Peripheral Keratitis – Mooren's ulcer

Dr. Akhil Agarwal, Dr. Neelima Mehrotra,
Dr. J.S Verma, Dr. Amrita Mishra, Dr. Puja, Dr. Mohd Uzair Zakai

Corneal periphery is arbitrarily considered as an area of 3.5-4.5 mm from the visual axis coinciding with the flattening of the corneal curvature .

Anatomy of peripheral cornea and Importance

The peripheral cornea has distinct morphological and immunological characteristics that predisposes it to inflammatory reactions . Corneal periphery is about 0.7 mm in thickness as against the central 0.5 mm . Unlike the avascular , the limbus and the peripheral cornea derive part of their nutrient supply from the capillary artery ,which extends approximately 1-2 mm in the cornea involvement of vascular supply can result in inflammatory cell recruitment and corneal necrosis due to liberated collagenolytic and proteolytic enzymes from these cells. Additionally, Langerhans cells are present in great number figure and along with antigen presenting limbal macrophages perpetuate and immune mediated corneal disease.

Channels from subconjunctival lymphatics accompany the limbal capillaries into the peripheral cornea and provide the access to the afferent arm of the immune system. In addition , the limbus and adjacent conjunctiva serves as the reservoir for various cells of the immune system & proinflammatory of cytokines .

Peripheral keratitis classification

A. Local Causes

1. Infection : bacterial , viral , fungal , chlamydial, parasitic
2. Hypersensitivity or Immune Mediated
   - a. Marginal Keratities
   - b. Phlectenulosis
   - c. Vernal disease
   - d. Immune rings
   - e. Moorens ulcer
   - f. Anaphylactic marginal keratitis
   - g. Rosacea keratitis
3. Traumatic or Toxic
4. Miscellaneous
   - a. Superior Limbic keratitis
   - b. Keratoconjunctivitis sicca
   - c. Exposure keratopathy
   - d. Neuroparalytic keratitis

B. Systemic Causes :

1. Metabolic Disease : Superior Limbic keratoconjuctivitis
2. Systemic Vasculitides

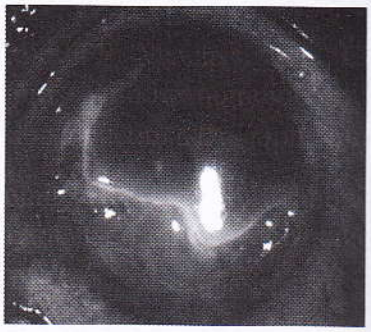
a. Rheumatoid arthritis
b. JRA
c. SLE
d. Relapsing Polychondrities
e. Sjogren's syndrome
f. Wegeners granulomatosis
g. Polyarteritiesnodosa

3. Dermatological Conditions : Ectodermal Dysplasia , rosaceae , psoriasis
4. Miscellaneous : blood dyscrasis inflammatory bowel disease .

C. Non Inflammatory Conditions Of Peripheral Cornea.

1. Degenerations.
   a. Pinguecula.
   b. White limbal girdle of vogt
   c. Band keratopathy
   d. Pterygium
   e. Post irradiation scleromalacia
   f. Dellen
   g. Terriens degenerations
   h. Pellucids degenerations
2. Metabolic disease & deposits of substances:
   a.Chalcosis: KF ring
   b.Iron deposits : ferry line , stockers line
   c.Gold deposits in chrysiasis (in treatment of RA)
   d.Drug deposits :eg phenothiazines
   e.Mucopolysaccharides
   f.Lipids in hyperlipidemia
3. Dysplastic & Neoplastic Conditions
   a.Limbal melanoma
   b. Limbalepibulbar dermoid
   c. Squamous cell carcinoma intra epithelial epithelioma

Mooren's ulcer



Mooren's ulcer is a painful, progressive, chronic ulcerative keratitis that begins peripherally and progresses circumferentially and centrally. It is an idiopathic disease occurring in complete absence of any diagnosable systemic disorder that could be responsible for the progressive destruction of the cornea. Bowman published the first report of Mooren's ulcer in 1849. Later, in 1854, McKenzie described it as 'chronic serpiginous ulcer of the cornea or *ulcus roden*.'[1]The disorder was named as Mooren's ulcer after DrMooren, who was the first to clearly describe this insidious corneal problem and define it as a clinical entity in 1863 and 1867.[2]

Etiology

Mooren's ulcer has been associated with different entities, often leading to the conjecture that there may be a causal relationship. Multiple studies including collaborative studies have reported association between Mooren's ulcer and hepatitis C infection.[3-4] Many of these patients responded to interferon

therapy.[5,6] Infectious associations have been reported with hookworm infestation.[7,8] These authors proposed that molecular mimicry might be involved, with the infecting agent stimulating an autoimmune response to corneal antigens through cross-reacting epitopes. Alternatively, they also proposed that deposition of immune complexes in limbal or peripheral corneal tissues led to an immune response and release of proteolytic enzymes.

Pathogenesis

The pathogenesis of Mooren's ulcer remains uncertain. The cellular population found in the conjunctiva adjacent to the ulcer and in the peripheral edge of the ulcer is primarily plasma cells, lymphocytes, and macrophages.[9-11] In addition, there are neutrophils, eosinophils, and mast cells. There is increased binding of IgG, IgM, and C3 to the epithelium of conjunctiva adjacent to the ulcer.[9] Kafkala et al., in a recent publication, demonstrated upregulation of various adhesion and co-stimulatory molecules in epithelial cells in the conjunctiva of Mooren's ulcer patients.[12] In this study, the ratio of CD4/CD8 cells and B7-2/antigen-presenting cells were significantly higher in Mooren's ulcer specimen. Gottsch and colleagues demonstrated antibodies to an autoantigen that exists in corneal stroma.[13] The antigen, known as 'cornea-associated antigen', has an amino acid sequence identical to that of calgranulin C of neutrophils. The human leukocyte antigen (HLA) system is a critical component for immune recognition and various studies have identified association between HLA-DR17 and the occurrence of Mooren's ulcer.[14,15] All this evidence supports an autoimmune basis for the disease. Mooren's ulcer may represent a final common pathway to a variety of insults to the cornea in susceptible patients. Trauma or infection may alter normal corneal antigens, which may lead to an autoimmune response.

Types

Wood and Kaufman described two clinical types of Mooren's ulcer.

The first, limited type, is usually unilateral, with mild to moderate symptoms, and generally responds well to medical and surgical treatment. This type is believed to occur in older patients and is known as typical or benign Mooren's ulcer.

The second type is bilateral although both eyes may not be affected simultaneously, with relatively more pain and generally a poor response to therapy. The bilateral variety primarily occurs in younger patients and is known as atypical or malignant Mooren's ulcer. This variety of the ulcer progresses relentlessly and is more likely to result in corneal perforation.

Clinical Features

Symptoms

Patients with Mooren's ulcer usually complain –

- redness,
- tearing, and
- photophobia,
- pain is typically the outstanding feature.
- The pain often is incapacitating and may well be out of proportion to the inflammation.
- There may also be a complaint of decreased visual acuity, which may be secondary to associated iritis, central corneal involvement, or irregular astigmatism due to peripheral corneal thinning.

Signs

- Typically, Mooren's ulcer begins as a crescent-shaped gray white infiltrate in the peripheral cornea. Epithelial breakdown and stromal melting follow this. Eventually it develops into a characteristic

chronic crescent-shaped peripheral ulcer. The ulcer is concentric to limbus; the leading edges are undermined, infiltrated, and deepithelialized. The ulcer progresses circumferentially and centrally.

- As it progresses, it creates an overhanging edge at its central border.
- Though the ulcer may begin as a shallow furrow in the peripheral cornea, over time it may involve the limbus. The adjacent conjunctiva and sclera are usually inflamed and hyperemic.
- Mooren's ulcer most of the cornea is lost, leaving behind a central island surrounded by area of grossly thinned, scarred, and vascularized tissue. Although the disease is characterized by progressive thinning, corneal perforation is uncommon .
- Iritis sometimes is associated with Mooren's ulcer. Hypopyon is rare unless secondary infection is present.
- Glaucoma and cataract may complicate the process

Differential Diagnosis:

Some conditions with peripheral thinning and ectasia like Terrien's and Pellucid'smarginal degenerations may confused with Mooren's. But both are non-inflammatory conditions and affect only the cornea with no scleral involvement. Also, the epithelium is usually intact unlike in Mooren's. Terriens is mostly bilateral and asymptomatic till long time after onset. It may occur at any age and Mooren's is usually is a disease of > 20 year olds.

Catarrhal Ulcer (Marginal Ulcer) may be distinguished by lucid interval between limbus and affected cornea and lack of pain which is characteristic of Mooren's

Characteristic	Mooren's Ulcer	Terrien's Degeneration `	Pellucid Degeneration
Pain	+	-	-
Visual Loss	+	+/-	+/-
Location	Anywhere	Superior	Inferior
Progression	Rapid	Slow	Slow
Central Imvolvement	+	-	-
Epithelial Defect	+	-	-
Stromal Thinning	+	+	+
Ulcer Characteristics	Central Overhanging edge	Liquid Deposition	Central flattening
Ulcer Visualization	+	+	-
Ocular Inflammation	+	-	-
Visual Threat	Central Opacification Perforation	Astigmatism	Astigmatism
Treatment	Immunosupressives Conjuctival Resection Tectonic Keratoplasty PK	Contact Lenses Tectonic Keratoplasty	Contact Lenses Tectonic Keratoplasty

Treatment

The goals of treatment in Mooren's ulcer are to stop the ulcerative process and allow reepithelialization of the cornea.

Four strategies underlie most of these treatments:
(1) local immunosuppression,
(2) systemic immunosuppression,
(3) removal of local stimulatory antigens, and
(4) removal of distant stimulatory antigens.

The following **stepwise** approach to management is recommended:
(1) topical corticosteroids,
(2) conjunctival resection,
(3) systemic immunosuppression, and
(4) additional surgery.

***Topical corticosteroids*:** These are used aggressively on an hourly basis, along with topical prophylactic antibiotics and cycloplegic medications. When the cornea shows signs of reepithelialization the steroid therapy is tapered gradually over months.

***Conjunctival resection*:** This removes involved conjunctiva and blocks collagenase and the immune response to corneal antigen by providing a biological barrier. In this procedure, conjunctiva adjacent to the corneal ulcer is resected up to 2 clock hours on either side to bare sclera and extends 3–4 mm from the limbus. Postoperatively, topical corticosteroids and antibiotics are continued

Systemic immunosuppression

Those cases of bilateral or progressive Mooren's ulcer that fail therapeutic steroids and conjunctival resection Systemic corticosteroids can be given to suppress inflammation and arrest progressive corneal thinning. The recommended dosage for oral prednisolone is 1–1.5 mg/kg body weight/day. The dosage is adjusted according to the severity of the disease and is tapered slowly when improvement occurs.

Other systemic immunosuppressants used in the management of Mooren's ulcer are: cyclophosphamide (2 mg/kg/ day), methotrexate (7.5–15 mg once weekly), and azathioprine (2 mg/kg/day). The degree of fall in white blood cell count is considered as the most reliable indicator of immunosuppression produced by cyclophosphamide.

Oral ciclosporin A (3–4 mg/kg/day) has been successfully used to treat a case of bilateral Mooren's ulcer unresponsive to local therapy as well as systemic immunosuppression.

Other agents

***Topical ciclosporin*:** Recently, topical ciclosporin 0.5% ophthalmic solution 4 to 6 times daily has been successfully used to treat Mooren's ulcer without the potential side effects of oral immunosuppressants.[16]

Interferon alpha-2b: Treating chronic hepatitis C patients with subconjunctival injections of interferon alpha-2b over a 6-month period has been shown to improve healing of Mooren's ulcer after other more conventional forms of treatment for the ulcer have failed.[17,18]

Additional Surgery

Various surgical procedures used are:

***Keratoepithelioplasty*:** In this procedure the ulcerated corneal tissue and adjacent conjunctiva are removed and donor corneal lenticules with intact epithelium are sutured onto bare sclera.[19] There are two theories to

explain success with this procedure. According to one theory, intact corneal epithelium has antiangiogenic properties and the Bowman's layer is quite resistant to cell invasion. Another theory is that the transplanted lenticules mask the biological signal of surgical damage to corneoscleral tissue

***Lamellar keratectomy*:** In this procedure four-fifths of the corneal thickness is excised. The procedure controls the inflammatory process by removal of the corneal antigenic stimulus.

***Lamellar keratoplasty*(LKP):** LKP is widely used at present for the treatment of Mooren's ulcer. The procedure removes antigenic targets of the cornea, prevents immunological reactions, reconstructs the anatomy and prevents it from perforating, and improves vision. The surgical procedure involves removal of necrotic ulcerative cornea and reconstruction of anatomical structure using lamellar donor lenticule.
Tissue adhesive and bandage contact lens: In cases of perforation or impending perforation, tissue adhesive with bandage contact lens may be used to seal small perforations.

Tectonic grafts (patch graft or penetrating keratoplasty): Large perforations cannot be managed by tissue adhesive and require tectonic grafts such as a patch graft or penetrating keratoplasty.

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