Phlyctens usually originated at the limbus (Krachmer) typically presenting as 1 - 3 mm, hard, slightly elevated yellowish-white nodule with dilated conjunctival vessels approaching it. Recurrent lesions tend to extent farther into the central cornea. Phlyctens are frequently associated with staphylococcal blepharo conjunctivitis. Tuberculosis should be considered in cases presenting with phlyctenules in endemic regions.

Figure 3. Corneal Phlycten (RE)

Herpes simplex can cause limbal ulceration.[15] A history of previous herpetic disease and occasionally a dendritic appearance to the edge of ulcer will suggest correct diagnosis. Corneal sensation may be markedly decreased

Dendritic and geographical ulcers near corneal limbus shows peripheral corneal infiltrates and epithelial staining and can be mistaken for a bacterial corneal infiltrate or other marginal infiltrate[16,17] Any case presenting with stromal thinning and peripheral corneal infiltrate, an infectious cause should be ruled out indirectly suggesting infection to be a commonest cause of Peripheral ulcerative keratitis (Kenyon Foster CS).

CONCLUSIONS

PUK is an inflammatory disorder of peripheral cornea with varied aetiologies (commonly associated with autoimmune disease). In the study conducted, the commonest aetiology of PUK was noninfectious (accounting for 71.88%). Marginal keratitis associated with staphylococcal blepharoconjunctivitis was the commonest presentation. Infectious cause for PUK was 28.12%. In my study, the low prevalence of PUK associated with CVD could better be explained by

1. ignorance of patients and delayed presentation
2. economic constraints
3. rapid progression with involvement of central cornea

To conclude, when any patient presents with PUK, a detailed personal and family history with specific attention given to systemic autoimmune diseases should be obtained. Infectious aetiologies (primary or secondary) should be excluded by appropriate examination and corneal cultures.

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