Mooren's Ulcer:

Diagnosis and Management

Quan Dong Nguyen, M.D.

Abstract

Background: Mooren's ulcer (MU) is a rare and painful peripheral corneal ulceration which occurs in the absence of any associated scleritis, and any detectable systemic disease. The authors present a case of unilateral Mooren's ulcer in a young, healthy man, which requires conjunctival resection for adequate control. Clinical manifestations, pathophysiology, and current recommended therapeutic modalities for Mooren's ulcer are discussed.

Materials and Methods: An 18-year-old man developed episodic discomfort in his left eye for three years. The patient had been treated with topical steroid, and topical and oral non-steroidal anti-inflammatory medications without complete resolution.

Results: A diagnosis of Mooren's ulcer was made. The patient underwent conjunctival resection and keratectomy. Six months after his surgery, the patient was completely free of any discomfort. His visual acuity also returned to normal level (20/20)

Conclusion: Mooren's ulcer is a rare type of peripheral ulcerative keratitis. The diagnosis, one of exclusion, is made after complete evaluations for underlying systemic condition are non-revealing. The management of MU can be quite challenging, and often frustrating, and should be executed in a systematic and step-wise approach.

I. Introduction

Mooren's Ulcer was first described by Bowman in 1849 [2] and McKenzie in 1854 as "chronic serpiginous ulcer of the cornea or *ulcus roden* " [16]. However, it was Mooren who was the first to publish several cases of this condition in 1863 and was also the first to clearly describe this corneal condition and define it as a clinical entity [20].

Mooren's Ulcer is a painful, relentless, chronic ulcerative keratitis that begins peripherally and progresses circumferentially and centrally. By definition, it is idiopathic, occurring in the complete absence of any diagnosable systemic disorder that could be responsible for the progressive destruction of the cornea. Thus, MU is a peripheral ulcerative keratitis, with *no*associated scleritis.[23]

Case

An 18-year-old Caucasian man presented complaining of recurrent episodes of severe discomfort in his left eye for three years. The patient has been treated by other ophthalmologists with Predforte, Inflammase Forte, Ocufen, and *per orem* non-steroidal anti-inflammatory drugs with occasional relief.

The patient is otherwise healthy. He has no family history of any ocular disease. He has no known drug allergy. His medications at the time of presentation include only Inflammase Forte OS bid and Advil prn.

Visual acuity was 20/20 OD and 20/25 OS. There was no afferent pupillary defect. Ocular motility and intraocular pressures were normal in both eyes. Anterior segment examination was normal in the right eye. On the left eye, there was an area of peripheral perilimbal corneal thinning from

4:00 o'clock to 8:00 o'clock, with excavation. The thinning was about 30% from 4 to 7 o'clock, and 60% from 7 to 8 o'clock. (Figures 1 and 2) There was no fluorescein staining of the corneal surface. Dilated funduscopic exam was normal, OU.

Figure 1

Figure 2

The chest X-ray and the following laboratory studies were normal: complete blood count (CBC), sedimentation rate (ESR), fluorescent treponemal antibody absorption test (FTA-ABS), rapid plasma reagin (RPR), angiotensin converting enzyme (ACE), anti-neutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), rheumatoid factor (RF), and soluble interleukin-2 receptor (sIL-2R).

Based on the clinical presentation and negative workup for underlying systemic diseases, a diagnosis of Mooren's Ulcer was made. Because of the history of recurrent attacks while on medical treatments, the patient opted for surgical therapy. Ten day after his presentation to MEEI, the patient underwent conjunctival resection and keratectomy, OS, with placement of Histocryl

tissue adhesive and contact lens post-operatively. (**Figure 3**) Inflammase Forte and Polytrim were also initiated. Histopathological study revealed normal number of plasma cells and slightly increase number of goblet cells.

Figure 3

His post-operative course was very uneventful with progressive removal of the adhesive. Six-month post-op, all tissue adhesive and contact lens had been removed. The patient was comfortable. His visual acuity was 20/20 OU, and both eyes were quiet.

II. Epidemiology

MU is a rare disorder, typically seen in healthy, adult men with no evidence of systemic disease. However, MU can occur at any age and in both sexes. What is usually taught and published concerning the epidemiology of MU is based on the work of Wood and Kaufman. In 1971, Wood and Kaufman, having reported 9 cases, concluded that there were two clinical types of MU.[28] The first, *limited type*, was the typical or benign Mooren's ulcer. This type was usually unilateral, with mild to moderate symptoms, responded well to medical and surgical treatment, and tended to occur in older patients. The second type was bilateral and was considered *atypical* or *malignant* Mooren's ulcer. There was often more pain and poor response to therapy. The bilateral variety was thought to occur more in younger patients. [28] Subsequent authors have suggested a bilaterality rate of 25% for the benign type and 75% for the malignant type.

In 1990, Lewallen and Courtright , in their review of the published series of MU, found that 43% of older patients had bilateral disease, whereas bilateral disease was present in only one-third of patients younger than 35 years.[14] Also, whites were more than twice as likely to have bilateral disease than blacks. These authors recognized that their data might be flawed by a collection period of more than 85 years, differences in the basic criteria for definition of the disease, and poor documentation and follow-up. Thus, Lewallen and Courtright did not suggest that their own statistical analysis is necessarily more accurate in describing the epidemiology of MU, but did suggest that what was commonly believed might be similarly inaccurate. [1, 14]

Recently, Watson, based on clinical presentation and anterior segment fluorescein angiographic findings, divided MU into three distinct varieties. *Unilateral Mooren's ulceration*(UM) is a painful progressive corneal ulceration in elderly patients and is associated with non-perfusion of the

superficial vascular plexus of the anterior segment. *Bilateral aggressive Mooren's ulceration* (BAM), which occurs in young patients, progresses circumferentially, then centrally in the cornea. There is vascular leakage and new vessel formation, extending into the base of the ulcer. *Bilateral indolent Mooren's ulceration* (BIM), which usually occurs in middle-aged patients presenting with progressive peripheral corneal guttering in both eyes, with little inflammatory response. There is no change from normal vascular architecture except an extension of new vessels into the ulcer. [27]

III. Etiology

Mooren's ulcer has been associated with different entities, often leading to the conjecture that there may be a causal relationship. Infectious associations have been reported with helminthiasis and hepatitis C. Schanzlin speculated that the antigen-antibody reaction to helminth toxins deposited in the peripheral cornea provoked the inflammation and ulceration. [24] Recently, in two patients with bilateral Mooren's ulcers, chronic hepatitis C infection was documented.[17, 28] The ulcers and the hepatitis improved after treatment with interferon alpha2b.[17] The authors proposed that molecular mimicry may be involved, with the hepatitis C virus 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 may lead to an immune response and release of proteolytic enzymes. Other infections that have been associated with MU include herpes simplex and zoster [5, 18], syphilis, and tuberculosis. In addition, there are other associations reported with physical trauma, foreign bodies, chemical burns, surgical procedures such as cataract extraction and penetrating keratoplasty. [23]

IV. Pathophysiology

The precise pathophysiological mechanism of MU remains unknown, but there is evidence to suggest that it is an autoimmune process, with both cell-mediated and humoral components. Plasma cells, neutrophils, mast cells, and eosinophils have been found in the involved areas. Brown has reported high levels of proleolytic enzymes in affected conjunctiva.[3] Foster and colleagues found numerous activated neutrophils in involved areas, and thus proposed that these neutrophils are the source of proteases and collagenases that degrade the corneal stroma. They also showed that there was specific stimulation to blastogenic transformation and proliferation of lymphocytes of patients with MU by normal corneal stroma.[7] Additional evidence for cell-mediated autoimmune process include demonstration of a positive macrophage migration inhibition response to corneal antigens presented to lymphocytes from MU patients.[19] Systemically, there is decrease in number of suppressor T cells relative to number of helper T-cells. Therefore, unregulated helper T-cells may induce production of autoantibodies, resulting in the deposition of immune complexes, complement activation, inflammatory cell infiltration, and proteolytic enzyme release.[21]

Schaap and colleagues, using indirect immunofluorescent techniques, demonstrated circulating IgG antibodies to human corneal and conjunctival epithelium in patients with MU.[25] Elevated IgA levels and circulating immune complexes have also been reported.[19] Martin and colleagues have proposed a mechanism for the perpetuation of the ulcerative process, suggesting that a systemic disease, infection, or trauma may alter corneal antigens, stimulating both humoral and cellular responses. In the process, complement activation leads to neutrophil chemotaxis and degranulation with release of collagenases, causing corneal melting and further alteration and exposure of altered corneal antigens, thus perpetuating the process.[15] This cycle continues until the entire cornea is consumed.

Recently, Gottsch and associates demonstrated cellular and humoral immune responses to bovine corneal antigen in a patient with MU.[11] Serum from this patient was used to purify a cornea-associated antigen (Co-Ag) from bovine corneal stromal extracts. The Co-Ag protein is found to contain 70 amino acids in a single chain and lacks cysteine, tryptophan, and methionine

residues. These results have suggested that Co-Ag is a new member of the Ca2+ binding protein of the S-100 family of proteins and could provide an important framework to search for sequence similarity with microbial proteins as possible substrate for molecular mimicry and for identification of possible pathogenic epitopes in Co-Ag. Nevertheless, it is still unknown if cell-mediated and/or humoral immune mechanisms are involved directly in the pathogenesis of MU. It may be that they just accompany the corneal destruction that is caused by another mechanism.

V. Clinical Features

Patients with MU typically present with redness, tearing, photophobia, but pain is the most outstanding feature. The pain often is incapacitating and may be out of proportion to the inflammation. There may be a decrease in visual acuity secondary to associated iritis, central corneal involvement, irregular astigmatism due to peripheral corneal thinning. The disease may begin with several patchy, peripheral stromal infiltrates which coalesce, more often in the medial and lateral quadrants than in the superior and inferior ones.[23]

Often, there is involvement of the limbus, in contrast to other forms of PUK, such as that seen in rheumatoid arthritis.[9, 22] The ulcerative process first spreads circumferentially and then centrally to involve the entire cornea. The anterior one-third to one-half of the stroma is involved, characteristically with a steep, overhanging edge. The leading and central edge typically is undermined. This may not be easily apparent on slit-lamp examination, and probing of this edge may reveal a surprising degree of stromal destruction. Healing and vascularization , over a course of 4-18 months.

Portions of ulcer may be quiescent, while others are active. The end-stage result is typically a scarred, vascularized cornea that may be thinned to less than half of its original thickness. As the end stage of the process approaches, the patients may experience relief from the excruciating pain that has been present throughout the course of the disease

Complications from MU may include iritis, hypopyon, glaucoma, and cataract. Perforation may occur in 35 to 40% of cases, often associated with minor trauma to the weakened cornea.[23]

VI. Evaluation

Mooren's Ulcer is idiopathic. The characteristic features must occur in absence of any systemic process that may cause PUK. Thus, it is a diagnosis of exclusion. Infectious etiologies should be excluded by appropriate cultures, because microbial keratitis can rapidly progress and are usually amendable to antibiotic therapy. Non-inflammatory corneal degeneration, such as Terrien's or Pellucid marginal degeneration, in which the epithelium remains intact and pain is absent, can often be excluded. A thorough medical history and examination is required, as is comprehensive laboratory investigation.

Typical investigation may include: CBC with differentials, ESR, RF, complement fixation, ANA, ANCA, circulating immune complexes, LFTs, VDRL, FTA-ABS, urinalysis, electrolytes, serum electrophoresis, and chest roentgenogram. Additional testing is done as indicated by the review of systems and physical examination.

The differential diagnosis for Mooren's ulcer is that for peripheral ulcerative keratitis, and can be quite extensive. However, a careful review of system can often narrow the differential to a limited number of entities. A partial list of diseases may include [23]:

- Rheumatoid Arthritis

Wegener's Granulomatosis

Polyarteritis Nodosa

Other Collagen Vascular Diseases

Systemic lupus erythematosus

Progressive systemic sclerosis

Relapsing polychondritis

Staphylococcal Marginal Keratitis

Terrien's Degeneration

Senile Furrow Degeneration

Ocular Rosacea

Inflammatory Bowel Disease

Giant Cell Arteritis

Pellucid Degeneration

Leukemia

VII. Management

Most experts would agree on a step-wise approach to the management of Mooren's ulcer, which is outlined as follows:

1. Topical Steroids

Initial therapy should include intensive topical program: prednisolone acetate or prednisolone phosphate 1%, hourly, in association with cycloplegics and prophylactic antibiotics.[1, 6] If epithelial healing does not occur within 2 to 3 days, the frequency of topical steroid can be increased to every half hour. Once healing occurs, topical steroids can be tapered slowly over several months. Such management, especially in the unilateral, benign form, has yielded good results.

Oral pulse therapy (Prednisone 60 to 100 mg daily) can be considered when topical therapy is ineffective after 7 to 10 days or in cases where topical steroids may be contraindicated because of precariously deep ulcer or infiltrate.[9] Topical tetracycline or medroxyprogesterone can be used for anticollagenolytic properties. Therapeutic soft contact lens or patching of the eye may be beneficial at this stage. [1]

2. Conjunctival Resection

If the ulcer progresses despite the steroid regimen, conjunctival resection should be performed.[1, 6] Under topical and subconjunctival anesthesia, the conjunctiva is excised to bare sclera,

extending at least two clock hours to either side of the peripheral ulcer, and about 4 mm posterior to the corneoscleral limbus and parallel to the ulcer.[8] The overhanging lip of ulcerating cornea may also be removed. Postoperatively, a firm pressure dressing should be used. Multiple resections may be needed. It is thought that the conjunctiva adjacent to the ulcer contain inflammatory cells that may produce antibodies against the cornea and cytokines, which amplify the inflammation and recruit additional inflammatory cells.[23]

Cryotherapy of limbal conjunctiva has been advocated by some surgeons and may have a similar effect.[] Conjunctival resection and thermocoagulation have also been found to give some relief at the site of the ulcers, but recurrence can occur at same or other sites (up to 50%).[]

Keratoepithelioplasty has also been performed in patients with Mooren's ulcer.[] Donor corneal lenticles are sutured onto scleral bed after conjunctival excision. The lenticles form a biological barrier between host cornea and the reepithelializing conjunctiva, and the immune components it may carry. Application of isobutyl cyanoacrylate, a tissue adhesive, may work in the same way but perhaps more simply and without the risk the risk of epithelial rejection.[]

3. Immunosuppressive Chemotherapy

Those cases of bilateral or progressive MU that fail therapeutic steroids and conjunctival resection will require systemic cytotoxic chemotherapy to bring a halt to the progressive corneal destruction.[10] At the Immunology and Uveitis Service at the Massachusetts Eye and Ear Infirmary, we believe that the evidence for the efficacy of systemic immunosuppressive chemotherapy for progressive bilateral MU is quite strong, and that such treatment should be employed sooner rather than later in the care of such patients, before the corneal destruction has become too extensive to need for surgery.

The most commonly used agents are :

-Cyclophosphamide (2 mg/kg/day): degree of fall in WBC is the most reliable indicator of immunosuppression produced by cyclophosphamide

-Methotrexate (7.5 to 15 mg once weekly)

-Azathioprine (2 mg/kg/day)

More recently, oral Cyclosporin A (3-4 mg/kg/day) has been successfully used to treat a case of bilateral MU unresponsive to local therapy with topical corticosteroids, silver nitrate, and conjunctival resection, as well as systemic immunosuppression with corticosteroids, cyclophosphamide, and azathioprine.[12] Cyclosporin A works by suppression of the helper T-cell population and stimulation of the depressed population of suppressor and cytotoxic T cells present in patients with MU.[23]

Adverse effects of these cytotoxic and immunosuppressive medications, such as anemia, alopecia, nausea, nephrotoxicity, and hepatotoxicity, are *rare* but *possible*. Therefore, the administering physician must be vigilant about their onset.

Topical Cyclosporin A (0.05%) solution has also been tried with "success" in a number of patients with MU. Local or systemic side effects attributable to topical cyclosporin A were generally not observed.[30]

4. Additional Surgical Procedures

When topical steroids, conjunctival resection, and systemic immunosuppressives have failed in the management of MU, additional surgical procedures may be considered. Superficial lamellar keratectomy has been shown to arrest the inflammatory process and allow healing.[4] Some cases may progress to perforation despite management as just detailed. Small perforations may be treated with application of tissue adhesive and placement of a soft contact lens to provide comfort and to prevent dislodging of the glue. When a perforation is too large for tissue adhesive to seal the leak, some type of patch graft will be necessary, from a small tapered plug of corneal tissue to a penetrating keratoplasty. In case of larger perforations, a partial penetrating keratoplasty may be performed. It should be emphasized that the prognosis of corneal graft in the setting of acute inflammation in patients with MU is very poor.[1, 8]

5. Rehabilitation

Penetrating keratoplasty may be performed once the active ulceration has ceased and the remaining cornea has been completely opacified, even in the face of a thinned and vascularized cornea.[6, 8] In these instances, a 13-mm tectonic corneal graft is first sutured in place with interrupted 10-0 nylon or prolene sutures with the recipient bite extending into the sclera so that the suture will not pull through the thin host cornea and then a 7.5 or 8.0-mm therapeutic graft is placed. In the absence of donor corneas, free lamellar scleral autograft can be used to restore corneal defect, followed by penetrating keratoplasty later.[26]

Because of the immune system's remarkable memory, surgical attempts at rehabilitation in MU should be done only with concurrent immunosuppression, even when the active disease has been arrested, because attempts at penetrating keratoplasty often are associated with recurrence and graft failure. Some authors believe that the risks of recurrence is so great that patients are best served not by any intervention but by maintaining the current status, i.e. the vision provided by their own thinned, scarred cornea.

VIII. Summary

Mooren's Ulcer is a distinct entity , but it is a *diagnosis of exclusion.* Other causes of peripheral ulcerative keratitis should be ruled out, such as infections, collagen vascular diseases, and degenerative processes. Precise pathophysiology of Mooren's Ulcer remains uncertain. Advances have been made in its step-approach management; however, significant percentage of cases remain refractory to available therapies, and result in severe visual morbidity.

REFERENCES

1. Chow C, Foster CS. Mooren's Ulcer. Int Ophthalmol Clin, 36:1-13, 1996.

2. Bowman W. Case 12, p 112 in The parts concerned in the operations of the eye (1849), cited by Nettleship, E: Chronic Serpiginous Ulcer of the Cornea (Mooren's Ulcer). Trans Ophthamol Soc UK 22:103-104, 1902.
3. Brown S. Mooren's Ulcer: Histopathology and proteolytic enzymes of adjacent conjunctiva. Br J Ophthalmol, 59:670-674, 1975.
4. Brown S, Mondino B. Penetrating keratoplasty in Mooren's Ulcer. Am J Ophthalmol, 89:255-258, 1980.
5. Brown SI, Mondino BJ. Therapy of Mooren's Ulcer. Am J Ophthalmol 98:1-6, 1984.
6. Dinzis P, Mondino B. Management of non-infectious corneal ulcers. Surv Ophthalmol, 32:94-110, 1987.
7. Foster CS, Kenyon K, Greiner G, et al. The immunopathology of Mooren's Ulcer. Am J Ophthalmol, 88:149-159, 1979.

8. Foster CS. Immunologic disorders of the conjunctiva, cornea, and sclera. In: Albert DA and Jakobiec FA, eds. Principles and Practice of Ophthalmology, pp 200-203. Saunders, Philadelphia, 1994

9. Frangieh T and Kenyon K. Mooren's Ulcer. In: Brightbill FS, ed. Corneal Surgery: Theory, Technique, and Tissue, Second Edition, pp 328-335. Mosby, Saint Louis, 1993.

10. Genvert G, Sakauye C, Arentsen J. Treatment of marginal corneal ulcer with cryotherapy and conjunctival recession or resection. Cornea, 3: 256-261, 1984-1985.

11. Gottsch J, Liu S, Stark W. Mooren's Ulcer and evidence of stromal graft rejection after penetrating keratoplasty. Am J Ophthalmol 113:412-417, 1992.

12. Hill J, Potter P. Treatment of Mooren's Ulcer with cyclosporine A: Report of three cases. Br J Ophthalmol, 71:11-15, 1987.

13. Kinoshuita S, Ohashi Y, Ohji M, et al. Long-term results of keratoepithelioplasty in Mooren's ulcer. Ophthalmology, 98:438-445, 1991.

14. Lewallen S and Courtright P. Problems with current concepts of the epidemiology of Mooren's corneal ulcer. Ann Ophthalmol 22:52-55, 1990.

15. Martin N, Stark W, Maumenee A. Treatment of Mooren's and Mooren's-like ulcer by lamellar keratectomy: Report of six eyes and literature review. Ophthalmic Surg, 18:564-569, 1987.

16. McKenzie H. Disease of the Eye. 1854, p 631.

17. Moazami G, Auran J, Florakis G, et al. Interferon treatment of Mooren's Ulcer associated with hepatitis C. Am J Ophthalmol 119: 365-366, 1995.

18. Mondino BJ, Brown SI, Mondzelewski JP. Peripheral corneal ulcer with herpes zoster ophthalmicus. Am J Ophthalmol 86:611-614, 1978.

19. Mondino B, Brown S, Rabin B. Cellular immunity in Mooren's Ulcer. Am J Ophthalmol, 85:788-791, 1978.

20. Mooren A: Ulcus Rodens. Ophthalmiatrische Beobachtungen. Berlin, AH: 107-110, 1867.

21. Murray P, Rahi A. Pathogenesis of Mooren's Ulcer: Some new concepts. Br J Ophthalmol, 68:182-186, 1984.

22. Robin JB, Dugel R. Immunologic disorders of the cornea and conjunctiva. In: Kaufman HE, Baron BA, McDonald MB, Saltman SR, eds. The Cornea, pp 511-561. Churchill Livingstone, New York, 1988.

23. Sangwan VS, Zafirakis P, Foster CS. Mooren's Ulcer: Current concepts in management. Indian J Ophthalmol, 45: 7-17, 1997

24. Schanzlin, D. Mooren's Ulceration. In: Smolin G, Thoft R, eds. The Cornea, pp 408-414. Little Brown, Boston, 1994.

25. Schapp OL, Feltkemp TE, Breebart AC. Circulating antibodies to corneal tissue in a patient suffering from Mooren's Ulcer (ulcus rodens cornea). Clin Exp Immunol, 5:365-370, 1969.

26. Stilma J. Conjunctival excision or lamellar scleral autograft in 38 Mooren's ulcers from Sierra Leone. Br J Ophthalmol, 67:465-478, 1993.

27. Watson PG. Management of Mooren's Ulceration. Eye, 11: 349-356, 1997.

28. Wilson S, Lee W, Murakami C, et al. Mooren's type Hepatitis C-virus associated corneal ulceration. Ophthalmology, 101: 736-745, 1994.

29. Wood T and Kaufman H. Mooren's Ulcer. Am J Ophthalmol 71:417-422, 1971.

30. Zhao J, Jin X. Immunological analysis and treatment of Mooren's Ulcer with cyclosporine A applied topically. Cornea, 12: 481-488, 1993.