Clinical characteristics of Mooren's ulcer in South India

Muthaiah Srinivasan, Michael E Zegans, Joseph R Zelefsky, Arunava Kundu, Thomas Lietman, John P Whitcher, Emmett T Cunningham Jr

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See end of article for authors' affiliations

Correspondence to:
Dr ET Cunningham, Jr, West Coast Retina Medical Group, Inc, 185 Berry Street, Lobby 5, Suite 130, San Francisco, California 94107-1739, USA; emmett_cunningham@yahoo.com

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Aim: To describe the clinical characteristics at presentation of a large cohort of patients with Mooren's ulcer in South India.

Methods: The medical records of patients with Mooren's ulcer examined in the cornea clinic at Aravind Eye Hospital Madurai, Tamil Nadu, India, over a 10-year period were reviewed in this retrospective observational case series.

Results: The cohort contained 242 eyes of 166 patients. All patients were from South India, and men outnumbered women by a ratio of 4.7:1. The median and mean ages at presentation were 65 and 61 years, respectively, with a range of 13–95 years. One eye was affected in 90 of 166 (54%) patients. Visual acuity in the affected eye at presentation ranged from 6/6 to light perception, and was 6/12 or better in 34 of 242 (14%) eyes, between 6/12 and 3/60 in 168 (69%) eyes, and worse than 3/60 in 40 (17%) eyes. Partial peripheral corneal ulceration was observed in 222 (92%) eyes, complete peripheral corneal ulceration was observed in 15 (6%) eyes and total corneal ulceration was observed in 5 (2%) eyes. For those 222 eyes with partial peripheral ulceration, 152 (68%) showed temporal involvement, 129 (58%) showed nasal involvement, 116 (52%) showed inferior involvement and 30 (14%) showed superior involvement. Perforation was observed in 26 (11%) eyes, and was more common in eyes with peripheral as compared with total ulceration ($p < 0.001$). Identified risk factors in the cohort included evidence of prior corneal surgery (22%), corneal trauma (17%) and corneal infection (2%).

Conclusions: Mooren's ulcer is a rare and potentially blinding eye condition observed not infrequently in the cornea clinic at Aravind Eye Hospital. Men are affected more often than women and may present with either unilateral or bilateral disease. Perforation is observed in approximately 1 in 10 affected eyes at presentation and occurs most often in the setting of peripheral ulceration. The occurrence of prior corneal surgery, trauma or infection in nearly one third of patients supports theories of exposure to corneal antigen in the pathogenesis of this disorder.

Mooren's ulcer, previously termed rodent or chronic serpiginous ulcer, is an uncommon condition characterised by severe pain, conjunctival and episcleral injection, and peripheral corneal ulceration.^{1–6} Neovascularisation typically extends well into the ulcer bed from the limbus, and the central margin of the ulcer often has an overhanging edge, portions of which may show areas of grey-white opacification. Recurrences and progression are common. Ulceration tends to proceed either circumferentially, leaving a central island of oedematous, opacified cornea, or transversely, relentlessly replacing the corneal stroma with a thin fibrovascular membrane. Corneal perforation is a frequent, and often blinding, complication. The adjacent scleral and underlying Descemet's membrane seems to be largely spared by the inflammatory process.⁶

Since the earliest descriptions of Mooren's ulcer,^{7–10} much of what is known of the demographics, history and clinical presentation of this condition has been gleaned from a relatively limited number of small case series and isolated case reports.^{11–29} Liberal interpretation of these studies has given rise to widely held concepts regarding age, gender and race as predictors of severity and laterality, views that have been questioned in light of the varied composition and small size of these reported cohorts.^{30–31} We present here the demographic, historical and clinical characteristics of a large cohort of patients with Mooren's ulcer seen at Aravind Eye Hospital, Madurai, Tamil Nadu, India.

PATIENTS AND METHODS

Institutional review board approval from the Aravind Eye Hospital and the University of California, San Francisco School

of Medicine, San Francisco, California, USA, was obtained. Mooren's ulcer was defined clinically as acute, painful ulceration of the cornea up to, but not involving, the sclera⁶ in the absence of evidence of current ocular infection or systemic rheumatological diagnoses or symptoms based on history, review of systems and directed laboratory testing.³² In patients with peripheral or partial corneal involvement, characteristic findings included deep vessels extending into the ulcer bed from the limbus, and an overhanging, and often opacified, corneal edge (fig 1A). In some patients, complete peripheral ulceration, leaving only a central island of cornea, had occurred by the time of the first visit (fig 1B). In patients with total corneal involvement, the corneal stroma was replaced by a fibrovascular scar covering an intact Descemet's membrane (fig 1C). We refer to these three patterns of ulceration as partial peripheral, complete peripheral and total corneal ulceration, respectively. Patients with partial peripheral involvement were further classified according to the location of ulcer. The eye was divided into nasal, temporal, superior and inferior quadrants. A quadrant was said to be involved if it contained more than one continuous clock hour of the ulcer.

The medical records of patients seen in the cornea clinic at Aravind Eye Hospital between May 1985 and February 1996, who met the clinical definition of Mooren's ulcer were reviewed retrospectively. Demographic, historical and clinical data were collected from the initial clinic visit. All patients had been examined by a single ophthalmologist (MS).

Statistical significance and p values comparing ratios were determined using the χ^2 test. When the expected number of individuals in each cell was less than five, a two-tailed Fisher

Figure 1 The clinical spectrum of Mooren's ulcer, seen in the cornea clinic at Aravind Eye Hospital. (A) Peripheral or partial Mooren's ulcer showing conjunctival and episcleral injection, ulceration up to, but sparing, the sclera, deep vessels in the ulcer bed, and overhanging and opacified central ulcer margin. There is a small descemetocoele within the ulcer. (B) A total peripheral Mooren's ulcer with a central island of oedematous, opacified cornea. (C) Complete Mooren's ulcer with loss of all stromal tissue, replaced here with a fibrovascular membrane overlying an intact Descemet's membrane.

exact test was used. Statistical significance and *p* values comparing means were determined using a two-tailed *t* test. When the expected number of individuals in each group was <30, a Mann-Whitney *U* test was used.

RESULTS

The records of a total of 242 eyes from 166 patients with Mooren's ulcer were examined. All patients were from South India. The cohort was composed of 137 men and 29 women, a ratio of 4.7:1 (table 1; fig 2). Age at presentation ranged from 13 to 95 years (fig 2). The overall mean and median ages of the cohort were 61 and 65 years, respectively. Men had higher mean (63 vs 50) and median (65 vs 55) ages than women ($p<0.001$).

One eye was affected in 90 of 166 (54%) patients (fig 3). Patients with bilateral ulceration had a mean age of 64 vs 58 years for patients with unilateral involvement ($p<0.02$). Laterality did not differ significantly between men and women (table 1).

Of the total 242 eyes affected, partial peripheral corneal ulceration was observed in 222 (92%) eyes, complete peripheral

corneal ulceration was observed in 15 (6%) eyes and total corneal ulceration was observed in 5 (2%) eyes. For those eyes with partial peripheral ulceration, 152 of 222 (68%) eyes showed temporal involvement, 129 of 222 (58%) eyes showed nasal involvement, 116 of 222 (52%) eyes showed inferior involvement and 30 of 222 (14%) eyes showed superior involvement (fig 4). Overall, inferior involvement was more likely than superior corneal involvement ($p<0.001$), and involvement of the intrapalpebral cornea (temporal and nasal quadrants combined) was more likely than superior and inferior corneal involvement combined ($p<0.001$). Neither pattern nor location of corneal ulceration differed significantly with age or sex (table 1).

Visual acuity at presentation ranged from 6/6 to light perception. Of the 242 affected eyes, vision was 6/12 or better in 35 (14%) eyes, between 6/12 and 3/60 in 168 (69%) eyes and worse than 3/60 in 39 (16%) eyes. These figures were comparable for both men and women, and seemed not to vary significantly with age.

Potential risk factors that were recorded in this cohort included prior corneal surgery (22%), trauma (17%) and infection (2%). Each of the 36 affected eyes with prior ocular surgery had undergone extracapsular cataract extraction after a superior limbal incision. Peripheral corneal ulceration developed in each of these patients, and although 25 of these 36 (69%) eyes showed either intrapalpebral or inferior ulceration, 11 of the 36 (31%) eyes with prior ocular surgery showed ulceration at or contiguous with the prior surgical wound. The rate of superior involvement was higher than expected when compared with 19 of 186 (10%) eyes with superior ulceration but no prior ocular surgery ($p<0.001$). The rates of prior corneal surgery, trauma and infection were comparable for men and women (table 1).

Perforation was observed at presentation in 26 of 242 (11%) affected eyes. Although the absolute number of corneal perforations increased with age (fig 5), the rate of perforation was higher for patients aged <60 years (11 of 41; 27%) than for patients aged ≥ 60 years (12 of 125; 10%; $p=0.03$; fig 6). Perforation occurred in 14 of 222 (6%) eyes with partial peripheral ulceration, in 11 of 15 (73%) eyes with complete peripheral ulceration and in 1 of 5 (20%) eyes with total corneal involvement. This pattern was significantly different from the overall distribution pattern of ulceration found in patients without perforation ($p<0.001$), and was largely due to the high rate of perforation observed in patients with complete peripheral ulceration (fig 7). The rate and pattern of perforation were not significantly different between men and women (table 1). Perforation was not seen more commonly in patients with bilateral involvement.

DISCUSSION

We have presented the clinical characteristics of 242 eyes of 166 patients with Mooren's ulcer seen over nearly 10 years at Aravind Eye Hospital in Madurai, South India. All patients were from the state of Tamil Nadu in South India. Men outnumbered women by nearly 5 to 1, and were, on average, 10–15 years older than women at presentation. Although Mooren's ulcer occurred in all age groups, the vast majority of cases presented between 40 and 70 years of age. Unilateral involvement was slightly more common overall, although bilateral cases increased slightly with age. Partial peripheral corneal ulceration was observed in over 90% of affected eyes. The intrapalpebral limbus was involved most often, followed by the inferior and then the superior limbus. Perforation was present at presentation in about 1 in 10 cases, and was most common in eyes with partial or complete peripheral ulceration as compared with total ulceration, and affected a higher

Table 1 Characteristics of Mooren's ulcer by gender for the total cohort of 166 patients

	Men (n = 137; 203 eyes)	Women (n = 29; 39 eyes)	p Value*
Age (years)			
Median	65	55	<0.001 (M-W)
Mean	63	50	<0.001 (t test)
Range	13–95	20–78	
Laterality (%)			
Unilateral	72/137, 52	19/29, 66	0.18 (χ^2 test)
Bilateral	66/137, 48	10/29, 34	Same
Pattern of ulceration (%)			
Partial peripheral	185/203, 91	37/39, 95	<0.001
Complete peripheral	14/203, 2	1/39, 2.5	($2 \times 3 \chi^2$ test)
Total	4/203, 2	1/39, 2.5	
Perforations (%)	22/203, 11	4/39, 10	0.99 (χ^2 test)
Risk factors (%)			
Surgery	33/137, 24	3/29, 10	0.07 (χ^2 test)
Trauma	24/137, 18	4/29, 14	0.37 (χ^2 test)
Infection	4/137, 3	0/29, 0	0.35 (χ^2 test)
None	80/137, 58	22/29, 76	0.08 (χ^2 test)

M-W, Mann-Whitney U test.

*Not corrected for multiple testing.

Figure 2 Frequency of Mooren's ulcer for men and women by age at presentation. Men outnumbered women by a ratio of 4.7:1. Both the mean (50 vs 63 years; $p < 0.001$) and median (55 vs 65 years) ages at presentation tended to be lower for women than for men.

proportion of patients aged <60 years. A history of corneal surgery (22%), trauma (17%) and infection (2%) was common, suggesting that prior disruption of the corneal tissue may play a role in the pathogenesis of Mooren's ulcer. Previous cataract surgery was associated with an increased risk of partial peripheral ulceration affecting the superior limbus at or contiguous with the site of the cataract incision, although most patients with Mooren's ulcer who had had cataract

extraction presented with ulceration away from the surgical wound.

Previously published descriptions of clinic-based cohorts of patients with Mooren's ulcer have provided conflicting data on the importance of age, gender and race as predictors of both laterality and severity. Kietzman,²⁸ for example, described 37 patients with Mooren's ulcer seen in Nigeria between 1963 and 1966. He suggested that the disease in this region most often

Figure 3 Frequency of Mooren's ulcer for patients with bilateral and unilateral involvement by age at presentation. One eye was affected in 90 of 166 (54%) patients. Patients with bilateral ulceration (mean age 63.5 years) tended to be older than patients with unilateral involvement (mean age 58 years; $p < 0.02$).

Figure 4 Location of Mooren's ulcer by quadrant involved at presentation. Involvement of multiple quadrants was counted for each quadrant involved.

affected men in their 20s and 30s, and that a subset of patients showed rapid progression with perforation occurring in more than one-third of patients. Wood and Kaufman¹⁹ reported nine additional patients from West Africa in 1971, emphasising that Mooren's ulceration is more common in men, tends to occur in the third or fourth decades of life, and may be more often bilateral and with a higher tendency to perforate in younger patients. These findings led Wood and Kaufman to suggest that there were two groups of patients with Mooren's ulcer in Africa: an older group that tends to develop unilateral disease which responds well to treatment and a younger group that is often bilateral, tends to respond poorly to treatment and is often associated with perforation. Later reports by Kabuni and Maertens²² of 16 patients from the Republic of Zaire, by Trojan²⁹ of 34 patients from Togo, by Majekodunmi²⁵ of 5 patients from Nigeria and by Stilma³⁰ of 30 patients from Sierra Leone were interpreted as supporting these notions. However, there seems to be a different clinical picture in South India. Gnanoss,²¹ for example, described 10 patients from South India with Mooren's ulcer in 1974. All 10 patients were men aged between 50 and 70 years; only 2 of 10 cases showed progression to complete peripheral ulceration, and none of the patients showed perforation. Zegans *et al*³³ also described a cohort of 21 patients with Mooren's ulcer from South India, in which 76% were men, the median age was 55 years, 63% were unilateral and 26% showed perforation. Zelfsky *et al*³⁴ conducted a prospective study of 15 patients with Mooren's ulcer in South India that confirmed a statistically significant association between hookworm infection and Mooren's ulcer formation. The mean age in that group of patients was 50 years, and 70% of the subjects were men. Chen *et al*³² presented their experience with 550

Figure 6 Proportion of Mooren's ulcer with and without perforation by age. Perforation tended to be more common in patients aged <60 years (11 of 41; 27%) than in patients aged ≥60 years (12 of 125; 10%; $p=0.03$).

patients seen over 36 years in Guangzhou, China. In this large cohort, Mooren's ulcer was slightly more common in men, was bilateral approximately one-third of the time and was associated with perforation in about 13% of cases. These authors also noted that two-thirds of patients with bilateral disease were aged >35 years, and that about 43% of perforations occurred in patients aged <35 years. Taken together, it seems that the clinical characteristics of Mooren's ulcer vary considerably from region to region, and that age, gender and race cannot be used as universal predictors of severity or natural history, at least not in Chinese or Asian Indian patients.

Considerable evidence now supports the notion that Mooren's ulcer is an immune-mediated disorder. Pathological examination of a number of conjunctival and corneal specimens taken from patients with active Mooren's ulcer have shown large numbers of infiltrating lymphocytes, plasma cells and neutrophils.³⁵⁻³⁶ Immune complexes have also been demonstrated systemically,³⁷⁻³⁸ an observation that has been strengthened by descriptions of serum antibodies directed against the corneal epithelial and stromal antigens in patients with Mooren's ulcer.³⁹ Moreover, patients with severe Mooren's ulcer have been shown to respond to systemic corticosteroid and non-corticosteroid immunosuppressive treatment.⁴⁰ Taken together, these observations have led to the now widely held theory that Mooren's ulcer is an autoimmune disorder directed against the cornea.⁴¹

The cascade of events in the pathogenesis of Mooren's ulcer has yet to be identified fully. Many studies have implicated

Figure 5 Frequency and proportion of Mooren's ulcer with and without perforation by age at presentation. Perforation was observed in 26 of 242 (11%) affected eyes at presentation. Although the distribution of the number of perforations by age was skewed to the left, and grossly similar to the distribution of the number of patients by age, the distribution of the rate of perforations by age was skewed to the right, such that patients with perforation (mean age 62 years) tended to be younger than patients without perforation (mean age 54 years; $p=0.05$).

Figure 7 Proportion of Mooren's ulcer with partial peripheral, total peripheral and complete ulceration for patients with and without perforation at presentation. Patients with perforation were more likely to have had peripheral ulceration as compared with complete corneal ulceration at presentation ($p < 0.001$).

corneal trauma and surgery as risk factors for Mooren's ulcer⁴²⁻⁴⁷; however, it is noteworthy that well over one-third of South Indian patients with Mooren's ulcer provide a history of corneal surgery, trauma or infection and that this rate significantly exceeds the rate reported by control groups.⁶ The increased risk of superior limbal ulceration in our patients who underwent prior extracapsular cataract extraction, along with previous reports of Mooren's ulcer after corneal surgery, would also seem to support this theory. Similarly, coexisting intestinal hookworm infestation, as first noted in patients from Africa^{17 26 30 48} and now confirmed in patients from South India,³⁴ also seems to play a role in the pathogenesis of this disorder. This is perhaps not surprising since parasites are well known to trigger an autoimmune response in disorders such as schistosomiasis and Chagas disease.⁴⁹⁻⁵¹

Although hookworm infection and corneal trauma are seemingly unique and distinct entities, their contributions to the pathogenesis of Mooren's ulcer may, in fact, be complementary. Recent studies have identified calgranulin C, a protein both involved in the immune response to parasitic infections and which also happens to be found in the corneal stroma as perhaps central to the pathogenesis of Mooren's ulcer.^{52 53} Specifically, it has been suggested that Mooren's ulcer might represent an autoimmune response to corneal calgranulin C triggered by an aberrant host response normally concealed corneal calgranulin C, either by exposing corneal calgranulin C through surgery, trauma or infection, or through intestinal infestation by hookworm.⁵⁴ It is unclear why men develop Mooren's ulcer more often than women in South India, although epidemiological studies have suggested that the rate of intestinal hookworm infestation,⁵⁵ ocular trauma⁵⁶ and cataract surgery⁵⁷ are all greater for men than for women in this region. Such data most likely do not reflect limited access to eye care for women in South India, as the number of outpatient visits at Aravind Eye Hospital has historically been distributed more or less equally among men and women.

In summary, Mooren's ulcer is a painful and potentially blinding eye condition observed in the cornea clinic at Aravind Eye Hospital. In South India, men are affected much more frequently than women, usually later in life. Perforation is observed in approximately 1 in 10 affected eyes at presentation, and occurs most commonly in the setting of peripheral ulceration. The occurrence of prior corneal surgery, trauma or infection in over one-third of patients supports theories of exposure to corneal antigens in the early pathogenesis of this disorder.

Authors' affiliations

Muthaiah Srinivasan, Arunava Kundu, Aravind Eye Hospital & Postgraduate Institute of Ophthalmology, Madurai, Tamil Nadu, India
Michael E Zegans*, **Thomas Lietman**, **John P Whitcher**, **Emmett T Cunningham Jr†**, Department of Ophthalmology, The Francis I Proctor Foundation, University of California, San Francisco School of Medicine, San Francisco, California, USA
Joseph R Zelefsky, Department of Ophthalmology, New York University School of Medicine, New York, New York, USA

*Current address: Section of Ophthalmology, Department of Surgery, Dartmouth Medical School, Lebanon, New Hampshire, USA.

†Current address: Departments of Ophthalmology, California Pacific Medical Center, San Francisco, California, and Stanford University, Stanford, California, USA.

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