OCULAR MANIFESTATIONS OF GRAFT VERSUS HOST DISEASE FOLLOWING BONE MARROW TRANSPLANTATION

CLAES K., KESTELYN P.**

ABSTRACT

The ocular manifestations of **G**raft **V**ersus **H**ost **D**isease (GVHD) include keratoconjunctivitis sicca, cicatricial lagophthalmos, sterile conjunctivitis, corneal epithelial defects, corneal ulceration and melting. These manifestations are more frequent in patients with chronic GVHD than in patients with acute GVHD. The more severe ocular complications are associated with severe sytemic chronic GVHD and poorer survival. Recent improvements in the systemic management of these patients have led to the more frequent recognition of the ocular problems. The high prevalence of ocular involvement and potentially severe ocular problems in GVHD patients necessitate close ophthalmic monitoring.

RÉSUMÉ

Les manifestations oculaires de **G**raft **V**ersus **H**ost **D**isease (GVHD) englobent la kératoconjonctivite sèche, la lagophtalmie cicatricielle, la conjonctivite stérile, les lésions cornéennes épithéliales, les ulcères cornéens et le ''corneal melting''. Ces manifestations sont plus fréquentes chez les patients avec '' chronic GVHD '' que chez les patients avec '' acute GVHD ''. Les lésions oculaires les plus graves sont plutôt associées avec la forme grave systémique de GVHD avec un mauvais pronostic. Les progrès récents de la thérapie systémique de ces patients ont pour conséquence que les manifestations oculaires sont détectées plus fréquemment. Un examen ophtalmologique approfondi semble nécessaire vu la prévalence et la gravité des problèmes oculaires chez ces patients.

SAMENVATTING

De oculaire manifestaties van **G**raft **V**ersus **H**ost **D**isease (GVHD) omvatten keratoconjunctivitis sicca, cicatriciële lagoftalmie, steriele conjunctivitis, cornea-epitheeldefecten, cornea-ulcera en corneal melting. Deze manifestaties treden frequenter op bij patiënten met chronische GVHD dan bij patiënten met acute GVHD. De meer ernstige oogletsels zijn meestal geassocieerd met ernstige systemische chronische GVHD met slechtere overlevingskans. De recente vorderingen in de systemische behandeling van deze patiënten hebben echter tot gevolg dat de oogproblemen vaker herkend worden. Gezien de prevalentie en de ernst van de oogproblemen bij deze patiënten lijkt nauwgezet oftalmologisch onderzoek noodzakelijk.

KEY WORDS

Allograft
Bone marrow transplantation
Graft Versus Host Disease
Keratoconjunctivitis sicca

MOTS CLÉS

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* *Department of Ophthalmology, Ghent University Hospital, Belgium*

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INTRODUCTION

Bone marrow transplantation (BMT) is the treatment of choice for many hematological disorders. One can distinguish autologous, syngeneic and allogeneic BMT. In the first type the patient's own marrow is taken while he is in remission and stored for reinfusion at a later date. In the second type the donor is a monozygotic twin of the acceptor. In the allogeneic BMT marrow from a tissue matched donor is infused. Prior to infusion of the marrow the patients receive high-dose chemotherapy alone or in combination with total body irradiation (TBI) to eradicate all host malignant tissue and to minimise rejection of the donor marrow.

GVHD is the major noninfective complication of allogeneic BMT and occurs in about 50% of patients; about 25% has a lethal outcome (14). Ocular problems occur in 45 to 60% of GVHD patients (5,6).

Two distinct clinical syndromes of GVHD have been described; acute GVHD (a GVHD) and chronic GVHD (c GVHD). Acute GVHD develops within 3 to 4 weeks after allogeneic BMT and is characterised by severe liver dysfunction and cutaneous lesions of the erythematous type. The incidence ranges from 25 to 80% depending upon the age of the patient (12). Ocular manifestations are rare (7.2%) (8). They present as a pseudomembranous conjunctivitis and can be accompanied by corneal lesions. Chronic GVHD develops generally 3 to 6 months after allogeneic BMT and presents with a sclerodermoid or lichenoid skin reaction, oral and esophageal mucositis, pulmonary insufficiency, chronic liver dysfunction and ocular disease. The incidence ranges from 35 to 50% (4,15). About 80% of these patients have ocular problems: most often a Sjögren-like syndrome (1,11,13).

The natural course of ocular GVHD may be categorized into four stages. The initial subclinical stage manifests with tearing, mild nonspecific discomfort and photophobia. The eyes are slightly red and may have mild chemosis. The basal tear secretion can be normal. This stage can last for a few days to as long as 1 month before patients start to develop other systemic manifestations of GVHD or progress to a more severe form of ocular GVHD.

A patient in the active stage of ocular GVHD usually has other systemic manifestations of GVHD. The ocular manifestations vary from mucopurulent conjunctivitis and pseudomembranous conjunctivitis to punctate keratitis and corneal erosions. After this stage follows either the convalescent stage of the disease or progression to the necrotizing stage with corneal melting and sometimes perforation. The convalescent stage is characterized by a secondary sicca syndrome. The most frequent ocular manifestations of GVHD include keratoconjunctivitis sicca (KCS), cicatricial lagophtalmos, sterile conjunctivitis, corneal epithelial defects, corneal ulceration and corneal melting (5,6,9). Severe ocular manifestations such as pseudomembranous conjunctivitis, corneal epithelial defects and corneal melting are associated with severe systemic c GVHD and a poor survival (8,10).

PATIENTS AND METHODS

Four patients with severe ocular GVHD were followed. The patients were referred from the hematologic department of Ghent University Hospital for evaluation once they had been diagnosed with systemic GVHD based on skin or liver biopsy. The ophthalmological examination included visual acuity measurement, slit lamp examination and ophthalmoscopy, determination of tear film break-up time and Schirmer's test.

CASE REPORTS

Case 1

The first patient was a 53-year-old man who underwent allogeneic BMT for acute lymphocytic leukemia (ALL). He developed c GVHD, 4 months after BMT, characterized by severe liver dysfunction and eye problems. Systemic immunosuppressive drugs were started.

On the initial ocular examination, 18 weeks after BMT, his visual acuity was 9/10 in the right eye and 12/10 in the left eye. On slit lamp examination he showed interpalpebral Rose Bengal staining and extensive superficial punctate epithelial defects with filaments in both eyes. The break-up time was 2 seconds in both eyes.

Schirmer's testing after topical anesthesia showed 3 mm of wetting in the right eye and 2 mm in the left eye after five minutes. Treatment included preservative-free lubrication.

At the last consultation, one year and seven months after BMT, the patient had only mild keratoconjunctivitis sicca. In fundo a microvasculopathy with a small amount of preretinal and intraretinal hemorrhages and cotton-wool exsudates was visible.

Case 2

The second patient was a 36-years-old man, who underwent allogeneic BMT for acute myelogenous leukemia (AML). He developed c GVHD, 14 months after BMT, characterized by severe skin rashes, oral ulcers and eye pain. Systemic immunosuppressive drugs were started.

On the initial eye examination, 14 months after BMT, a visual acuity of 6/10 in the right eye and 10/10 in the left eye was measured. Slit lamp examination revealed swollen eyelids, conjunctival injection and confluent punctate epithelial erosions, more in the right than in the left eye. Rose Bengal staining was positive in the interpalpebral conjunctiva, the upper and lower bulbar conjunctiva, the whole corneal surface of the right eye and the central corneal surface of the left eye. Schirmer's testing after topical anesthesia showed 2 mm of wetting in the right eye and 3 mm in the left eye. Under intensive lubrication and eye patching, the epithelial erosions healed and the vision improved to 10/10 OU but he developed poliosis and severe ulcerative blepharitis. The conjunctival lesions persisted.

At the last consultation, one year and eight months after BMT, the patient had a visual acuity of 10/10 OU. The eyelid margins were irregular and there was scarring of the lower tarsal conjunctiva. There were still some punctate epithelial erosions present on the right cornea. Schirmer's testing with topical anesthesia showed 4 mm of wetting in the right eye and 5 mm in the left eye. Rose Bengal staining pattern changed to inferior and superior corneal staining in the right eye and dense staining at the eyelid margins and inferior and superior limbal conjunctiva OU.

Case 3

The third patient was a 52-year-old man who underwent allogeneic BMT for myelodysplasia. He developed c GVHD, 9 months after BMT, characterized by liver dysfunction and ocular problems. Systemic immunosuppressive drugs were started.

On the initial ocular examination, 9 months after BMT, a visual acuity of 10/10 in the right eye and 3/10 in the left eye was measured. Both eyes were injected and the eyelids were swollen. Slit lamp examination showed in the right eye: severe superficial punctate keratopathy with two little corneal epithelial defects. In the left eye there was a 40% corneal epithelial defect and a zone of corneal melting in the inferior perilimbal region. Treatment included preservative-free lubrication, prednisolone 1% and eye patching. Topical cyclosporin A 2% was abandoned by the patient after a few instillations. The clinical response was fairly good: the stromal melting stopped but a zone of stromal thinning persisted.

At the last consultation, one year and nine months after BMT, his visual acuity was 10/10 in the right eye, and 9/10 in the left eye. He suffered from recurrent epithelial erosions because of nearly absent tear secretion: Schirmer's testing after topical anesthesia showed no wetting after five minutes. The zone of stromal thinning was still present.

Case 4

The fourth patient was a 48-year-old female who underwent allogeneic BMT for Morbus Kahler. She developed c GVHD 8 months after BMT characterized by liver dysfunction, pulmonary insufficiency and ocular problems. Systemic immunosuppressive drugs were started.

On the initial ocular examination, 8 months after BMT, she had a visual acuity of 10/10 in the right eye and 2/10 in the left eye. Slit lamp examination showed severe punctate epithelial erosions with filaments in the right eye. Schirmer's testing after topical anesthesia showed 2 mm wetting after five minutes. In the left eye there was conjunctival injection and an impending corneal perforation. Schirmer's testing after topical anesthesia showed no wetting after five minutes. Two days later, the ul-

ceration perforated with incarceration of the iris. Cultures and scrapings were sterile. The perforation was treated with an autologous scleral patch, topical antibiotics, steroids, atropine 1% and cyclosporin A 2%. Three days postoperatively she was transferred to the intensive care unit because of pulmonary aspergillosis. The aspergillus infection became systemic and she developed an endophthalmitis with secondary retinal detachment in the left eye. The fundus of the right eye remained normal.
At that moment she refused surgery. Eventually an intravitreal injection of amphotericine B was given. One year after scleral patching, enucleation was performed because of irritation and pain. Preoperatively, the anterior segment was calm, the lens cataractous, but the posterior segment was completely necrosed.
At the last consultation, one week after enucleation and one year and eight months after BMT, she had mild keratoconjunctivitis sicca and a visual acuity of 10/10 in the right eye. The result of the anatomopathologic examination of the enucleation specimen was not known yet.

DISCUSSION

GVHD is an immunological reaction initiated by donor T-lymphocytes which act against host tissues, including the eyes. The pathogenesis of the ocular changes is not completely understood.
Secondary keratoconjunctivitis sicca (KCS) may occur as a result of the pre-transplant regimen, which may include total body irradiation and/or chemotherapy. Orbital irradiation, even at the dosage regimen used for marrow transplantation, is a contributory factor to the development of KCS (2,3). KCS can also result from a toxic reaction to either methotrexate or azathioprine (5,7). Secondary KCS can also occur as a result of an immune process after transplantation: the graft versus host reaction (7,11,13). The ocular changes seen at the convalescent stage of the ocular GVHD are likely due to the previously active immunological process: the inflammation destroys the meibomian glands located at the eyelid margins, the surface epithelium of the conjunctiva and cornea, the goblet cells, and the lacrimal glands. This results in severe ocular surface problems.
The most serious ocular manifestations of GVHD appear quite similar to those of keratoconjunctivitis sicca from other causes. As in other dry eye patients, the often dramatic ocular problems require constant surveillance.
Treatment of patients with ocular GVHD is dual: it includes the treatment of the systemic manifestations and the treatment of the ocular manifestations of GVHD (10). The systemic treatment of GVHD consists of corticosteroids, cyclosporin and/or other immunosuppressive medication. The ocular therapy includes topical ocular lubricants, antibiotics and steroids, eye patching, bandage soft contact lenses, punctal occlusion, conjunctival patch, scleral flap and/or tarsorrhaphy. The patient's responses to the therapies attempted were as expected but could not prevent the evolution to corneal melting and severe secondary KCS. The addition of topical cyclosporin A 1%, a potent immunosuppressor especially for T-helper cells, can probably help in the management of epithelial keratitis and the melting process and can probably minimize the immune destruction responsible for the development of keratitis sicca (10). Unfortunately, topical cyclosporin A 1% is not commercially avalaible. Cyclosporin A 2% in olive oil, as used in our patients, is so irritating that most of our patients abandonned it after a few instillations.
Ocular symptoms may be the first presentation of GVHD and they may be seen in the absence of systemic manifestations of GVHD. The initial stage of ocular GVHD manifests as tearing, mild nonspecific discomfort and photophobia. These symptoms can easily be missed or attributed to simple dry eyes while the patient shows already important ocular lesions at the first ophthalmological examination. In our first two cases, the eye findings on initial ophthalmological examination were compatible with an active stage of ocular GVHD. In the other two cases the eye findings were compatible with the necrotizing stage. Therefore, in the four cases presented here, the initial stage of ocular GVHD was subclinical or not recognised.
Focusing on the many life-threatening problems present in this group of patients may explain why the ocular complications are seen with such a delay.
Our second case was still in the active stage of ocular GVHD and the three other patients were in the convalescent stage. The long-term follow-up of these three patients is about one year

and a half after the onset of ocular GVHD. At the end of the follow-up, the first patient showed only mild secondary KCS, the third patient suffered from debilitating secondary KCS and the left eye of the fourth patient had been enucleated. Ocular GVHD can thus severely affect the quality of life in these patients, even when the systemic GVHD is under control.

Ocular complications of GVHD are very frequent and often debilitating. Since the prognosis of patients with GVHD improved considerably, detailed ocular examination should be performed routinely prior to the onset of eye symptoms. Ophthalmologists and oncologists need to be aware of the possibility of ocular GVHD in patients who have undergone an allogeneic BMT.

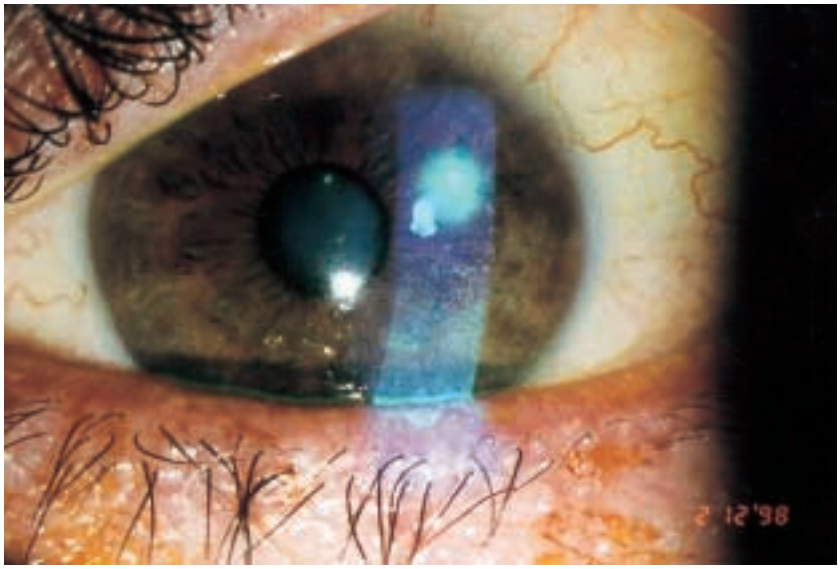

fig. 1.: Left eye of a patient with ocular GVHD in the convalescent stage: severe KCS.

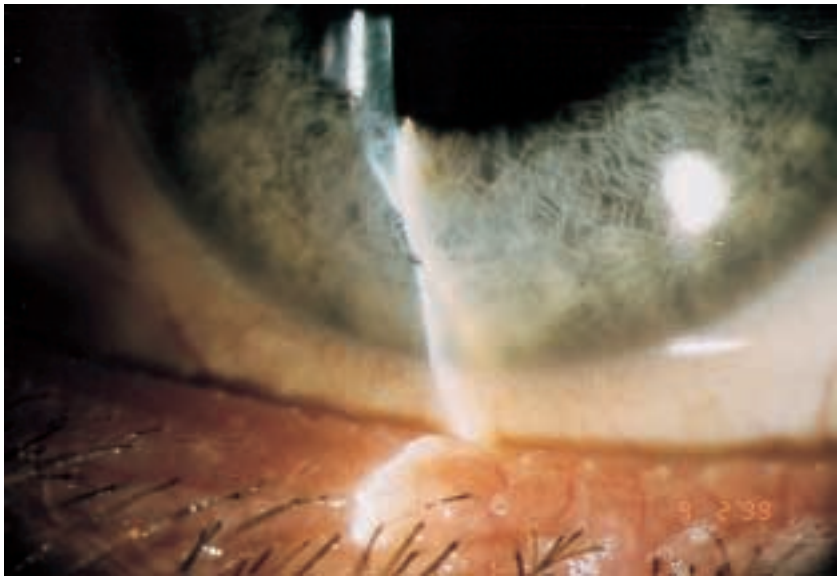

fig. 2.: Left eye of a patient with ocular GVHD in the necrotizing stage: impending corneal perforation.

REFERENCES

(1) AROCKER-ME., SKORPIK F., GRABNER G., HINTERBERGER W., GADNER H. – Manifestations of graft-versus-host disease following allogenic bone marrow transplantation. Eur J Ophthalmol, 1991, 1: 28-32.

(2) BAUTISTA JUANES JA., THEISCHEN M., BEELEN DW., PAULEIKHOFF D., KOCH JM., WAUBKE TN., WESSING A. – Okuläre Komplikationen bei Langzeitüberlebenden nach Knochenmarktransplantation. Eine prospektive Studie mit 21 Patienten. Klin Monatsbl Augenheilkd, 1993, 202: 110-115.

(3) BRAY LC., CAREY PJ., PROCTOR SJ., EVANS RGB., HAMILTON PJ. – Ocular complications of bone marrow transplantation. Br J Ophthalmol, 1991, 75: 611-614.

(4) COSKUNCAN NM., JABS DA., DUNN JP., HALLER JA., GREEN WR., VOGELSANG GB., SANTOS GW. – The Eye in Bone Marrow Transplantation. Arch Ophthalmol, 1994, 112: 372-379.

(5) FRANKLIN RM., KENYON KR., TUTSCHKA PJ., SARAL R., GREEN RW., SANTOS GW. – Ocular Manifestations of Graft-vs-Host Disease. Ophthalmology, 1983, 90: 4-12.

(6) HIRST LW., JABS DA., TUTSCHKA PJ., GREEN RW., SANTOS GW. – The Eye in Bone Marrow Transplantation. Clinical Study. Arch Ophthalmol, 1983, 101: 580-584.

(7) JABS DA., HIRST LW., GREEN RW., TUTSCHKA PJ., SANTOS GW., BESCHORNER WE. – The Eye in Bone Marrow Transplantation. Histopathology. Arch Ophthalmol, 1983, 101: 585 - 590.

(8) JABS DA., WINGARD J., GREEN RW., FARMER ER., VOGELSANG G., SARAL R. – The Eye in Bone Marrow Transplantation. Conjunctival Graft-vs-Host Disease. Arch Ophthalmol, 1989, 107: 1343 - 1348.

(9) JACK MK., JACK GM., SALE GE., SHULMAN HM., SULLIVAN KM. – Ocular Manifestations of Graft-vs-Host Disease. Arch Ophthalmol, 1983, 101: 1080 - 1084.

(10) KIANG E., TESAVIBUL N., YEE R., KELLAWAY J., PRZEPIORKA D. – The use of topical cyclosporin A in ocular graft-versus-host-disease. Bone Marrow Transplantation, 1998, 22: 147-151.

(11) LIVESEY SJ., HOLMES JA., WHITTAKER JA. – Ocular Complications of Bone Marrow Transplantation. Eye, 1989, 3: 271 - 276.

(12) SULLIVAN KM. – Acute and chronic graft-versus-host disease in man. Int J. Cell Clon, 1986, 4 (supp. 1): 42-93.

(13) TICHELLI A., DUELL T., WEISS M., SOCIE G., LJUNGMAN P., COHEN A., VAN LINT M., GRATWOHL A., KOLB HJ for the European Group for Blood and Marrow Transplantation (EBMT) Working Party on Late Effects: Late-onset keratoconjunctivitis sicca syndrome after bone marrow transplantation: incidence and risk factors. Bone Marrow Transplantation, 1996, 17: 1105 - 1111.

(14) TUTSCHKA PJ., BARTIN MM. – Graft-vs-Host disease. Transplant proc., 1981, 13: 1267-1269.

(15) WINGARD JR., PIANTADOSI S., VOGELSANG GB. – Predictors of death from chronic graft-versus-host disease after bone marrow transplantation. Blood, 1989, 74: 1428 - 1435.

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Mailing address:
K. Claes
Dienst Oogziekten
U.Z. Gent
De Pintelaan 185
B - 9000 Gent