Paracentral Corneal Melting in Four Patients With Chronic Graft-Versus-Host Disease

Neil Chungfat, MD, MEng[1,2]; Jocelyn Rowe, MD[1,3];
Neal P. Barney, MD[1]; Sarah Nehls, MD[1]

The authors have no financial interest in the subject matter of this poster

[1] University of Wisconsin Department of Ophthalmology and Visual Sciences, Madison, WI
[2] University of California Francis I Proctor Foundation, San Francisco, CA
[3] Mount Sinai Hospital, Chicago, IL

Study

- Background
  - Graft-versus-host disease (GVHD) is classically divided into acute and chronic entities.
  - The incidence of chronic GVHD is 50-70% among patients who receive hematopoietic stem cell transplants.[1-3]
  - GVHD may involve skin, oral mucosa, eyes, GI, genitalia, liver, lung, muscles and joints.[4]
  - Ocular symptoms manifest as features of aqueous deficiency dry-eye (foreign-body sensation, pain, dryness).

- Purpose
  - To identify the symptomatology and clinical course of patients with chronic GVHD who developed sterile corneal melting

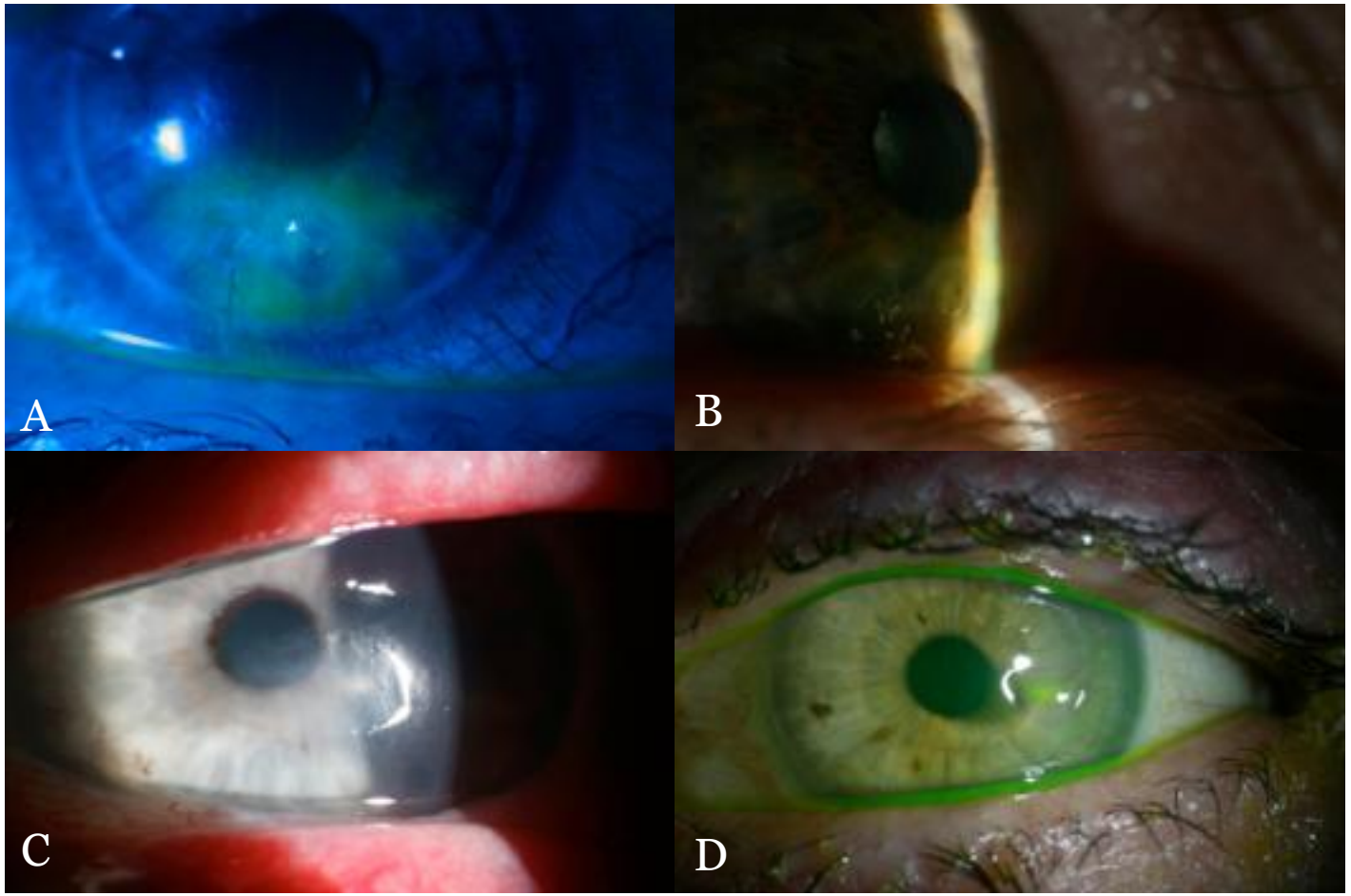
- Materials and Methods
  - Retrospective case review with approval from the University of Wisconsin-Madison (UW-Madison) Institutional Review Board.
  - Inclusion criteria: Patients seen at the UW-Madison Cornea clinic between 2008 and 2012 with a diagnosis of GVHD complicated by corneal thinning or perforation

Results

	Patient 1	Patient 2	Patient 3	Patient 4
Age	26	49	54	66
Malignancy	ALL	AML	CML	AML
Time from transplant to melt	40 months	23 years	16 months	25 months
Other systemic involvement	Skin, mouth, lungs	Mouth	Skin, mouth, liver	None

ALL = acute leukocytic leukemia; AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia

Results



Two patients (A, B) had complete corneal melts. One (A) required penetrating keratoplasty that later melted in a similar inferior paracentral location within the graft. The second (B) was glued and did not require surgical intervention. Two patients (C, D) had paracentral areas of thinning that were addressed successfully with conservative measures.

Melt characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Melt type	Full thickness	Full thickness	Partial	Partial
Melt location	6 o'clock paracentral with recurrence in same location	5:30 o'clock paracentral	4 o'clock paracentral	3:30 o'clock paracentral
Culture	Pathology of corneal button without organisms	Rare Strep. viridans	Negative	Not performed (no infiltrate)
Initial treatment	Glue + BCL	Glue + BCL	Lubricating and antibiotic drops, acyclovir, punctal plugs	Lubricating and antibiotic drops, punctal plugs
Vision before and after treatment	LP 20/60	20/60 2 '/200	20/300 20/50	20/80 20/20

BCL = bandage contact lens
LP = light perception

Treatments

	Patient 1	Patient 2	Patient 3	Patient 4
Punctal plugs	+	+	+	+
Artificial tears (PF)	+	+	+	+
Autologous tears	+	- (tried previously without relief)	+	+
Antibiotic drops	+	+	+	+
Surgery	PKP x 2	PKP x 1	None	None
Other	Vitamin C, PKP x 2	Doxycycline, Restasis	Acyclovir	Vitamin C

PF = preservative free
PKP = penetrating keratoplasty

Discussion

- Corneal perforation is a rare but vision threatening complication of GVHD that can vary both in severity and response to treatment.
- Thus far, perforation has been described only in individual case reports and small series. [5-11]
- Both the non-infectious etiology in 3 cases and paracentral location appear to be shared features among the cases presented here as well as those described elsewhere.[5, 7-11]

Etiology of melting in GVHD

- Does corneal melting result from a direct immunologic process or indirectly as a complication from sicca syndrome?
- One study found histologic evidence of a direct cytotoxic etiology consistent with immune dysregulation.[10]
- Apoptotic epithelial cells and keratocytes have also been noted in perforated GVHD corneas,[12] which could result from a cytotoxic reaction though keratocyte apoptosis may also be seen in dry eye disease unrelated to GVHD.[13]

Does eye disease parallel severity of GVHD?

- Patient 1 had recurrent melt in a similar location as the initial site of perforation.
- This patient was the youngest patient in our series with multi-system involvement of GVHD including bronchiolitis obliterans.
- Currently, it remains unclear if the level of ocular disease parallels the overall severity of GVHD.

Timing of GVHD Onset

- Flares of dry eye symptoms that coincide with the tapering of immunosupressants have been described. [14]
- It has been hypothesized that the symptoms of chronic GVHD manifest at about three months post-transplant because of the coincident changes made to immunosuppressive medications at that time.[15]
- Some graft-versus-tumor effect is desirable and therefore complete suppression of GVHD is generally not favored.

Conclusions

- Dry eye is a significant source of morbidity in patients with chronic GVHD.
- Close follow-up is necessary to control symptoms and monitor for sight-threatening complications including corneal thinning, ulceration, and perforation.
- The link between immunologic dysfunction and corneal disease remains unclear at this time.

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*. Oct 1974;18(4):295-304.

2. Santos GW. Bone marrow transplantation. *Adv Intern Med*. 1979;24:157-182.

3. Bray LC, Carey PJ, Proctor SJ, Evans RG, Hamilton PJ. Ocular complications of bone

4. Hessen M, Akpek EK. Ocular graft-versus-host disease. *Curr Op Allergy Clin Immunol*. 2012;12:540-547.

5. Yeh PT, Hou YC, Lin WC, Wang IJ, Hu FR. Recurrent corneal perforation and acute calcareous corneal degeneration in chronic graft-versus-host disease. *J Formos Med Assoc*. Apr 2006;105(4):334-339.

6. Koch KR, Joussen AM, Huber KK. Ocular involvement in chronic graft-versus-host disease: therapeutic approaches to complicated courses. *Cornea*. Jan 2011;30(1):107-113.

7. Inagaki E, Ogawa Y, Matsumoto Y, Kawakita T, Shimmura S, Tsubota K. Four cases of corneal perforation in patients with chronic graft-versus-host disease. *Mol Vis*. 2011;17:598-606.

8. Heath JD, Acheson JF, Schulenburg WE. Penetrating keratoplasty in severe ocular graft versus host disease. *Br J Ophthalmol*. Aug 1993;77(8):525-526.

9. Yuta K, Kami M, Matsumoto Y, Murashige N, Suzuki S. Deep lamellar keratoplasty for corneal perforation due to chronic graft-versus-host disease following allogeneic hematopoietic stem-cell transplantation. *Haematologica*. Mar 2005;90(3):ECR15.

10. Suzuki M, Usui T, Kinoshita N, Yamagami S, Amano S. A case of sterile corneal perforation after bone marrow transplantation. *Eye (Lond)*. Jan 2007;21(1):114-116.

11. Tranos PG, Forbes J, Jagger J. Corneal perforation in chronic graft-versus-host disease. *Eye (Lond)*. Feb 2001;15(Pt 1):111-113.

12. Yoshida A, Kawano Y, Kato K, et al. Apoptosis in perforated cornea of a patient with graft-versus-host disease. *Can J Ophthalmol*. Aug 2006;41(4):472-475.

13. Nakamura S, Shibuya M, Saito Y, et al. Protective effect of D-beta-hydroxybutyrate on corneal epithelia in dry eye conditions through suppression of apoptosis. *Invest Ophthalmol Vis Sci*. Nov 2003;44(11):4682-4688.

14. 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*. May 2001;20(4):430-434.

15. Ogawa Y, Okamoto S, Wakui M, et al. Dry eye after haematopoietic stem cell transplantation. *Br J Ophthalmol*. Oct 1999;83(10):1125-1130.