Case Report

Recurrent Corneal Perforation due to Chronic Graft versus Host Disease; a Clinicopathologic Report

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Abstract

Purpose: To describe a case of chronic graft versus host disease (GVHD) leading to severe dry eye and recurrent corneal perforation in both eyes, its stepwise management and histopathological reports.
Case Report: A 22-year-old woman with a history of thalassemia and subsequent high-dose chemotherapy followed by allogeneic bone marrow transplant (BMT) was referred to Farabi Eye Hospital. Despite aggressive medical and surgical intervention, corneal vascularization in her right eye progressed and led to corneal perforation. Cyanoacrylate glue was applied to seal the perforation, however it recurred. Multilayer amniotic membrane transplantation (AMT) was performed to seal the corneal perforation, which was effective for a short period. Subsequently, the corneal perforation recurred and penetrating keratoplasty was performed. After a few months deep vascularization and descemetocele occurred in the fellow left eye and the patient finally underwent therapeutic lamellar keratoplasty.
Conclusion: Patients with GVHD are at risk of severe dry eye and subsequent corneal vascularization. Recurrent and recalcitrant corneal perforation resistant to cyanoacrylate glue and multilayer AMT may occur. Proper systemic and ocular management alongside close collaboration with the hematologist is strongly recommended to control the condition.

Keywords: Corneal Ulcer; Corneal Perforation; Graft-versus-host disease; Dry Eye

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INTRODUCTION

Patients who undergo bone marrow transplantation (BMT) are at risk of developing graft versus host disease (GVHD).[1] GVHD which occurs within the first 100 days of transplantation is termed 'acute' and those developing after 100 days are called 'chronic'. Of patients with chronic GVHD, 60 to 90% have ocular involvement. The most frequent finding in these patients is dry eye (up to 90%).[2] The presence of ocular GVHD has no association with age, gender, or specific conditioning regimens.[3] Chronic GVHD may cause irreparable damage to the cornea including ulceration, thinning and melting.[4]

Herein, we describe a case of corneal vascularization and perforation secondary to chronic GVHD and its stepwise management, as well as the results of histopathological evaluation.

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CASE REPORT

A 22-year-old woman with a history of thalassemia was referred to our clinic for decreased vision and ocular discomfort. She had received high-dose chemotherapy followed by allogeneic bone marrow transplantation (BMT) and had been prescribed frequent lubricants as well as topical antibiotics at another center.

Upon admission, the patient complained of foreign body sensation and painful sore gritty eyes. Corrected visual acuity was 3/10 and 7/10 in the right and left eyes, respectively. The diagnosis was severe dry eye secondary to chronic GVHD. Despite aggressive medical and surgical interventions such as topical cyclosporine and steroids, blepharorrhaphy, and upper and lower punctal occlusion, she experienced worsening of the condition followed by further deterioration of vision in her right eye. A significant decrease in tear meniscus, blepharitis and development of superficial corneal vascularization were noted during follow-up. Corneal vascularization progressed and led to corneal perforation. Slit lamp examination revealed a small Seidel-positive corneal perforation approximately 1.5 mm × 1 mm in size in her right eye [Figure 1]. Bandage contact lens (BCL) was applied as a temporary management and the patient was admitted. Cyanoacrylate glue was applied to seal the perforation site but was ineffective. Multilayer amniotic membrane transplantation (AMT) was performed to seal the corneal perforation [Figure 2]. The corneal perforation was sealed for 3 weeks following resorption of the AMT [Figure 3]. However, corneal perforation recurred six months later [Figure 4]. Penetrating keratoplasty (PK) together with a deep subconjunctival and intrastromal bevacizumab injection in the donor cornea were performed simultaneously in the right eye [Figure 5]. The corneal bottom was sent for histopathologic and bacteriologic evaluations which revealed corneal vascularization, inflammation, stromal edema and stromal degeneration [Figure 6]. Bacteriologic evaluations were negative.

In subsequent examinations, despite full medical/surgical treatment such as frequent lubrication with preservative-free artificial tears, topical cyclosporine and steroids, autologous serum, lateral tarsorrhaphy, and punctual occlusion; deep corneal stromal vascularization and descemetocele developed in the fellow left eye and the patient underwent therapeutic lamellar keratoplasty.

At this stage, her hematologist was consulted and asked to intensify the immunosuppression. The dosage of systemic mycophenolate mofetil, prednisolone acetate, and cyclosporine were increased to 2 g daily, 50 mg daily, and 150 mg daily, respectively. After intensifying the systemic regimen, the dry eye improved significantly, and the dosage was gradually tapered to 1 g daily, 10 mg daily, and 50 mg daily for mycophenolate mofetil, prednisolone acetate, and cyclosporine A, respectively. With maximum ocular and systemic treatment, the graft remained clear during the subsequent three years [Figure 7].

DISCUSSION

Patients with GVHD can develop severe dry eye that may lead to epithelial thinning and corneal erosions.[5] If not treated properly, progressive corneal vascularization may occur and visual acuity may be affected.[6] Subsequently, subtle perforations may develop in patients with GVHD.[7] When patients develop subtle

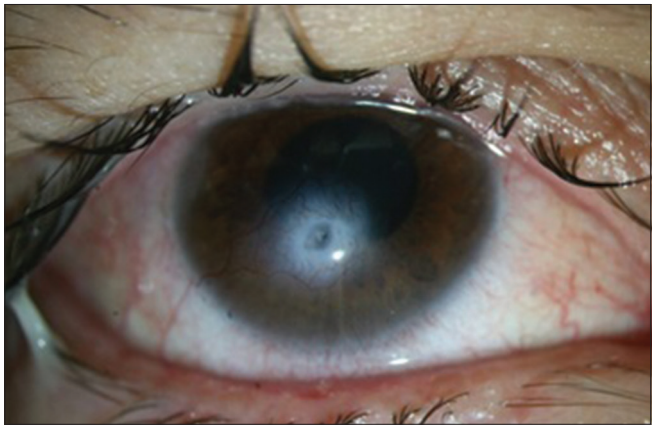

Figure 1. Slit lamp photograph of the right eye. The pupil is dilated and slightly displaced superiorly and the anterior chamber is slightly shallow. There is an opaque corneal ulcer with gray edges. The iris is tented forward and adherent to the perforation site. Corneal vascularization is evident in the paracentral and inferotemporal areas.

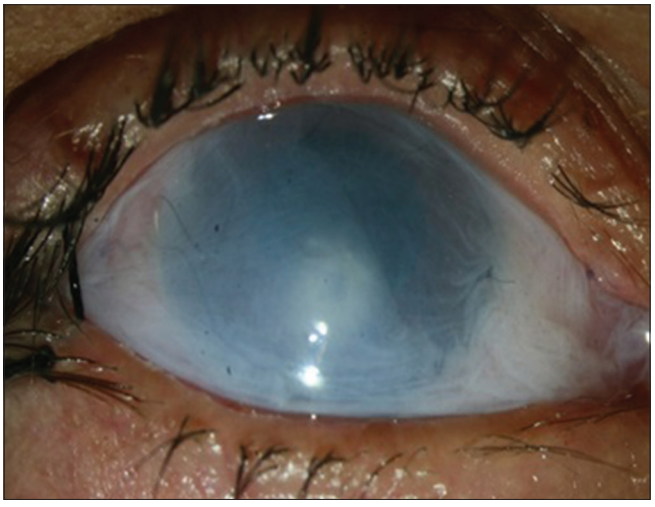

Figure 2. Appearance of the same eye as in Figure 1, after multilayer amniotic membrane transplantation (graft and patch) to seal the corneal perforation.

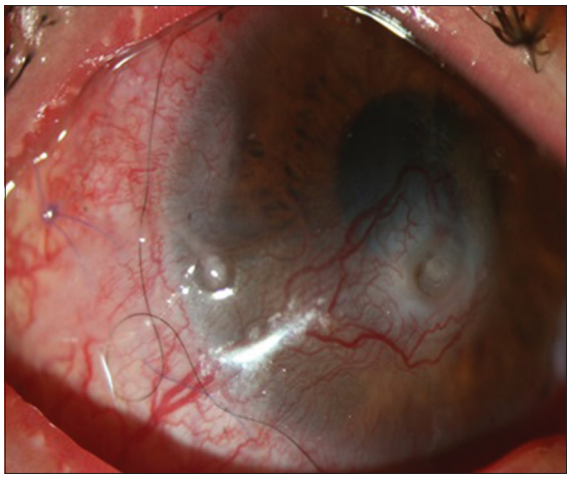

Figure 3. The corneal perforation remained sealed after resorption of the amniotic membrane.

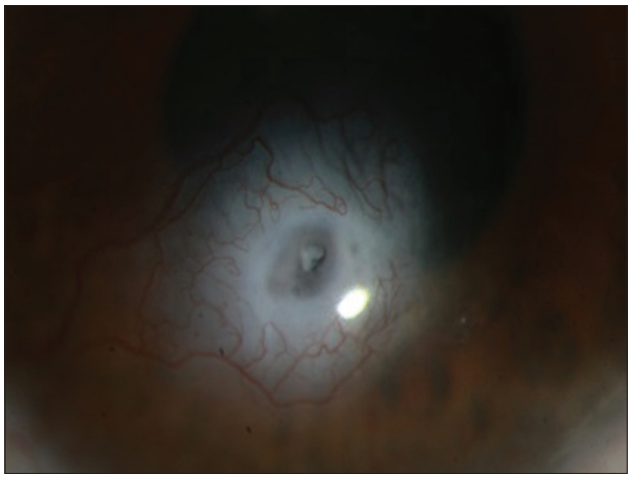

Figure 4. Recurrent corneal perforation developed three months after amniotic membrane transplantation.

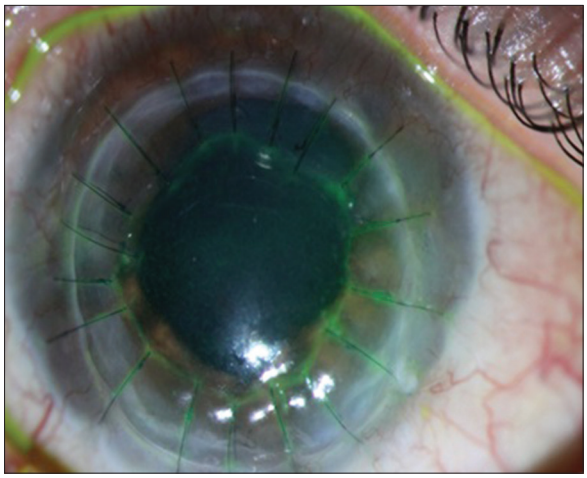

Figure 5. Appearance of the right eye one week after penetrating keratoplasty together with a deep intrastromal injection of bevacizumab.

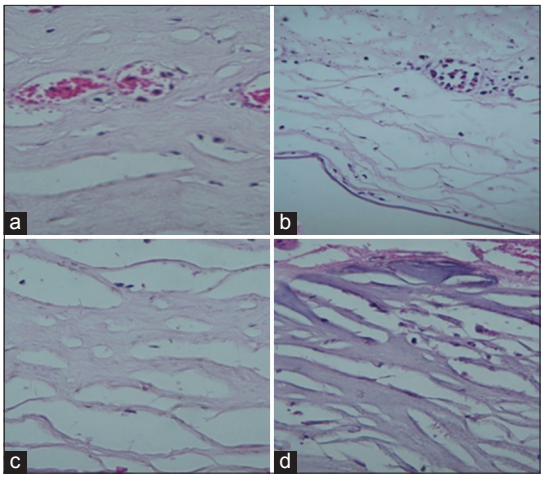

Figure 6. Photomicrograph displaying different histopathological changes involving the cornea: corneal vascularization (a), corneal intrastromal inflammation (b), stromal corneal edema (c), and stromal corneal degeneration (d).

corneal defects associated with GVHD, they require careful monitoring because serious complications, such as corneal vascularization and perforation, may ensue. It has been shown that bevacizumab may be considered for management of intrastromal corneal vascularization.[8] Therefore, we administered a deep intrastromal bevacizumab injection during PK in the right eye since the patient had developed progressive stromal vascularization.

Sterile corneal perforations in the paracentral region of the cornea are uncommon after BMT.[9] Such perforations are rare but should be noted as a grave complication. Suzuki et al presented a similar case. Although the exact process of perforation was unclear, the sequence of events that might lead to corneal ulceration have been postulated to be severe dry eye due to sicca syndrome, which is a complication of chronic GVHD.[10] Severe dry eye, chronic sterile conjunctivitis, scleritis, corneal ulcer and perforation, cataracts, central serous chorioretinopathy, multifocal choroiditis, and uveitis are among other complications reported in patients with GVHD.[9-16]

Ocular surface involvement includes loss of or significant reduction in the amount of conjunctival goblet cells, and conjunctival and corneal epithelial keratinization and squamous metaplasia.[11,12] Mild peripheral corneal vascularization may be seen in GVHD patients with dry eyes; however, progressive neovascularization has also been reported in this condition.[6] One possible mechanism for progressive corneal vascularization in such cases is an immune-mediated limbitis, which may cause partial stem cell deficiency because of altered conditions in the microenvironment of stem cells. Limbal stem cell dysfunction together with severe dry eye may

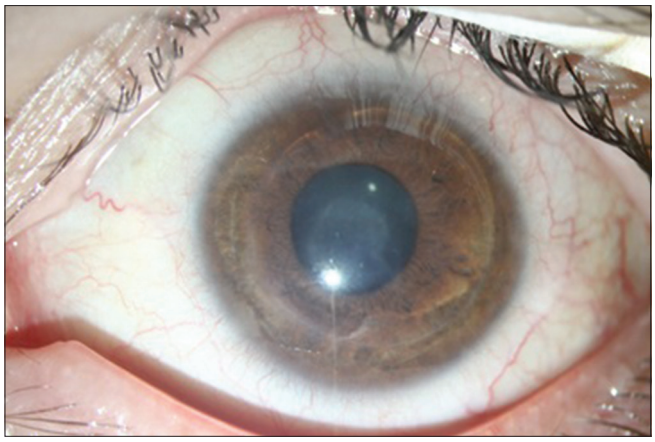

Figure 7. Appearance of the left eye, three years following therapeutic lamellar keratoplasty and a deep intrastromal injection of bevacizumab.

compose a vicious cycle, eventually leading to corneal neovascularization.[17]

The conjunctiva and lacrimal gland are two sites with the most prevalent histopathological changes in chronic ocular GVHD which predominantly consist of keratinization. One of the main causes of severe dry eye in chronic ocular GVHD is involvement of the lacrimal glands. $CD34^+$ fibroblasts play an important role in the pathogenesis of lacrimal gland fibrosis.[18] There is a relationship between dry eye syndrome and chronic GVHD activity in other organs. However, in some patients, such as ours, dry eye syndrome is the only manifestation of chronic GVHD.[19]

Current therapies for dry eye related to chronic GVHD include tear supplements (artificial tears and autologous serum), nonspecific immunosuppressants (steroidal and non-steroidal topical or systemic preparations) and punctal plugs. Other recent treatment modalities include cyclosporine A, tacrolimus and retinoic acid.[20,21]

In summary, sterile corneal ulceration may develop following BMT, leading to thinning and perforation of the cornea. Special attention should be paid to the diagnosis and management of dry eye before corneal neovascularization develops. Collaboration with the hematologist is mandatory for management of ocular complications caused by GVHD, especially dry eye–induced morbidities. Therapy consists of intensive management of dry eye and sufficient systemic immune suppression to control the systemic disease.

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Conflicts of Interest

There are no conflicts of interest.

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