DOI: 10.4274/tjo.galenos.2020.88137
Turk J Ophthalmol 2021;51:134-138

Original Article

Ocular Findings of Pediatric Dry Eye Related to Graft-Versus-Host Disease

Pınar Bingöl Kızıltunç*, Tuna Çelik Büyüktepe*, Fatime Nilüfer Yalçındağ*, Mehmet Ertem**, Elif İnce**, Talia İleri**, Huban Atilla*

*Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**Ankara University Faculty of Medicine, Department of Pediatric Hematology, Ankara, Turkey

Abstract

Objectives: To evaluate the frequency and findings of dry eye associated with ocular graft-versus-host disease (GVHD) in pediatric hematopoietic stem cell transplantation (HSCT) patients.

Materials and Methods: Retrospectively the records of pediatric patients with ocular GVHD were evaluated and ophthalmologic examination findings as well as Schirmer test results, tear film break-up time, and corneal staining grades were recorded. In severe dry eye patients topical cyclosporine-A was prescribed and the results were evaluated.

Results: GVHD was detected in 51 (23.4%) of 218 HSCT patients, 4 of whom died during follow-up. Thirty (63.8%) of the remaining 47 patients had chronic ocular GVHD and 4 patients with severe dry eye were treated with topical cyclosporine-A with a median follow-up of 12.1 months. Severe dry eye symptoms and findings significantly improved in 2 patients. However, 1 patient had to stop treatment due to side effects.

Conclusion: In children, chronic ocular GVHD is a common finding of GVHD after HSCT. Therefore, these patients should be examined periodically for dry eye.

Keywords: Cyclosporine-A, dry eye, graft-versus-host disease, pediatric, Schirmer test

Introduction

Hematopoietic stem cell transplantation (HSCT) is the mainstay therapy for malignant and benign hematological diseases like thalassemia major, aplastic anemia, leukemia, and metabolic diseases like Hurler syndrome.[1,2,3] Graft-versus-host disease (GVHD) is a clinical disease with multiple organ and system involvement due to the donor-derived T cells recognizing host antigens as foreign, and is the main cause of morbidity and mortality after HSCT.[4] Ocular involvement can occur as a manifestation of GVHD and is referred to as ocular GVHD. Although ocular involvement is more common in chronic GVHD, it can also be seen in acute GVHD.[5] Ocular findings of chronic ocular GVHD include generalized ocular surface inflammation, dry eye syndrome, superficial punctate keratitis, persistent epithelial defects, symblepharon formation, sterile and infectious stromal ulceration, lacrimal gland and meibomian gland dysfunction due to cicatricial conjunctivitis, cataracts, uveitis, retinal vasculitis, retinal hemorrhage, and optic neuropathy.

Address for Correspondence: Pınar Bingöl Kızıltunç, Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: pinarbingol84@gmail.com **ORCID-ID:** orcid.org/0000-0003-4394-7926
Received: 11.05.2020 **Accepted:** 29.08.2020

Cite this article as: Bingöl Kızıltunç P, Çelik Büyüktepe T, Yalçındağ FN, Ertem M, İnce E, İleri T, Atilla H. Ocular Findings of Pediatric Dry Eye Related to Graft-Versus-Host Disease. Turk J Ophthalmol 2021;51:134-138

The aim of this study was to determine the frequency of dry eye associated with chronic ocular GVHD in pediatric HSCT patients and to explore the findings of dry eye associated with chronic ocular GVHD.

Materials and Methods

In this retrospective study, we evaluated the medical records of 218 pediatric patients who underwent allogenic HSCT between 1996 and 2015. We noted patient characteristics including gender, age, primary hematologic diseases, and follow-up period.

In our clinic we routinely perform a detailed ophthalmologic examination to all patients with HSCT before and after transplantation. Hence we could evaluate the results of ophthalmological examinations in 51 patients with GVHD every 3 months, as well as the monthly examination results of patients with severe dry eye findings.

We recorded patient complaints such as decrease in vision, dryness, photophobia, foreign body sensation, irritation, redness, burning, itching, or any other ocular discomfort. Besides full ophthalmic examination, tear stability by tear film break-up time (TFBUT) using fluorescein impregnated paper strips (ERC Fluorescein strip, ERC Medical Products, Ankara, Turkey) were classified into 4 groups based on severity (>10 s, 6-10 s, ≤5 s).[6] We assessed corneal fluorescein staining under cobalt blue illumination to enhance staining details and graded according to the Oxford scale (grade 0-5).[7] We estimated tear production by the 5-minute Schirmer test (without anesthetics) with sterile strips placed in the inferior fornix. We classified Schirmer test results into 4 groups based on severity (>10 mm, 10-6 mm, ≤5 mm).[6]

We diagnosed ocular GVHD based on the National Institutes of Health Consensus criteria (a low Schirmer test value [≤5 mm/5 min]) or new keratoconjunctivitis sicca by slit lamp examination with moderate Schirmer test value (6-10 mm/5 min) in the presence of another affected organ system.[8] We graded dry eye according to Dry Eye Workshop Criteria.[6] Severe dry eye criteria were tear production less than 5 mm/5 min with Schirmer test, TFBUT less than 5 seconds, marked central corneal staining, and presence of filamentary keratitis. We recorded pre-treatment and post-treatment ophthalmological examination findings of patients who were treated with cyclosporine-A due to severe dry eye symptoms.

The local ethics committee approved this study (report number: 08-496-18, date: 07 May 2018), which was conducted adhering to the Declaration of Helsinki.

Results

Of all the included HSCT patients (n=218), 51 patients (23.4%) had chronic systemic GVHD. Four patients died during the follow-up period; therefore, the records of 47 patients with chronic GVHD were included. Twenty-four patients (51%) were female and 23 (49%) were male. The mean age was 11.8±2.9 (range: 3-18) years and median follow-up period was 22.3 (9-72) months. The primary hematologic diseases of patients for allogenic HSCT are shown in Table 1.

In the follow-up period, chronic ocular GVHD developed in 30 of 47 patients (63.8%). Apart from dry eye syndrome, there were no associated anterior and posterior segment findings of GVHD. The most common complaints of dry eye syndrome were burning, stinging, foreign body sensation, and photophobia and were detected in 44% of the patients. The results of examination including Schirmer test, TFBUT, and corneal staining for dry eye are shown in Table 2.

Artificial tears without preservatives and ointments were prescribed as medical treatment to the patients with dry eye symptoms. Four patients (13.3%) with Schirmer test less than 5 mm/5 min were accepted as severe dry eye and topical cyclosporine-A was added to artificial tears and ointment.

Patients with severe dry eye used topical cyclosporine-A 0.05% (Restasis, Allergan, USA) twice daily and the mean

Table 1. Primary hematologic diseases of hematopoietic stem cell transplantation patients

Primary hematologic disease	Number of patients, n (%)
Thalassemia major	28 (59.6)
Fanconi aplastic anemia	4 (8.5)
Acute lymphoblastic leukemia	4 (8.5)
Acute myeloid leukemia	3 (6.4)
Other	8 (17)
Total	47 (100)

Table 2. Dry eye examination findings

Schirmer test		Tear film break-up time		Corneal staining	
Value (mm/5 min)	Number of patients, n (%)	Value (s)	Number of patients, n (%)	Score	Number of patients, n (%)
>10	19 (40.4)	>10	18 (38.3)	Grade I	15 (31.9)
6-10	8 (17)	6-10	9 (19.1)	Grade II	15 (31.9)
≤5	4 (8.5)	≤5	4 (8.5)	Grade III	3 (6.4)
No data	16 (34.1)	No data	16 (34.1)	Grade IV	2 (4.2)
				Grade V	2 (4.2)
				No data	10 (21.4)

duration of cyclosporine-A treatment was 13.25 (9-19) months. One patient (25%) stopped treatment because of side effects such as burning and irritation; a punctal plug was inserted in this patient. There were no other side effects in the remaining 3 patients (75%). Pre-treatment and post-treatment findings of the 4 patients with severe dry eye are seen in Table 3.

Discussion

The frequency of ocular findings in GVHD patients was reported as 45-60% in different studies and dry eye syndrome is the most frequent ocular finding in ocular GVHD.[9,10] Severe complications such as corneal vascularization, keratitis, and corneal perforation can occur due to dry eye syndrome.

The prevalence of systemic GVHD in younger patients is lower than in adults. Different studies reported chronic GVHD in the pediatric population at rates of 22% to 29%.[11,12,13] In our series, we found the prevalence of chronic GVHD similar to the other studies (23.4%). The frequency of dry eye syndrome due to ocular GVHD is also different in the pediatric population. The prevalence of dry eye syndrome in adult patients after HSCT is up to 44%.[10,14] However, the prevalence of dry eye syndrome in children is difficult to extrapolate as they can report their symptoms less than adults and also all examination methods cannot be performed easily in children. De Marco et al.[15] investigated 33 children with HSCT and 24.4% of these patients had tear hyposecretion. Suh et al.[16] reported that ocular changes developed in 51% of pediatric patients after HSCT and the frequency of dry eye syndrome was 12.5% at a mean age of 8.4 years. Hoehn et al.[17] found the prevalence of dry eye syndrome in 14-year-olds as 41.4%. In our series, dry eye was detected in 30 (63.8%) of 47 patients with GVHD at a mean age of 11.8 years. This higher frequency in our study may be due to our routine evaluation of these patients before and after HSCT regardless to the presence of any complaints.

In children, the clinical features of dry eye syndrome are similar to those in adults, but they rarely complain of dry eye symptoms. Therefore, dry eye symptoms affect the quality of life, especially at younger ages. Ng et al.[18] found that 51.7% of pediatric patients with HSCT had tear abnormalities and one third of patients had corneal staining, but none of them had dry eye symptoms. The frequency of dry eye complaints such as foreign body sensation, red eyes, discharge, and photophobia in pediatric patients was 48% in Fahnehjelm's study.[19] However, corneal staining and a short TFBUT and/or pathological Schirmer was present in 62% of patients. In our study, 44% of patients had complaints related to dry eye. Although pediatric patients with HSCT do not have any complaints, they should be examined routinely for ocular GVHD.

Prevention of evaporation, maintenance of lubrication, tear preservation, and inflammation control are the mainstay of treatment of dry eye syndrome in ocular GVHD. In our study, all patients with dry eye were prescribed artificial tears without preservatives and ointments, and patients with severe dry eye additionally received topical cyclosporine-A.

T-cell related inflammatory processes, apoptosis, and fibrosis are the causes of ocular surface disease and dry eye in ocular GVHD. Westekemper et al.[20] showed the expression of Th1-associated chemokines in the conjunctiva of patients with chronic GVHD. Cyclosporine-A is an effective treatment modality in ocular GVHD. The main mechanism of cyclosporine-A in the treatment of ocular GVHD is related to T-cell activation and downregulation of inflammatory cytokines in the conjunctiva.[21] Cyclosporine-A also decreases epithelial cell turnover and increases conjunctival goblet cell density. The concentration of cyclosporine-A in the conjunctiva is higher after topical use compared with systemic use.[22] Furthermore, topical use eliminates the systemic side effects of the drug. Therefore, with its local immunosuppressive effect, topical cyclosporine-A may be more effective and safer than systemic immunosuppressive agents in the treatment of ocular GVHD. Topical cyclosporine-A both improves Schirmer test and TFBUT, and increases the conjunctival goblet cells and reduces punctate keratopathy.[23,24]

Previous studies evaluated the effect of different concentrations and dosage of topical cyclosporine-A.[25,26] A topical cyclosporine-A concentration of 0.05% was found to be safe and effective in the treatment of moderate to severe dry eye.[23,27] Clinical signs and symptoms can improve in 4 weeks, but sustained improvement was shown with decreased immune activation markers and inflammatory cytokines and increased conjunctival goblet cell number after 6 months of treatment.[23] Kiang et al.[25] found that

Table 3. examination findings of patients with severe dry eye

		Pre-treatment			Post-treatment			
Patient, diagnosis	Age (years)	TFBUT (s), OD/OS	Schirmer (mm/5 min), OD/OS	Corneal staining (grade),OD/OS	TFBUT (s), OD/OS	Schirmer (mm/5 min), OD/OS	Corneal staining (grade) OD/OS	Treatment duration (months)
1, ALL	16	5/7	4/2	III/III	5/6	3/2	III/III	19
2, TM	10	6/8	4/4	II/II	10/>10	>10/>10	0/I	14
3, ALL	3	4/4	No data	I/I	4/4	No data	I/I	9
4, ALL	9	3/4	4/4	II/II	>10/>10	10/>10	0/I	11

ALL: Acute lymphoblastic leukemia, TM: Thalassemia major, TFBUT: Tear film break-up time, OD: Right eye, OS: Left eye

topical cyclosporine-A 1% used 6-8 times/day in the active or necrotizing stage of ocular GVHD helps to promote the healing process and decrease the immunological activity of the donor lymphocytes in adult patients. Malta et al.[26] evaluated the effect of topical cyclosporine-A 0.05% in the prophylaxis and treatment of ocular GVHD and found that adults and children who did not receive cyclosporine-A until at least 6 months after HSCT had significantly more severe dry eye symptoms than patients who received topical cyclosporine-A starting 1 month before HSCT. Use of topical cyclosporine-A 0.05% improved corneal fluorescein staining in all eyes and dry eye symptoms in 62.5% of patients in a study by Lelli et al.[28] Studies about the use of topical cyclosporine-A in pediatric GVHD patients are rare. Fahnehjelm et al.[19] reported that corneal findings improved in 2 pediatric patients who used topical cyclosporine-A with a concentration of 0.1% for 1 year. In our study, the concentration of topical cyclosporine-A was 0.05%, dosing was twice daily, and the mean duration of treatment was 13.25 (9-19) months. This concentration improved dry eye findings, with improved Schirmer test and TFBUT results and reduced corneal staining, in 2 patients (50%). One patient (25%) had to stop treatment because of side effects, mainly burning, redness, and irritation.

When we considered the limitations of our study, we only gave topical cyclosporine-A to severe dry eye patients. Therefore, this group was small. In addition, we only evaluated the effect of topical cyclosporine-A at a concentration of 0.05%. Further studies with large study populations and different concentrations may be more helpful to establish the effect of topical cyclosporine-A in pediatric patients with GVHD-associated dry eye syndrome.

Conclusion

In conclusion, dry eye is an important and common finding of GVHD in children. Therefore, all patients with HSCT should be examined, even if patients do not have complaints.

Ethics

Ethics Committee Approval: Ankara University, School of Medicine (report number: 08-496-49 18, date: 07 May 2018).

Informed Consent: The study is retrospective.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: P.B.K., T.Ç.B., H.A., F.N.Y., Concept: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Design: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Data Collection or Processing: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Analysis or Interpretation: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Literature Search: P.B.K., T.Ç.B., H.A., F.N.Y., M.E., E.İ., T.İ., Writing: P.B.K., T.Ç.B., H.A., E.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Strocchio L, Locatelli F. Hematopoietic Stem Cell Transplantation in Thalassemia. Hematol Oncol Clin North Am. 2018;32:317-328.
2. Kim H. Treatments for children and adolescents with AML. Blood Res. 2020;55(Suppl 1):5-13.
3. Tan EY, Boelens JJ, Jones SA, Wynn RF. Hematopoietic Stem Cell Transplantation in Inborn Errors of Metabolism. Front Pediatr. 2019;7:433.
4. Atkinson K. Bone marrow transplantation. Med J Aust. 1992;157:408-411.
5. Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: a review. Surv Ophthalmol. 2013;58:233-251.
6. No authors listed. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5:75-92.
7. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea. 2003;22:640-650.
8. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Przepiorka D, Couriel D, Cowen EW, Dinndorf P, Farrell A, Hartzman R, Henslee-Downey J, Jacobsohn D, McDonald G, Mittleman B, Rizzo JD, Robinson M, Schubert M, Schultz K, Shulman H, Turner M, Vogelsang G, Flowers ME. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11:945-956.
9. Franklin RM, Kenyon KR, Tutschka PJ, Saral R, Green WR, Santos GW. Ocular manifestations of graft-vs-host disease. Ophthalmology. 1983;90:4-13.
10. Hirst LW, Jabs DA, Tutschka PJ, Green WR, Santos GW. The eye in bone marrow transplantation. I. Clinical study. Arch Ophthalmol. 1983;101:580-584.
11. Zecca M, Prete A, Rondelli R, Lanino E, Balduzzi A, Messina C, Fagioli F, Porta F, Favre C, Pession A, Locatelli F; AIEOP-BMT Group. Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. Blood 2002;100:1192-1200.
12. Kondo M, Kojima S, Horibe K, Kato K, Matsuyama T. Risk factors for chronic graft-versus-host disease after allogeneic stem cell transplantation in children. Bone Marrow Transplant. 2001;27:727-730.
13. Eisner MD, August CS. Impact of donor and recipient characteristics on the development of acute and chronic graft-versus-host disease following pediatric bone marrow transplantation. Bone Marrow Transplant. 1995;15:663-668.
14. Bray LC, Carey PJ, Proctor SJ, Evans RG, Hamilton PJ. Ocular complications of bone marrow transplantation. Br J Ophthalmol. 1991;75:611-614.
15. De Marco R, Dassio DA, Vittone P. A retrospective study of ocular side effects in children undergoing bone marrow transplantation. Eur J Ophthalmol. 1996;6:436-439.
16. Suh DW, Ruttum MS, Stuckenschneider BJ, Mieler WF, Kivlin JD. Ocular findings after bone marrow transplantation in a pediatric population. Ophthalmology. 1999;106:1564-1570.
17. Hoehn ME, Calderwood J, Gannon E, Cook B, Rochester R, Hartford C, Triplett B, Sunkara A, Kang G, Walton RC. Ocular complications in a young pediatric population following bone marrow transplantation. J AAPOS. 2018;22:102-106.
18. Ng JS, Lam DS, Li CK, Chik KW, Cheng GP, Yuen PM, Tso MO. Ocular complications of pediatric bone marrow transplantation. Ophthalmology. 1999;106:160-164.
19. Fahnehjelm KT, Törnquist AL, Winiarski J. Dry-eye syndrome after allogeneic stem-cell transplantation in children. Acta Ophthalmol. 2008;86:253-258.
20. Westekemper H, Meller S, Citak S, Schulte C, Steuhl KP, Homey B, Meller D. Differential chemokine expression in chronic GVHD of the conjunctiva. Bone Marrow Transplant. 2010;45:1340-1346.
21. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: a twenty-five-year review. Cornea. 2000;19:644-649.
22. Pfau B, Kruse FE, Rohrschneider K, Zorn M, Fiehn W, Burk RO, Völcker HE. [Comparison between local and systemic administration of cyclosporin A on

the effective level in conjunctiva, aqueous humor and serum]. Ophthalmologe. 1995;92:833-839.
23. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. Ophthalmology. 2000;107:631-639.
24. Wang Y, Ogawa Y, Dogru M, Kawai M, Tatematsu Y, Uchino M, Okada N, Igarashi A, Kujira A, Fujishima H, Okamoto S, Shimazaki J, Tsubota K. Ocular surface and tear functions after topical cyclosporine treatment in dry eye patients with chronic graft-versus-host disease. Bone Marrow Transplant. 2008;41:293-302.
25. Kiang E, Tesavibul N, Yee R, Kellaway J, Przepiorka D. The use of topical cyclosporin A in ocular graft-versus-host-disease. Bone Marrow Transplant. 1998;22: 147-151.
26. Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A, Mian SI. Treatment of ocular graft-versus-host disease with topical cyclosporine 0.05%. Cornea. 2010;29:1392-1396.
27. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The Cyclosporin A Phase 2 Study Group. Ophthalmology. 2000;107:967-974.
28. Lelli GJ Jr, Musch DC, Gupta A, Farjo QA, Nairus TM, Mian SI. Ophthalmic cyclosporine use in ocular GVHD. Cornea. 2006;25:635-638.