# Ciclosporin eye drops in ocular graft-versus-host disease: a case report


## ABSTRACT

**Aims:** to report a case of severe ocular graft-versus-host disease (GVHD) managed with topical ciclosporin.
Introduction: The ocular graft-versus host disease is a rare and often misdiagnosed etiology of dry eye syndrome.
**Case:** We report a case of young women, presented for a severe and bilateral ocular surface inflammation with filamentous keratitis, posterior blepharitis, Meibomian dysfunction and neovascular invasion. Ocular GVHD was diagnosed due to severe dry eye symptoms and a history of allogeneic haematopoietic stem cell transplantation. Immunosuppressive treatment resulted in a spectacular anatomical and clinical improvement, symptoms were rapidly resolved and the visual acuity improved.
**Conclusion:** Ocular GVHD should be considered in any severe dry eye syndrome associated with allogeneic bone marrow transplantation. Topical immunosuppressive therapies have revolutionised the curative management of these patients.



*Keywords: dry eye syndrome; ocular graft-versus-host disease; topical ciclosporin treatment; prevention.*


## 1. INTRODUCTION

Ocular Graft-Versus-Host-Disease (oGVHD) remains a major cause of long-term morbidity and disability in patients who have undergone allo-haematopoietic stem cell transplant (allo-HSCT). This condition, often misdiagnosed as an etiology of eye dry syndrome, can have a significant impact on visual function and quality of life, highlighting the importance of early detection and appropriate management.

## 2. CASE REPORT

We report the case of a 36-year-old female patient, who presented for a three months history of redness and ocular discomfort with a foreign body sensation, progressing rapidly without any tendency to remission despite symptomatic treatment with artificial tears. Her medical history included myeloblastic leukemia, which had been treated with a bone marrow allograft fifteen months previously. Ciclosporin 25 mg/day was her systemic treatment.
On clinical examination, visual acuity was a 2/10 on the right and 6/10 on the left eye. Slit-lamp examination revealed diffuse conjunctival hyperhemia, posterior blepharitis with meibomian gland dysfunction and a bilateral conjunctival palpebral fibrovascular membrane (figure.1).

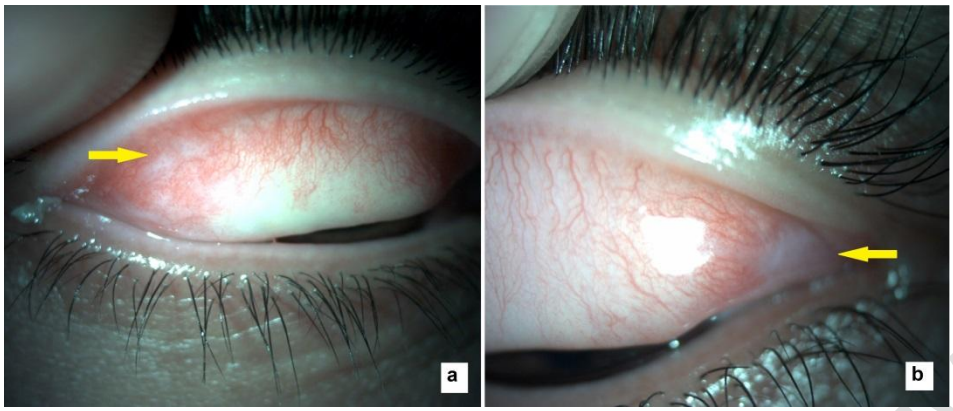


**Fig. 1.Image showing fibrovascular remodelling of the upper eyelids(yellow narrow). 1a/ right upper eyelid. 1b/ left upper eyelid.**

Corneal analysis revealed a diffuse loss of corneal reflex in the right eye with predominantly inferior quasi-global filamentous keratitis, associated to an inferonasal neovascular appeal, sectorial inferotemporal limbal insufficiency and dense and diffuse superficial punctate keratitis after fluorescein staining (figure.2).

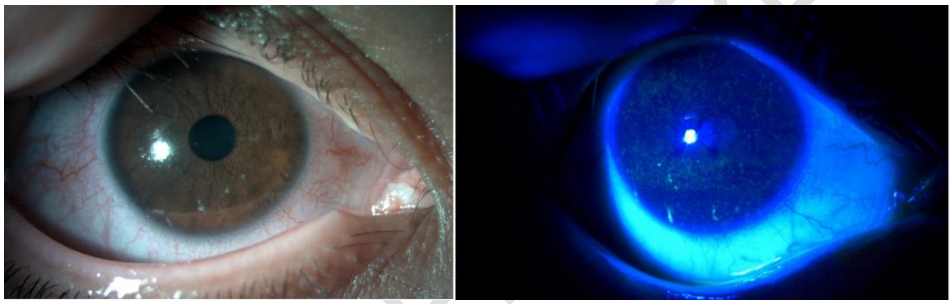

**Fig. 2. Image showing filamentous keratitis of the right eye and diffuse superficial punctate keratitis after fluorescein staining.**

There was no corneal thinning or ulceration. The anterior chamber was calm and the iris was normal with no sign of uveitis. The fundus exam revealed no abnormality. The Schirmer test was pathological (< 5 mm after 5 minutes) and the Break-up Time test was almost instantaneous. The left eye examination showed a central and inferior filamentous keratitis with a dense, diffuse superficial punctate keratitis.
In view of the bilateral nature of the dryness, the fibrocascular changes, the palpebral inflammation associated to the worsening of the symptoms despite topical symptomatic treatment, and the history of allogeneic hematological stem cell transplantation (allo-HSCT), The diagnosis of ocular GVH (graft-versus-host disease) was considered, and topical treatment was initiated with short courses of corticosteroids and an immunosuppressive 2% ciclosporin eye drop, in addition to palpebral hygiene measures and artificial tears. Within three weeks after starting treatment, the patient regained 4/10 visual acuity in her right eye, the disabling symptoms had largely resolved and the local clinical signs had clearly regressed. After 3 months of treatment, the visual acuity was 6/10 in the right eye and 8/10 in the left, and both eyes had clear corneas(figure.3).

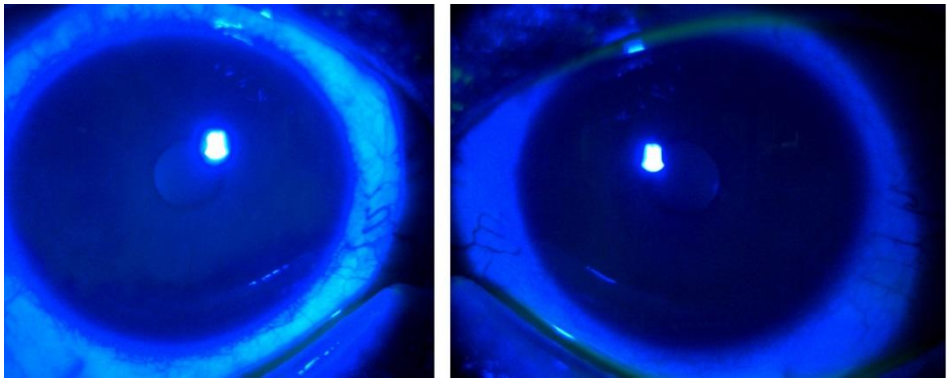

**Fig. 3.Image showing cicatrisation ad-intgrum of the right and the left cornea.**

## 3. DISCUSSION

Graft-versus-host disease (GVHD) is an immunological response in which the cells of the donor's immune system attack the cells of the patient receiving a haematopoietic stem cell transplant [1]. Ocular GVH is thought to affect between 40% and 90% of patients with chronic GVH [1].The main clinical manifestation of ocular GVH is dry eye [1]. It has three components: reduced aqueous secretion by infiltrated and inflammatory lacrimal glands, reduced lipid secretion due to meibomian gland dysfunction, and reduced mucus secretion associated with the disappearance of caliciform cells. More severe clinical signs may includ keratoconjunctivitis sicca, bilateral marginal keratitis, corneal ulceration, limbic insufficiency, conjunctival fibrosis, symblepharon, severe blepharitis, lacrimal gland fibrosis, anterior uveitis, etc. The diagnosis of ocular GVH should be suspected in any dry syndrome in a patient who has received an allogeneic haematopoietic stem cell transplant.
The functional symptoms described by patients are aspecific: dry, red eyes, ocular irritation, foreign body sensation, photophobia, etc. ... Slit lamp examination does not reveal any pathognomonic signs, but only signs of dry syndrome of varying severity. A classification was established in 2004 by Robinson et al (Table 1) [2], and treatment obviously depends on the severity of the clinical manifestation presented by each patient.

**Table 1. Chronic ocular GVH classification.**

| Grade | Clinical manifestations |
|---|---|
| Grade 1 | Conjunctival hyperaemia of the bulbar or palpebral conjunctiva |
| Grade 2 | Fibrovascular remodelling of the palpebral conjunctiva covering< 25% of the total surface area of at least one eyelid |
| Grade 3 | Fibrovascular remodelling of the palpebral conjunctiva covering 25-75% of the total surface area of at least one eyelid |
| Grade 4 | Remodelling of >75% of the conjunctivawith or without entropion scarring of at least one eyelid |

A consensus in 2006 [3] and a review of the literature in 2013 [4] defined four therapeutic goals: lubrication with preservative-free artificial tears, control of tear evaporation by treating meibomian gland dysfunction with lid care and, if necessary, doxycycline treatment, control of tear drainage with mechanical plugs and reduction of ocular surface inflammation. The latter is an important part of treatment. Topical corticosteroids may be used initially as a

short course to reduce ocular surface inflammation, scarring and fibrosis. Ciclosporin has revolutionised the functional and visual prognosis of ocular GVHD [5]. It increases corneal sensitivity, conjunctival keratocyte density and tear function.
Malta et al [5] even recommend a course of 0.05% ciclosporin eye drops one month before allogeneic transplantation in order to reduce the severity of ocular symptoms. Autologous serum, amniotic membrane grafts and scleral lenses may represent an alternative in the event of a pre-perforative defect. It seems important to provide a framework for the management of any planned ocular surgery in a patient with a history of allogeneic stem cell transplantation, although there is currently no consensus on the prevention of ocular GVH. In addition to the usual postoperative topical corticosteroids, treatment with cyclosporine ophthalmic solution 0.05% or 0.1% could limit these cases of severe ocular GVH. The methods of administering ciclosporin in these situations remains to be defined, and we propose that in our department, any planned surgery should be accompanied by the administration of ciclosporin eye drop in such cases, started 1 month before and continuing for at least 6 months after the surgery, in addition to standard postoperative topical corticosteroids. We also recommend extreme caution in cases of cataract surgery on pre-existing severe dryness; it is essential to check the inflammation of the ocular surface before proceeding with surgery.
Each figure should have a caption. The caption should be concise and typed separately, not on the figure area. Figures should be self-explanatory. Information presented in the figure should not be repeated in the table. All symbols and abbreviations used in the illustrations should be defined clearly. Figure legends should be given below the figures.] A sample figure is given in figure 1.

## 4. CONCLUSION

The major challenge is the early diagnosis of ocular GVH. This will allow early treatment of these patients and prevent progression to severe complications. The curative management of these patients has been revolutionised by topical immunosuppressive treatments. However, how best to prevent GVH remains to be determined.

## REFERENCES

1. Nassiri N, Eslani M, Panahi N, Mehravaran S, Ziaei A, DjalilianAR. Ocular graft versus host disease following allogeneic stemcell transplantation: a review of current knowledge and recommendations. J Ophthal Vis Res 2013;8:351—8.
2. Robinson MR, Lee SS, Rubin BI, Wayne AS, Pavletic SZ, Bishop MR,et al. Topical corticosteroid therapy for cicatricial conjunctivitisassociated with chronic graft-versus-host disease. Bone MarrowTransplant 2004;33:1031—5.
3. Couriel D, Carpenter PA, Cutler C, Bola˜nos-Meade J, TreisterNS, Gea-Banacloche J, et al. Ancillary therapy and supportivecare of chronic graft-versus host disease: national institutes of health consensus development project on criteria for clinicaltrials in chronic graft-versus host disease: V. Ancillary Therapyand Supportive Care Working Group Project. Biol Blood MarrowTranspl 2006;12:375—96.
4. Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: areview. Surv Ophthalmol 2013;58:233—50.
5. Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A,et al. Treatment of ocular graft-versus-host-disease with topicalcyclosporine 0.05 %. Cornea 2010;29:1392—6.