Case Report

Corneal Melt as the Initial Presentation of Primary Sjögren's Syndrome

FREDERICK B. VIVINO, PIERRE MINERVA, CHOU H. HUANG, and STEPHEN E. ORLIN

ABSTRACT. Corneal melting is a rare complication of Sjögren's syndrome (SS). Previously reported cases of corneal ulceration occurred in patients with established SS, usually secondary to RA. We describe the first case of corneal ulceration with stromal melting as the initial presentation of primary SS. A 79-year-old man without prior sicca symptoms developed a large sterile corneal ulcer that required extensive treatment over several months with ocular lubricants, systemic immunosuppressives, and surgical repair. Evaluation for an underlying connective tissue disease revealed positive antinuclear antibodies (1:640 speckled) and anti-SSA antibody. A lip biopsy established the diagnosis of SS. Ulceration later occurred in the contralateral eye. Two years after the last corneal ulcer and no longer taking prednisone, the patient's ocular disease remained quiescent taking azathioprine 175 mg and hydroxychloroquine 400 mg daily. This case highlights the potential for primary SS to present with serious ocular complications despite lack of a priori sicca symptoms, as well as the importance of immunosuppressive therapy in the treatment of this complication. (J Rheumatol 2001;28:379–82)

Key Indexing Terms:
SJÖGREN'S SYNDROME CORNEAL ULCER

Sjögren's syndrome (SS) is a chronic inflammatory disorder of exocrine glands characterized by the triad of keratoconjunctivitis sicca (KCS), xerostomia, and arthritis[1]. The disorder may be primary, as in our case, or secondary, most commonly associated with rheumatoid arthritis (RA). The many ocular complications of KCS including corneal ulceration with melting and perforation have been well documented[2]. In prior case reports, however, corneal melting occurred in patients with an established diagnosis of SS, usually secondary to RA[3-5]. We describe a case of repeated corneal melting and ulceration as the initial presentation of primary SS. Surgical patch grafting and immunosuppressive agents ultimately healed the corneal ulcers.

CASE REPORT

A 79-year-old man with hypertension, coronary artery disease, and osteoarthritis of the hip presented with a 5 day history of right eye pain without prior KCS or xerostomia. His only medications were diclofenac, nifedipine, and nadolol. Ophthalmologic examination revealed a large corneal ulcer with stromal melting and perforation in the inferior limbal area and moderate conjunctival injection. The iris plugged the wound inferiorly (Figure 1). Fluorescein staining showed severe dryness with epithelial defects. His visual acuity was limited to finger counting OD and was 20/30 OS. The ulcer progressed, with further stromal thinning and leakage of aqueous humor 2 days later. Consequently, he was admitted to the hospital for repair of the right corneal perforation with a therapeutic contact lens applied over a tissue adhesive. Evaluation for an underlying connective tissue disease (CTD) revealed a positive fluorescent antinuclear antibody test at a titer of 1:640 with a speckled pattern, as well as a positive SSA antibody. Anti-SSB, anti-Sm, anti-DNA, anti-RNP antibodies, complements, and rheumatoid factor were normal or nonreactive. Erythrocyte sedimentation rate was 32 mm/h. The remainder of the laboratory results were normal.

About 3 weeks later, the contact lens had fallen off, and the cornea melted further in the same area as the original ulceration with even more stromal loss than before the gluing. An emergent corneal transplant, tarsorrhaphy, and punctal occlusion were performed. In addition, immunosuppressive therapy was begun with 100 mg prednisone daily. Within 2 weeks, however, that same patch graft melted. Histological examination revealed marked loss of stromal tissue with scattered acute and chronic inflammatory cells (Figure 2). After oral azathioprine 50 mg daily was started, a second patch corneal transplant finally succeeded (Figure 3). Over the ensuing 4 months, prednisone dose was tapered while the dose of azathioprine was increased to 100 mg daily. The ocular symptoms and visual acuity improved to 20/60 OD.

During this interval, the patient noted xerophthalmia and xerostomia. A Tc-99m pertechnetate salivary scintigraphic scan and measurement of whole mouth unstimulated salivary flow (0.375 ml/min) were normal. A labial minor salivary gland biopsy confirmed the diagnosis of SS and revealed multifocal lymphocytic sialadenitis and fibrosis with a focus score of 7 per 4 mm^2.

The next 5 months were uneventful while treatment comprised azathioprine 75 mg daily and ocular lubricants. Then the patient suddenly developed decreased visual acuity OS 20/200. Examination with fluorescein staining showed 2 paracentral corneal ulcerations and KCS. Consequently, pressure patching and permanent punctal occlusion were performed, and prednisone restarted at 60 mg daily. The corneal ulcers gradually improved. The right eye had demonstrated no active disease over one year post-transplantation when, during prednisone taper, inflammatory keratitis associated

From the College of Medicine, Thomas Jefferson University; Fox Chase Cancer Center; and the Scheie Eye Institute, Philadelphia, Pennsylvania, USA.

F.B. Vivino, MD, Jefferson Medical College, Thomas Jefferson University; P. Minerva, MD, Fox Chase Cancer Center; C.H. Huang, MD; S.E. Orlin, MD, Scheie Eye Institute.

Address reprint requests to Dr. F.B. Vivino, Thomas Jefferson University, 1015 Walnut Street, Curtis Building, Room 613, Philadelphia, PA 19107.

Submitted May 10, 2000 revision accepted August 14, 2000.

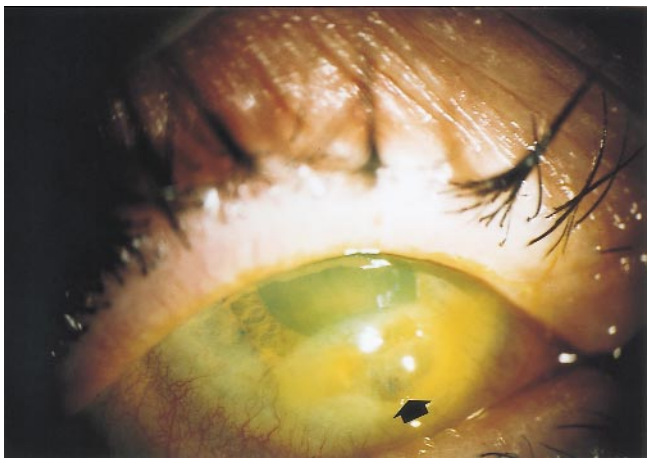

Figure 1. Slit lamp photograph showing marked inferior corneal thinning and ulceration OD with iris tissue plugging corneal perforation (arrow).

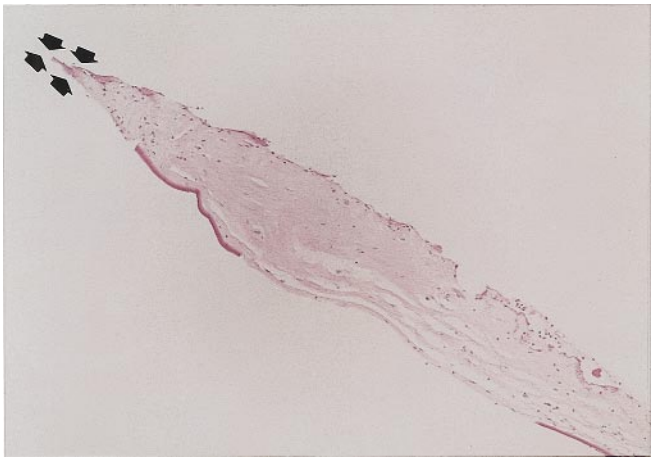

Figure 2. Photomicrograph of corneal specimen showing marked stromal melting and site of perforation (arrows). Paucity of inflammatory cells notable.

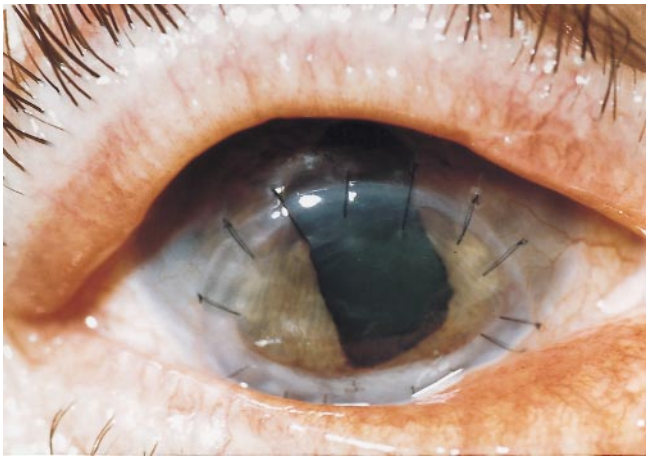

Figure 3. Photograph shows clear patch corneal transplant.

with stromal thinning developed around a suture abscess. The cornea eventually healed after treatment with increased doses of both prednisone and azathioprine (125 mg daily), as well as antibiotic ophthalmic drops. Fifteen months post-corneal transplantation, he developed polyarthritis involving the wrists, metacarpophalangeal joints, and knees bilaterally, for which hydroxychloroquine was added. Radiographs showed no erosions or other features of RA. Oral steroids were tapered, then discontinued.

Two and a half years after the second patch graft in the right eye, the patient developed further sterile ulceration and stromal melting within the patch. This healed with additional ocular lubrication and increased doses of azathioprine. A few months later, following temporary discontinuation of azathioprine for leukopenia, his left cornea melted and perforated, necessitating a corneal transplant OS. Azathioprine and high dose prednisone were restarted.

Two years after the last corneal perforation, no longer taking prednisone, the ocular, oral, and articular symptoms remained quiescent with azathioprine 175 mg and hydroxychloroquine 400 mg daily. He died of pneumonia while immunosuppressive therapy was being tapered.

DISCUSSION

SS is a chronic autoimmune rheumatic disorder that typically affects middle aged white women, and is characterized by lymphocyte mediated destruction of the exocrine glands and other body tissues. Xerophthalmia and xerostomia are the most common presenting symptoms. Occasionally, however, the extraglandular complications of SS including joint, skin, lung, kidney, and nervous system involvement may be the presenting manifestations[6,7]. Despite the many atypical features of this case, our patient met the modified European criteria for the diagnosis of SS[8] and demonstrated xerophthalmia, xerostomia, anti-SSA positivity, objective KCS, and focal lymphocyte sialadenitis during an extended period of followup.

KCS, as originally described, is considered to be present when diminished tear secretion and a punctate or filamentary keratitis coexist. The ocular complications of SS may be associated with blepharitis, infections (often asymptomatic), symblepharon with secondary exposure keratitis, pannus formation, marginal corneal melting, and, finally, corneal ulceration with perforation. The latter problem may be further complicated by uveitis, cataracts, glaucoma, and loss of vision, and requires immediate ophthalmologic attention[9].

Corneal ulcers in SS can be unilateral or bilateral, and may occur centrally, paracentrally, or marginally[10-16]. They typically develop in secondary SS with established KCS and xerostomia. When an underlying connective tissue disorder has not yet been diagnosed, the etiology of a corneal ulcer obviously proves more elusive. Infection must always be excluded initially by culturing for possible pathogens (*Staphylococcus aureus*, *Streptococcus*, *Pseudomonas*, *Enterobacter*). Other causes of corneal ulceration include nonbacterial infections, traumatic or surgical injuries, granulomatous disease, vasculitis, and neurologic and primary skin disorders[10] (Table 1).

The xerostomia and xerophthalmia of SS result from progressive infiltration of lacrimal and salivary glands by

Table 1. Differential diagnosis of a corneal ulcer*.

Infectious	**Postsurgical**	**Immunologic**	**Neurologic**
Bacterial	Delayed epithelial healing	Rheumatoid arthritis	Herpes zoster ophthalmica
Fungal	Homograft reaction	Sjögren's syndrome	Diabetes mellitus
Herpes simplex	Cataract surgery	Systemic lupus erythematosus	Fifth nerve palsy
Amebic		Wegener's granulomatosis	Seventh nerve palsy
		Churg-Strauss syndrome	
Dermatologic	**Traumatic**	Polyarteritis nodosa	**Others**
Ocular pemphigoid	Chemical injury	Mooren's ulcer	Acute leukemia
Stevens-Johnson	Thermal burns		Cutaneous porphyria
Rosacea		**Allergic**	Gold toxicity
Lylles disease		Staphylococcal hypersensitivity	Terrien degeneration
		marginal ulcer	
		Vernal conjunctivitis	

* Modified from Kenyon[10].

plasma cells and lymphocytes, predominantly CD4+ cells. The pathogenesis of corneal ulcers in SS is less well understood. Disruption of the normal lacrimal secretory function in SS results in epithelial breakdown of the ocular surface. Persistent epithelial defects may stimulate infiltration of the corneal stroma by inflammatory cells and cause lysosomal enzymatic degradation of collagen and ground substance by collagenase and other proteases[10]. Stimulation of collagenase production by corneal fibroblasts or stromal keratocytes may further contribute to stromal degradation[12]. In patients with RA, an immune mediated mechanism plays a prominent role in the development of sterile corneal ulcers[18].

Controversy exists regarding the optimal treatment of sterile corneal ulceration in SS. Treatment goals generally include exclusion of infection, closure of the epithelial defect, limitation of further ulceration, and tectonic support of any stromal melting. Krachmer and Laibson reported 6 patients with RA and KCS who developed severe corneal thinning complicated by perforation or descemetocele formation[4]. Each case was associated with the prior use of topical steroid–antibiotic combinations prescribed for external ocular inflammation. The major treatment was penetrating keratoplasty. The authors cautioned against the use of topical steroids in SS patients with corneal thinning and postulated that local steroids may inhibit corneal repair by reducing fibroblast synthetic activity or by stimulating collagenase production.

Pfister and Murphy reported on 18 eyes with corneal ulceration and perforation associated with SS[3]. Half of these eyes had received prior topical corticosteroid treatment. Based on their experience, these authors also discouraged the use of topical steroids for patients with SS. Their recommended treatment included 3 essential elements: artificial tears, prophylactic antibiotics, and punctal occlusion. In addition, the authors advocated the use of soft contact lenses for epithelial defects, ulcerations, and small to intermediate perforations. Contact lens failures and larger perforations were treated with lamellar patch graft or penetrating keratoplasty.

Kervick, *et al* described 6 patients with RA complicated by paracentral perforating corneal ulcers[13]. All the patients had secondary SS. The initial management of these patients was based on the recommendations of Pfister and Murphy noted above. Regardless of initial treatment, all developed recurrent corneal ulcers. Two of the 6 patients were treated with tissue adhesive, bandage contact lens, punctal occlusion, and ocular lubricants, but no immunosuppressives. The other 4 patients underwent either lamellar or penetrating keratoplasty along with systemic immunosuppressive therapy (either oral methotrexate, oral or intravenous cyclophosphamide, or oral azathioprine), but ultimately all developed postoperative perforation of the donor tissue and recurrent keratolysis. Five of the 8 eyes with recurrent corneal ulcers were then treated with topical cyclosporine, which resulted in prompt control of keratolysis and rapid re-epithelialization of the ulcer. The authors therefore suggested that the use of topical cyclosporine was superior to treatment with systemic immunosuppressives. In their experience, immunosuppressive therapy provided better healing of peripheral rather than paracentral corneal ulcers in patients with RA.

In a more recent series of 29 patients (32 eyes) with RA complicated by corneal perforations, Bernauer, *et al* examined the relative success of available surgical options and the benefits of immunosuppressives with respect to graft survival[14]. In contrast to our case, most of their patients had SS secondary to longstanding RA complicated by KCS. Evaluation revealed pure necrotizing keratitis (n = 5), necrotizing keratitis with moderate to severe KCS (n = 15), or pure KCS (n = 12). Primary corneal repair was carried out with either tissue adhesive application, lamellar keratoplasty, or penetrating keratoplasty. In contrast to prior reports, patients also routinely received topical steroids and 0.5% chloramphenicol postoperatively for a minimum of 6 to 8 weeks. Other ophthalmologic procedures including

punctal occlusion were performed as needed. Seventy percent of eyes with necrotizing keratitis (with or without KCS) and 33% of eyes with KCS alone failed primary repair. Causes included recurrent melting at the graft-host junction, graft rejection, or infection. Many patients also received concurrent treatment with a variety of different immunosuppressive regimens including prednisone alone (n = 8), prednisone and cyclophosphamide (n = 10), prednisone with cyclosporine (n = 3), prednisone and methotrexate (n = 2), prednisone, methotrexate and cyclosporine (n = 1), and prednisone with azathioprine (n = 1). The data did not support superior efficacy of one immunosuppressive agent over another. However, the authors concluded that immunosuppression significantly improved the survival of first penetrating grafts (42% graft survival after one year versus 11% without immunosuppression; p = 0.02). Results of the study did not allow comment on the advantage of lamellar over penetrating corneal grafts. The authors also recommended delaying graft surgery, when possible, for 6 weeks with use of a tissue adhesive to allow time for adequate preoperative immunosuppression. In addition, as discussed, they further emphasized the importance of aggressively treating the KCS with copious tear substitutes and punctal occlusion to provide essential protection against an unstable corneal epithelium. Ocular surface moisture can also be maintained through either temporary or permanent tarsorrhaphy, which diminishes tear evaporation[12].

As apparent in our experience and others'[12], corneal melting may occur at any point during the patient's clinical course and does not always correlate with the activity of the CTD. Our patient actually developed inflammatory polyarthritis as his ocular surface disease became quiescent.

Although corneal perforation most commonly develops in RA patients with secondary SS, we describe this complication as the presenting manifestation of primary SS. Followup studies over a 4 year period revealed no evidence of any other CTD. Infection may cause or exacerbate corneal ulceration at any time and should always be excluded before consideration of treatment with immunosuppressives. In SS, aggressive treatment of dry eyes is also essential to promote corneal repair. A variety of surgical techniques and immunosuppressive regimens are available. Ultimately, choice of therapy will depend mostly on the clinical experience of the ophthalmologist and consulting rheumatologist.

REFERENCES

1. Sjogren J. Zur Kenntnis der Keratoconjunctivits sicca (Keratitis filiformis bei Hypunfunktion der Tranendrusen). Acta Ophthalmol 1933;11:1.
2. Brown SI, Grayson M. Marginal furrows: a characteristic lesion of rheumatoid arthritis. Arch Ophthalmol 1968;79:563-7.
3. Pfister RR, Murphy GE. Corneal ulceration and perforation associated with Sjögren's syndrome. Arch Ophthalmol 1980; 98:89-94.
4. Krachmer JH, Laibson PR. Corneal thinning and perforation in Sjögren's syndrome. Am J Ophthalmol 1974;78:917-20.
5. Gudas PP Jr, Altman B, Nicholson DH, Green WR. Corneal perforations in Sjögren's syndrome. Arch Ophthalmol 1973; 90:470-2.
6. Vivino FB, Katz WA. Sjogren's syndrome: Clinical picture and diagnostic tests. J Musculoskel Med 1995;12:40-52.
7. Vivino FB. Diagnosis and treatment of Sjogren's syndrome. The Female Patient 1999;24:65-70.
8. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. Ann Rheum Dis 1996;55:116-21.
9. Whaley K, Alspaugh MA. Sjögren's syndrome. In: Kelley WN, editor. Textbook of rheumatology. 3rd ed. Philadelphia: W.B. Saunders; 1989:999-1019.
10. Kenyon KR, Roberts CW. Noninfected corneal ulcers. Int Ophthalmol Clin 1984;24:179-97.
11. Gold DH. Ocular manifestations of connective tissue disease (collagen diseases). 11th ed. Philadelphia: Harper and Row; 1987:1-30.
12. Colon LE, Enzenauer RJ. Corneal thinning as the sole manifestation of active undifferentiated connective tissue disease. South J Med 1990;83:48-50.
13. Kervick GN, Pflugfelder SC, Haimovici R, et al. Paracentral rheumatoid corneal ulceration: clinical features and cyclosporine therapy. Ophthalmology 1992;99:80-8.
14. Bernauer W, Watson P. The management of corneal perforations associated with rheumatoid arthritis: an analysis of 32 eyes. Ophthalmology 1995;102:1325-37.
15. Petroutsos G, Drosos A, Psilas K. Repeated melting of corneal grafts in a patient with rheumatoid arthritis and SS. Eur J Ophthalmol 1992;2:36-8.
16. Leibowitz HM, Moore TE Jr. Keratoplasty. In: Leibowitz HM, Waring GO, editors. Corneal disorders: clinical diagnosis and management, 2nd ed. Philadelphia: W.B. Saunders; 1998:489-500; 842-69.
17. Berman M, Leary R, Gage J. Evidence for a role of the plasminogen activator-plasmin system in corneal ulceration. Invest Ophthalmol Vis Sci 1980;19:1204-21.
18. Michels M, Cobo M, Caldwell D, et al. Rheumatoid arthritis and sterile corneal ulceration: Analysis of tissue immune effector cells and ocular epithelial antigens using monoclonal antibodies. Arthritis Rheum 1984;27:606-14.