Progressive Corneal Vascularization Caused by Graft-Versus-Host Disease

Mehrdad Mohammadpour, MD

Purpose: To report a case with severe dry eye and progressive corneal vascularization caused by graft-versus-host disease (GVHD).

Methods: A case report and review of literature.

Results: A 50-year-old man with history of acute myeloblastic leukemia, high-dose chemotherapy for eradication of hematopoietic stem cells, subsequent allogenic bone marrow transplantation, and eventually GVHD was referred for decreased vision and photophobia. Ocular examinations revealed severe dry eye that finally led to progressive corneal vascularization not responding to medical therapy.

Conclusion: In any patient with GVHD, the physician should pay special attention to early diagnosis and treatment of dry eye before development of corneal neovascularization. Intimate collaboration of an ophthalmologist with the patient's oncologist may be sight saving.

Key Words: corneal vascularization, graft-versus-host disease

(*Cornea* 2007;26:225–226)

Graft-versus-host disease (GVHD) is a cell-mediated immune reaction with acute and chronic manifestations.[1] The acute form usually occurs in the first month after bone marrow transplantation and carries a better prognosis than the chronic form, which may develop 3 to 14 months after bone marrow transplantation in 20% of matched sibling transplants and 40% of matched unrelated bone marrow recipients.[2] Most commonly involved sites are skin, mouth, liver, gastrointestinal tract, and eye.

The ocular manifestations of GVHD include dry eye,[1,2] chronic conjunctivitis,[3] scleritis,[4] cataract,[5] and posterior segment involvement such as central serous chorioretinopathy.[6]

Dry eye is the most common ocular manifestation of GVHD that may severely affect the patient's quality of life.[3] The incidence of dry eye in GVHD is reported to be up to 57%.[2]

Corneal vascularization has a diverse etiology including long-standing ocular surface inflammation or infection, stem cell deficiency, and immune-mediated disorders.

Herein, I report a case with dry eye and progressive corneal vascularization secondary to chronic GVHD.

CASE REPORT

A 50-year-old man with a history of acute myeloblastic leukemia and subsequent high-dose chemotherapy for eradication of recipient hematopoietic stem cells followed by allogenic bone marrow transplantation in May 2004 was referred because of decreased vision, photophobia, and foreign body sensation in March 2005. He had received cyclophosphamide, cytarabine, and vincristine before bone marrow transplantation and systemic steroids after the procedure. The patient received a tapered dose of oral prednisolone (5 mg/d) for treatment of chronic GVHD when he was referred for ocular examinations. He had not undergone total-body irradiation and had no ocular follow-up examinations after bone marrow transplantation.

On presentation, his visual acuity was 20/40 in both eyes (Fig. 1). Slit-lamp examination showed significant decrease in tear meniscus (nearly diminished), meibomian gland dysfunction and blepharitis, punctate epithelial erosions, late fluorescein staining of the corneal epithelium, superficial corneal vascularization, and mild lens opacity in both eyes. Intraocular pressure was normal, and fundus examination was unremarkable. The diagnosis was severe dry eye causing corneal vascularization secondary to chronic GVHD. The patient received artificial tears and fluorometholone eye drops 6 times daily. The symptoms of dry eye were partially relieved. The patient was scheduled for punctal occlusion but he refused. The corneal vascularization progressed later during follow-up examinations and involved the central cornea, but the deep corneal stroma was spared. The meibomian glands showed marked inflammation and severe dysfunction. The conjunctiva showed cicatricial changes in both eyes. The basic Schirmer test in both eyes was 2 mm, compatible with advanced keratoconjunctivitis sicca. The patient also suffered from skin and gastrointestinal involvement, which was partially managed by immunosuppressive therapy prescribed by the oncologist.

DISCUSSION

GVHD is a multisystem immune-mediated reaction that is induced by donor cells against recipient tissues.[1] It may involve the eye months after the onset of the chronic form. The high incidence and potentially severe ocular problems in these patients suggest that close ophthalmic monitoring is important in patients undergoing allogenic hematopoietic stem cell transplantation.[2,3] Severe dry eye, cicatricial lagophthalmos,[3]

Received for publication April 27, 2006; accepted for publication August 2, 2006.

From the Ophthalmic Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.

The author states that he has no proprietary interest in the products named in this article.

Reprints: Mehrdad Mohammadpour, MD, Ophthalmic Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, Iran (e-mail: Mahammadpour@yahoo.com).

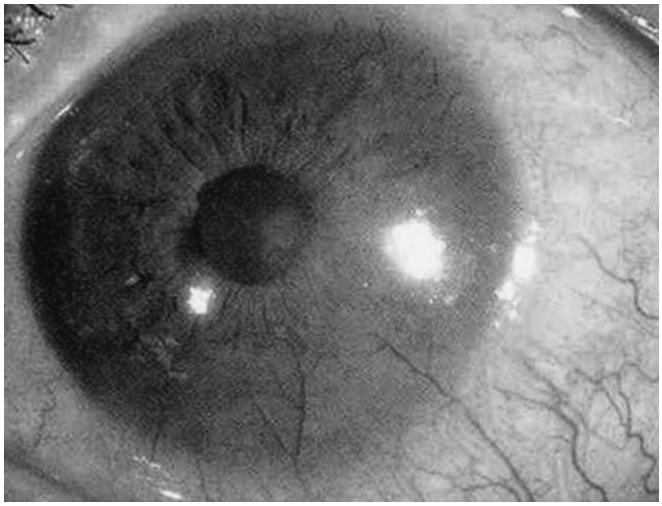

FIGURE 1. Corneal vascularization secondary to GVHD.

chronic sterile conjunctivitis, scleritis,[4] corneal ulcer,[5] cataract,[5] central serous chorioretinopathy,[6] multifocal choroiditis,[7] and uveitis[3] have been reported in these patients.

Ocular surface involvement includes loss or significant reduction in amount of conjunctival goblet cells, conjunctival and corneal epithelial keratinization, and squamous metaplasia.[2]

Although mild peripheral corneal vascularization is usually seen in GVHD patients with dry eyes, progressive neovascularization has not been reported in this condition.

One possible mechanism for progressive corneal vascularization in this case is an immune-mediated limbitis, which may cause partial stem cell deficiency because of altered conditions in the microenvironment where the stem cells grow and gradually differentiate into corneal epithelial cells.[8,9]

Limbal stem cell dysfunction together with severe dry eye may compose a vicious cycle, eventually leading to corneal neovascularization.

Although the patient did not consent to performing an impression cytology examination because of his poor general condition, the progression of corneal vascularization and late fluorescein staining of the corneal epithelium were in favor of some degree of stem cell deficiency caused by chronic limbal inflammation and severe dry eye induced by GVHD.

Current therapies for dry eye related to chronic GVHD include tear supplements (artificial tear and autologous serum[10]), nonspecific immunosuppressants[3] (steroidal and nonsteroidal in topical or systemic preparations), and punctal plugs. Other recent treatment modalities include cyclosporine A, tacrolimus, and retinoic acid.[11]

In conclusion, in patients with GVHD, special attention should be paid to diagnosis and management of dry eye before development of corneal neovascularization. It seems that intimate collaboration of the oncologist with an ophthalmologist is mandatory for management of the ocular complications of GVHD, especially dry eye–induced morbidities. The therapy consists of management of the dry eye and systemic immune suppression.

REFERENCES

1. Robinson MR, Lee SS, Rubin BI, et al. Topical corticosteroid therapy for cicatricial conjunctivitis associated with chronic graft-versus-host disease. *Bone Marrow Transplant*. 2004;33:1031–1035.
2. Sanders JE. Chronic graft-versus-host disease and late effects after hematopoietic stem cell transplantation. *Int J Hematol*. 2002;76(Suppl 2): 15–28.
3. Frankin RM, Kenyon KR, Tutschka PJ, et al. Ocular manifestations of graft-vs-host disease. *Ophthalmology.* 1983;90:4–13.
4. Kim RY, Anderlini P, Naderi AA, et al. Scleritis as the initial clinical manifestation of graft-versus-host disease after allogenic bone marrow transplantation. *Am J Ophthalmol*. 2002;133:843–845.
5. Saito T, Shinagawa K, Takenaka K, et al. Ocular manifestation of acute graft-versus- host disease after allogenic peripheral blood stem cell transplantation. *Int J Hematol*. 2002;75:332–334.
6. Cheng LL, Kwok AK, Wat NM, et al. Graft-vs-host-disease-associated conjunctival chemosis and central serous chorioretinopathy after bone marrow transplant. *Am J Ophthalmol*. 2002;134:293–295.
7. Alvarez MT, Hernaez JM, Ciances E, et al. Multifocal choroiditis after allogenic bone marrow transplantation. *Eur J Ophthalmol*. 2002;12: 135–137.
8. Mohammadpour M, Javadi MA. Keratitis associated with multiple endocrine deficiency. *Cornea*. 2006;25:112–114.
9. Ogawa Y, Kuwana M. Dry eye as a major complication associated with chronic graft-versus-host disease after hematopoietic stem cell transplantation. *Cornea*. 2003;22(7 Suppl):519–527.
10. Ogawa Y, Okamoto S, Mori T, et al. Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. *Bone Marrow Transplant*. 2003;31:579–583.
11. Anderon NG, Regillo C. Ocular manifestations of graft versus host disease. *Curr Opin Ophthalmol*. 2004;15:503–507.