Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Recurrent Corneal Perforation and Acute Calcareous Corneal Degeneration in Chronic Graft-Versus-Host Disease

Po-Ting Yeh,1,2 Yu-Chih Hou,1 Wei-Chou Lin,3 I-Jong Wang,1 Fung-Rong Hu1 *

Keratoconjunctivitis sicca (KCS) is a common complication of graft-versus-host disease (GVHD), and may lead to corneal epithelial defect and melting. In contrast, recurrent corneal calcareous degeneration and perforation is rare. A 46-year-old woman developed chronic GVHD after bone marrow transplantation for aplastic anemia. Severe KCS with corneal melting and calcium deposits were noted in the left eye. Penetrating keratoplasty was performed because of corneal perforation, but poor re-epithelialization and calcium deposition recurred. Lamellar keratectomy and amniotic membrane transplantation (AMT) were performed, but acute calcareous degeneration developed with subsequent recurrence of corneal perforation. After regraft, AMT and tarsorrhaphy, the corneal graft remained clear for 3 months. However, breakdown of the corneal epithelium occurred 3 weeks after spontaneous separation of tarsorrhaphy. Six months later, corneal perforation recurred again along with exacerbation of GVHD. Re-graft was performed, but the patient refused tarsorrhaphy and AMT. Poor re-epithelialization persisted after regraft. Corneal melting with impending corneal perforation ensued. Further corneal surgery was refused and the patient chose to undergo evisceration. This case demonstrates that the ocular complications of GVHD may be severe enough to lead to corneal perforation and calcareous degeneration that is recalcitrant to medical and surgical treatment. [J Formos Med Assoc 2006; 105(4):334–339]

Key Words: amniotic membrane transplantation, calcareous degeneration, graft-versus-host disease, keratoconjunctivitis sicca, tarsorrhaphy

Graft-versus-host disease (GVHD) is one of the major complications following bone marrow transplantation (BMT), occurring in 50–70% of patients.1,2 Chronic GVHD targets ocular and oral mucosal membranes, skin and the liver.3 The most common complication in the eyes is keratoconjunctivitis sicca (KCS),3 which may lead to corneal epithelial defect and corneal melting due to decreased tear production and altered composition of the tear film.4 In such cases, tear calcium concentration may be elevated, and the subsequent calcium salt will preferably precipitate in the cornea.5 Calcium deposition in the cornea can be classified into one of two types: calcific band keratopathy and calcareous corneal degeneration.5 Both of these findings have been reported in patients with chronic ocular inflammation or dry eye, or following ocular surgical procedures.5,6 In contrast, acute calcareous corneal degeneration has rarely been reported in patients with GVHD.
Here, we report a case of recurrent corneal perforation and calcareous degeneration caused by chronic GVHD.

**Case Report**

A 46-year-old woman developed severe aplastic anemia and received allogenic BMT in July 1996. In the days following the procedure, however, acute GVHD developed, with complications including severe pulmonary edema, systemic bacterial infection, acute hepatitis and jaundice. After intensive medical treatment (cyclosporine 250 mg twice a day for 2 weeks, gradually reduced to 60 mg twice a day for 1.5 months), her systemic condition stabilized. Then, several immunosuppressants were given, including cyclosporine (50–300 mg daily), mycophenolate (250–500 mg daily) and prednisolone (5–40 mg daily), and regularly adjusted by hematologists based on her systemic condition.

Unfortunately, severe KCS, scleroderma-like skin lesions, chronic liver dysfunction and dry mouth were noted, and chronic GVHD was diagnosed 6 months later. Because of progressively blurred vision, she visited our clinic. On initial examination, her vision was OD: 20/30 and OS: counting fingers. The right eye showed mild superficial punctate keratitis, and the left eye was markedly inflamed with a large epithelial defect and severe meibomitis. Schirmer’s test with anesthetics showed 2 mm in the right eye and 0 mm in the left eye. Permanent punctal occlusion was performed on both eyes, and topical 0.32% methylcellulose, 0.1% fluorometholone and artificial tear ointment were applied four times a day, but corneal epithelial defect persisted in the left eye. Despite pressure patching and therapeutic contact lens application several times, corneal melting and calcium deposits were noted in the left eye in April 2001. She was lost to follow-up for 3 months. Examination in July 2001 revealed corneal melting with a large corneal perforation (4–5 mm) in the paracentral area in the left eye with vision of hand motion (Figure 1). Emergency penetrating keratoplasty (PKP) combined with extracapsular cataract extraction were performed, and a posterior chamber intraocular lens was implanted in the left eye. Histologic examination of the removed corneal button revealed absence of epithelium and Bowman’s layer and thin corneal stroma with edematous change and architecture distortion. Most of the calcium was deposited in the deep stroma of the corneal button, with infiltration of predominant lymphocytes and some neutrophils (Figure 2). Postoperatively, the corneal epithelial defect persisted, and calcium deposition developed in October 2001. Lamellar keratectomy and amniotic membrane transplantation (AMT) were later performed, followed by application of topical preservative-free artificial tear every hour, 0.3% ciprofloxacin four times a day, and 0.1% dexamethasone four times a day. Unfortunately, acute calcareous degeneration recurred within 2 days. Afterward, the patient was lost to regular

**Figure 1.** The inflamed left eye shows severe meibomitis, calcium deposits (star) and corneal perforation with iris incarceration in the paracentral area (arrow). Neovascularization was also noted around the whole cornea.

**Figure 2.** Corneal stroma calcification (star) and inflammatory cell infiltration (arrow) with edematous change and architecture distortion (cornea, hematoxylin & eosin, original magnification × 100).
follow-up at our outpatient clinic. Six months later, descemetocele was noted in the left eye, and corneal perforation recurred again in August 2002. The patient underwent regraft, AMT and tarsorrhaphy. The postoperative course was smooth and epithelialization was complete within 1 week. The corneal graft remained clear for 3 months, and the best-corrected vision in her left eye was 20/100 during this period.

Due to spontaneous loosening of tarsorrhaphy, corneal epithelial defects developed within 3 weeks. The patient was not followed up again for 6 months due to her fear of visiting our hospital during the severe acute respiratory syndrome (SARS) outbreak. By the time she returned to our clinic in June 2003, calcium deposition and corneal melting had recurred in the left eye, despite intensive use of artificial tear drops and ointment treatment (Figure 3). Lamellar keratectomy was performed and a therapeutic soft contact lens was applied, but corneal melting continued to progress. At the same time, pulmonary edema with pneumonitis was noted and suspected as a sign of GVHD exacerbation. Intravenous methylprednisolone 40 mg every 12 hours for 7 days was added, together with cyclosporine (25–50 mg daily) and mycophenolate (250–500 mg daily), and her systemic condition stabilized. Regraft was performed again in July 2003 because of corneal perforation. Postoperatively, poor epithelialization was noted under treatment with oral prednisolone 20 mg daily, topical autologous serum, 0.32% methylcellulose and artificial tear ointment four times a day. Vision in the left eye decreased to counting fingers. The patient refused further surgical treatment such as tarsorrhaphy or AMT for cosmetic reasons. Pathologic examination of the removed corneal graft revealed dystrophic calcification with inflammatory cell infiltration and neovascularization in the edematous stroma. In March 2004, corneal perforation and dense corneal infiltration were noted with only light perception vision. She refused to undergo another PKP, but agreed to receive evisceration for the relief of pain in the blind eye.

**Discussion**

GVHD is an immunologic reaction in which donor T-lymphocytes attack host tissues, including skin, the gastrointestinal tract, the liver and the eyes. GVHD can be lethal, and can threaten vision as well. The main ocular symptom of GVHD is secondary KCS, and is a result of pre-transplant regimens such as total body irradiation and/or chemotherapy.3,7 KCS can also result from damage to the immune process in patients with GVHD: the lymphocytes destroy the meibomian glands, the epithelium of conjunctiva and cornea, the goblet cells and the lacrimal glands.8 KCS can induce corneal sequelae consisting of punctate corneal erosion, persistent corneal epithelial defect and sterile or infectious corneal ulcer. In severe KCS, persistent epithelial defect results in corneal stroma melting and perforation. In addition, meibomian gland dysfunction will worsen corneal condition.8

Although ocular surface manifestations of GVHD derive from immunologic reaction, treatment with immunosuppressants are thought to be effective for dry eye and associated eye disease. However, immunosuppressant therapy has not always shown satisfactory effects.9 Only some case reports described a potentially beneficial effect of FK506 plus prednisolone for dry eye in patients with GVHD.9 However, long-term treatment with FK506 plus prednisolone increases the risk of serious infections that can lead to death.9 Further-
more, long-term immunosuppression may also increase the likelihood of leukemic relapse.\textsuperscript{9}

The most common type of corneal calcification is band keratopathy, which is associated with chronic ocular inflammation (particularly in uveitis), altered calcium metabolism and complicated retinal detachment surgery.\textsuperscript{10} The histologic findings of band keratopathy include calcium deposits in Bowman's layer, the basement membrane of the corneal epithelium, and the superficial layer of the stroma.\textsuperscript{11} Another type of corneal calcification is calcareous degeneration, which occurs fairly rapidly in the cornea with persistent corneal epithelial defect, dry eye and inflamed stroma.\textsuperscript{5} Histologic examination shows that calcium salts are deposited as granules in all corneal layers.\textsuperscript{5,6} Corneal calcification has been described as occurring within 3 months in infantile hypercalcemia,\textsuperscript{12} within 8–10 weeks with vitamin D intoxication, within 52 days after acute iridocyclitis,\textsuperscript{13} and within a 24-hour period in a patient with severe dry eye and persistent epithelial defect.\textsuperscript{14} The precipitation of calcium and/or phosphate is influenced by elevation of either the level of calcium or phosphate, pH elevation, or tear concentration by evaporation. As water production decreases (such as in dry eye), calcium will deposit in the palpebral fissure due to the subsequent increase in calcium salt concentration.\textsuperscript{6} The actual mechanism of these two types of calcium deposition is not fully understood. However, acute calcareous degeneration usually occurs in patients with persistent epithelium defect and inflamed stroma, which may change the pH balance and contribute to calcification in the full thickness of the cornea. The occurrence of calcium deposition is more rapid and extensive in acute calcareous degeneration than in band keratopathy, which usually progresses slowly and is relatively superficial. The histopathologic findings in our patient revealed that most of the calcium deposits occurred in the deep stroma of the corneal graft, with severe leukocytic infiltration over a short period of time, which are characteristic findings of calcareous degeneration. There are several ophthalmologic factors predisposing to the development and recurrence of calcium deposition in this case, including dry eye, persistent epithelial defect, meibomian gland dysfunction and chronic conjunctival inflammation. Further, the topical usage of ciprofloxacin may have changed the pH of the cornea and accelerated calcium deposition in this case.\textsuperscript{15,16}

In some patients with compromised ocular surface defenses (including eye lid malfunction, abnormal tear film, trophic ulcer, chronic ocular inflammation, corneal infection), epithelial healing will be delayed, resulting in a persistent epithelial defect and stroma melting.\textsuperscript{4} The amniotic membrane contains several growth factors and cytokines that may decrease inflammatory reaction and suppress lymphocyte reaction. In addition, the amniotic membrane consists of a basement membrane that can facilitate the migration of epithelial cells, reinforce the adhesion of the basal epithelium, promote cell differentiation and prevent cell apoptosis. Previous studies have shown that AMT can be applied in patients with persistent epithelial defects of sterile ulceration and descemetocele formation, as an adjunct to limbal stem cell transplantation, and in patients with chemical and thermal injury to improve epithelialization and wound healing.\textsuperscript{17,18} However, in our patient, AMT \textit{per se} appeared to have limited effect in preventing corneal melting and reducing ocular inflammatory reaction, which may have been caused by other factors, such as severe dry eye, reactivation of chronic GVHD or severe blepharoconjunctivitis. Multilayer AMT may be a good choice to reconstruct the ocular surface in a GVHD patient with tiny corneal perforation.\textsuperscript{19} However, this patient had severe corneal melting with a large perforation. Multilayer AMT and biologic glue would not have enough strength to provide strong tectonic support in such a case.\textsuperscript{19–21} Massive perforations, thus, leave no alternative but corneal grafting to achieve tectonic stability and vision recovery.

Autologous serum provides vitamin A, epidermal growth factor, and transforming growth factor-\(\beta\). It has the elements necessary to equilibrate the ocular surface environment without changing the physiology of normal tear produc-
tion, and does not irritate the eyes. For patients with severe dry eye with no response to conventional treatment, autologous serum tear treatment is a good alternative method. However, autoserum had limited effect on corneal re-epithelialization in this case.

Tarsorrhaphy reduces tear evaporation by decreasing the palpebral fissure width. Ocular movements bring the exposed cornea into contact with the superior and inferior lacrimal strips and help tear film redistribution over the epithelial defects. In addition, reduction in lid movement after tarsorrhaphy decreases possible trauma to the healing epithelium from blinking. A half-open eye allows more oxygen to get to the corneal epithelium than does a patched eye. It also facilitates continuous administration of eye drops and examination of the cornea. Another advantage of tarsorrhaphy is reduced risk of corneal infection with respect to bandage lenses. Complications following tarsorrhaphy include trichiasis, adhesion lids, premature opening, pyogenic granuloma and keloid formation, but all of these conditions are rare and manageable. Patients are often reluctant to undergo this procedure, usually because of cosmetic concerns. In this case, tarsorrhaphy was performed to help stabilize the ocular surface for 3 months. However, breakdown of the corneal epithelium occurred 3 weeks after spontaneous loosening of tarsorrhaphy without relapse of GVHD. This case demonstrates that tarsorrhaphy offers a beneficial treatment modality for the management of persistent epithelial defects in cases of GVHD.

In conclusion, this rare case of chronic GVHD presented with recurrent corneal perforation and calcareous degeneration due to the complications of severe dry eye, meibomian gland dysfunction and reactivation of GVHD. This case illustrates that PKP can save the integrity of the globe in patients with a large corneal perforation. More aggressive treatments, including AMT, tarsorrhaphy, systemic immunosuppressive agents, and topical autologous serum, may help to preserve vision in such intractable cases. Tarsorrhaphy has a role in treating persistent epithelial defects. Close monitoring of the systemic condition and aggressive ocular treatment is very important in patients with chronic GVHD and severe dry eye.

References
1. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974; 18:295–304.
2. Santos GW. Bone marrow transplantation. Adv Intern Med 1979;24:157–82.
3. Arocker-Mettinger E, Skorpik F, Grabner G, et al. Manifestations of graft-versus-host disease following allogenic bone marrow transplantation. Eur J Ophthalmol 1991;1: 28–32.
4. Arffa RC. Tear film abnormalities. In: Craven L, Cox KJ, eds. Grayson’s Diseases of The Cornea, Volume 1, 4th edition. St Louis: Mosby, 1997:355–70.
5. Lavid FJ, Herreras JM, Calonge M, et al. Calcareous corneal degeneration: report of two cases. Cornea 1995;14:97–102.
6. Sharif KW, Casey TA, Casey R, et al. Penetrating keratoplasty for bilateral acute corneal calcification. Cornea 1992;11: 155–62.
7. Ogawa Y, Okamoto S, Wakui M, et al. Dry eye after hematopoietic stem cell transplantation. Br J Ophthalmol 1999;83:1125–30.
8. McCulley JP, Shine WE. The lipid layer of tears: dependent on meibomian gland function. Exp Eye Res 2004;78: 361–5.
9. Ogawa Y, Okamoto S, Kuwana M, et al. Successful treatment of dry eye in two patients with chronic graft-versus-host disease with systemic administration of FK506 and corticosteroids. Cornea 2001;20:430–4.
10. Duffey RJ, LoCascio JA. Calcium deposition in a corneal graft. Cornea 1987;6:212–5.
11. O’Connor R. Calcific band keratopathy. Trans Am Ophthalmol Soc 1972;70:58–81.
12. Kendall AC. Infantile hypercalcinia with keratopathy and sodium depletion. Br Med J 1957;11:682–5.
13. Smiley W, May E, Bywaters E. Ocular presentations of Still’s disease and their treatment. Ann Rheum Dis 1957; 16:371–5.
14. Freddo TF, Leibowitz HM. Bilateral acute corneal calcification. Ophthalmology 1985;92:537–42.
15. Eiferman RA, Snuder JP, Nordquist RE. Ciprofloxacin micro-precipitates and macroprecipitates in the human corneal epithelium. J Cataract Refract Surg 2001;27:1701–2.
16. Castillo A, Castillo JM, Toleldano N, et al. Deposits of topical norfloxacin in the treatment of bacterial keratitis. Cornea 1997;16:420–3.
17. Dua HS, Gomes JA, King AJ, et al. The amniotic membrane
in ophthalmology. *Surv Ophthalmol* 2004;49:51–77.

18. Sippel KC, Ma JK, Foster CS. Amniotic membrane surgery. *Curr Opin Ophthalmol* 2001;12:269–81.

19. Peris-Martinez C, Menezo JL, Diaz-Llopis M, et al. Multilayer amniotic membrane transplantation in severe ocular graft versus host disease. *Eur J Ophthalmol* 2001;11:183–6.

20. Heath JD, Acheson JF, Schulenburg WE. Penetrating keratoplasty in severe ocular graft versus host disease. *Br J Ophthalmol* 1993;77:525–6.

21. Sharma A, Kaur R, Kumar S, et al. Fibrin glue versus N-buty1-2-cyanoacrylate in corneal perforations. *Ophthalmology* 2003;110:291–8.

22. Rocha EM, Pelegrino FS, de Paiva CS, et al. GVHD dry eye treated with autologous serum tears. *Bone Marrow Transplant* 2000;25:1101–3.

23. Cosar CB, Cohen EJ, Rapuano CJ, et al. Tarsorrhaphy: clinical experience from a cornea practice. *Cornea* 2001;20:787–91.