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Upregulation of ICAM-1 expression in the conjunctiva of patients with chronic graft-versus-host disease

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PURPOSE. *To correlate conjunctival intercellular adhesion molecule 1 (ICAM-1) expression with cytologic and clinical findings of chronic graft-versus-host disease (GVHD).*
METHODS. *Seven patients with chronic GVHD-related keratoconjunctivitis and five age-matched normal controls were recruited for the study. Clinical examination included medical history, visual acuity, evaluation of ocular signs and symptoms (scored from 0 to 3), corneal fluorescein staining (scored from 0 to 5 on the basis of the number of corneal sectors involved), Schirmer test type I, and break-up time (BUT). Impression cytology samples were collected from the nasal and inferior bulbar conjunctiva of patients and controls. Goblet cells were counted in three randomly selected fields and averaged. Immunofluorescent staining for ICAM-1 was carried out and the percentage of cells expressing the marker was evaluated.*
RESULTS. *All patients showed signs and symptoms of keratoconjunctivitis sicca. Schirmer test type I and BUT were reduced (4.8±6.7 mm/5 min and 3.9±2.7 seconds, respectively). Goblet cells were significantly reduced in GVHD eyes with respect to normal eyes (65±30.5 and 192±16.9 cells/field respectively; $p<0.001$). Goblet cell number was directly related to Schirmer test values ($p<0.01$, $rho=0.817$) and inversely related to total sign score ($p<0.01$, $rho=-0.939$). ICAM-1 expression was increased in GVHD eyes with respect to normal controls, in which no staining was observed. ICAM-1 expression showed an inverse relation to goblet cell number ($p<0.01$, $rho=-0.852$) and Schirmer test values ($p<0.01$, $rho=-0.926$), and was directly correlated to total sign score ($p<0.01$, $rho=0.982$).*
CONCLUSIONS. *Conjunctival ICAM-1 expression is increased in GVHD patients. The severity of the disease is associated with tear parameters, goblet cell decrease, and inflammatory markers, such as ICAM-1. (Eur J Ophthalmol 2006; 16: 17-23)*

KEY WORDS. *Conjunctiva, Graft-versus-host disease, ICAM-1, Impression cytology*

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INTRODUCTION

Graft-versus-host disease (GVHD) is an immune-mediated disorder that occurs after allogenic hematopoietic stem cell transplantation (SCT), when donor T cells recognize major and/or minor histocompatibility antigens and react against the host (1). In GVHD patients, ocular involvement occurs in more than 50% of cases, with manifestations ranging from keratoconjunctivitis sicca to cicatricial lagophthalmos, sterile conjunctivitis, cataract formation, uveitis, and choroidal and retinal microvasculopathy (2-6). Dry eye is considered a major complication of chronic GVHD with a significant impact on the quality of life of these patients (6). Dry eye syndrome in patients subjected to stem cell transplantation is the consequence of total body irradiation, ocular toxicity of chemothera-

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peutic drugs, lachrymal gland infiltration and fibrosis, and ocular surface inflammation (2, 7); in addition, ocular surface inflammation could be stimulated by donor T cells through changes in mucous production (6, 8).

Inflammatory reactions are regulated by interactions between immune cells and resident cells. These interactions are dependent on the expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1). An upregulation of ICAM-1 has been described in affected skin and intestine of animal models of GVHD (9, 10). ICAM-1 expression was also found to be increased in peripheral blood T cells, serum, liver, and skin of human GVHD (11-14). In addition, blockade of ICAM-1 by a monoclonal antibody led to clinical improvement and increased survival after small bowel transplantation in rats (15, 16). However, at present there are no data regarding conjunctival ICAM-1 expression in GVHD patients with ocular involvement.

Thus, the aims of this study were to evaluate conjunctival ICAM-1 expression in chronic GVHD patients and to correlate it with epithelium changes and clinical characteristics of the disease.

METHODS

We examined seven patients (four men and three women [14 eyes]; mean age 39.1±16 years, range 15–58 years) with chronic GVHD referred to our Cornea and Ocular Surface Disease Center in 2003 (Tab. I). Patients were compared to five age-matched normal subjects (three men and two women; mean age 31±5.4 years, range 25–38 years).

After signing informed consent, all patients received a complete ocular examination including visual acuity, slit lamp evaluation, tonometry, and fundus examination. All symptoms referred by the patients, such as dryness, lid swelling, foreign body sensation, redness, photophobia, secretion, and burning, were collected and scored from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe). Total symptom score was also calculated. Ocular signs, such as hyperemia, chemosis, fibrosis, secretion, Meibomian gland dysfunction (MGD), filamentous keratitis, and corneal involvement (i.e., epithelial defects, superficial neovascularization, corneal pannus), were collected and scored from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe). Corneal fluorescein staining was evaluated and quantified from 0 to 5 based on the number of corneal sectors (temporal, inferior, nasal, superior, and central) involved. Tear film was evaluated by Schirmer test type I and break-up time (BUT). Total sign score was calculated as the sum of the score of ocular signs and corneal fluorescein staining.

Conjunctival impression cytology samples were collected using a membrane (Millicell CM 0.4 mm, Millipore, Bedford, MA) from the nasal and inferior bulbar conjunctiva of each eye in affected patients and controls (two samples were collected from each area, for a total of four samples per eye).

Of the two samples collected from each area, one was stained with Periodic acid-Schiff (PAS) reagent (Sigma-Aldrich, St. Louis, MO) to identify goblet cells, and the other sample was used to detect ICAM-1 expression by immunofluorescence.

PAS staining was carried out according to previously published procedures (17, 18). The membranes were

TABLE I - CLINICAL CHARACTERISTICS OF GRAFT-VERSUS-HOST DISEASE (GVHD) PATIENTS INCLUDED IN THE STUDY

Patient	Age, y/sex	Underlying disease	Months since SCT	Months since dry eye onset	Systemic therapy for GVHD	Topical therapy
1	45/M	NHL	36	18	None	Tear substitutes
2	35/M	ALL	54	48	CyA	Tear substitutes + NSAIDs
3	24/F	ALL	24	24	Steroid	Tear substitutes
4	57/F	ALL	36	16	Steroid	Tear substitutes + NSAIDs
5	40/F	CML	60	48	Dapsone	Tear substitutes + NSAIDs
6	58/M	AML	24	18	None	Tear substitutes
7	15/M	Fanconi anemia	66	60	Plasmapheresis	Tear substitutes + steroids

SCT = Stem cell transplantation; NHL = Non-Hodgkin lymphoma; ALL = Acute lymphoblastic leukemia; CyA = Cyclosporin A; NSAIDs = Non-steroidal antiinflammatory drugs; CML = Chronic myeloblastic leukemia; AML = Acute myeloblastic leukemia

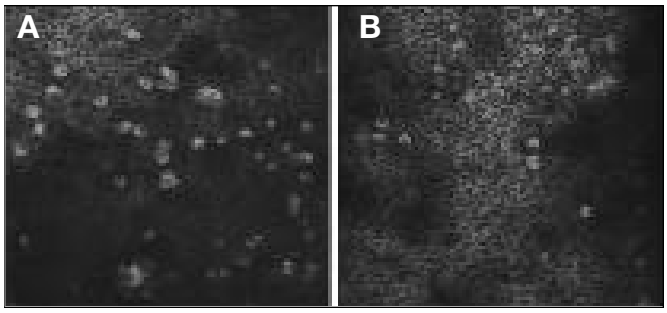

Fig. 1 - *Immunofluorescent staining for intercellular adhesion molecule 1 (ICAM-1) of conjunctival impression cytology samples in two graft-versus-host disease patients:* **(A)** *35% of cells expressing ICAM-1;* **(B)** *more than 70% of cells expressing ICAM-1 (x20 enlargement).*

placed on slides and mounted with Pristine mount (Invitrogen Life Techniques, Carlsbad, CA).Goblet cells were counted in three randomly selected microscopic fields (x20 enlargement) in a masked fashion and the mean value was calculated for each eye.

Immunofluorescence was performed using mouse anti-ICAM-1 antibody (Research Diagnostics Inc.) diluted 1:50 in 10 mM PB-137mM NaCl (PBS).

Specific binding of the primary antibody was detected using anti-mouse Cy3 (Jackson ImmunoResearch Laboratories Inc., PA), diluted 1:200 in PBS. To assess the specificity of ICAM-1-antibody binding, conjunctival impression cytology samples were exposed to non-specific purified mouse immunoglobulins.

The membranes were then placed on slides, mounted with an antifade solution (AF1, Cityfluor, Cambridge, UK), and viewed using a E2000U confocal microscope equipped with two lasers and a DAPI lamp (Nikon, Tokyo, Japan). The images were evaluated with Adobe Photoshop 7.0 program (Adobe Systems Inc., San Jose, CA).

Conjunctival cells expressing ICAM-1 were counted in three randomly selected microscopic fields (x20 enlargement) in a masked fashion. Values were expressed as the percentage of immunopositive cells per field.

Spearman rho test (software SPSS 8.0, SPSS Inc., Chicago, IL) was used as statistical analysis for all correlations.

RESULTS

The clinical characteristics of patients enrolled in the study are listed in Table I. All patients had received allogenic stem cell transplantation more than 2 years previously (on average 3.6±1.4 years) and had developed chronic GVHD with ocular manifestations since 33.1 ±18.2 months. Systemic therapy for GVHD included cyclosporin A (n=1), dapsone (n=1), plasmapheresis (n=1), and oral steroids (n=2). All patients were utilizing topical ophthalmic treatments, including tear substitutes alone (n=3) or associated with nonsteroidal anti-inflammatory drug eyedrops (n=3) or steroids (n=1).

TABLE II - CLINICAL SYMPTOMS REFERRED BY GRAFT-VERSUS-HOST DISEASE PATIENTS ENROLLED

Patient/eye	Dryness	Lid swelling	FBS	Redness	Photophobia	Secretion	Burning	Total symptom score
1/R	3	0	2	2	3	2	2	14
1/L	3	0	2	2	3	2	2	14
2/R	0	0	2	2	1	1	0	9
2/L	2	0	2	2	1	1	0	9
3/R	2	0	0	1	1	1	2	7
3/L	0	0	0	1	1	1	2	7
4/R	3	3	0	1	0	2	0	6
4/L	3	3	0	1	0	2	0	6
5/R	3	0	3	1	1	1	2	11
5/L	3	0	3	1	1	1	2	11
6/R	3	0	2	2	0	1	2	10
6/L	3	0	2	2	0	1	2	10
7/R	3	2	2	1	3	3	1	15
7/L	3	2	2	1	3	3	1	15

FBS= Foreign body sensation

All patients complained of ocular redness and secretion. Other symptoms referred by patients included dryness (n=6), foreign body sensation (n=5), photophobia (n=5), burning (n=5), and eyelid swelling (n=2). The mean value of total symptom score was 10.3± 3.4. All symptoms referred by patients are summarized in Table II.

At clinical examination, mean best-corrected visual acuity was 0.7±0.4 (from 18/300 to 20/20). All patients showed conjunctival hyperemia and secretion. Six patients showed Meibomian gland dysfunction (MGD), two had filamentous keratitis, and one had severe corneal involvement with superficial neovascularization and corneal pannus. Corneal fluorescein staining score showed a mean value of 3.6±1.9 corneal sectors involved (range 1 to 5 corneal sectors). The mean value of total sign score was 8.1±5.3.

Schirmer test type I was significantly reduced in GVHD patients with respect to normal subjects (4.8±6.7 mm/5 minutes versus 14.4±5.6 mm/5 minutes, $p<0.05$). Break-up time test was also significantly reduced in all patients (3.9±2.7 seconds versus 12.5±3.1 seconds, $p<0.05$). All ocular signs and tear function parameters of GVHD patients are summarized in Table III.

Conjunctival impression cytology samples from GVHD patients showed squamous metaplasia associated with a decreased number of goblet cells. Indeed, goblet cell number was reduced in GVHD patients (mean value 65±30.5, range 16 to 127 cells/field) with respect to normal controls (mean value 192±16.9, range 170 to 206 cells/field, $p<0.001$). Conjunctival epithelial expression of ICAM-1 (mean value 44.2±18.9%) was increased in affected eyes with respect to normal controls, in which no expression of ICAM-1 was found (Fig. 1, A and B). The increased ICAM-1 expression in GVHD samples showed an inverse relation to goblet cell number ($p<0.01$, rho=-0.852). Conjunctival ICAM-1 expression was inversely related to Schirmer test values ($p<0.01$, rho=-0.926) while goblet cell number showed a direct correlation ($p<0.01$, rho=0.817). No other correlations were found between cytologic features and clinical findings (duration of the disease, topical or systemic therapy, total symptoms score, fluorescein staining score, and BUT).

In order to evaluate if cytologic parameters could be useful markers of ocular GVHD severity, goblet cell number and ICAM-1 expression were correlated with total sign score of patients. Our data showed that conjunctival goblet cell number was inversely correlated to total sign score ($p<0.01$, rho=-0.939), while ICAM-1 expression was directly correlated to total sign score ($p<0.01$, rho=0.982).

DISCUSSION

In this report, we evaluated GVHD patients with chronic keratoconjunctivitis. All patients complained of ocular surface discomfort symptoms and showed clinical and

TABLE III - OCULAR SIGNS OF GRAFT-VERSUS-HOST DISEASE PATIENTS ENROLLED

Patient	Hyperemia	Chemosis	Fibrosis	Secretion	MGD	Corneal involvement	CFS	Schirmer test	BUT	Total score
1/R	2	0	0	1	0	0	5	2	3	8
1/L	2	0	0	1	0	1	2	2	5	6
2/R	1	0	0	1	1	0	5	3	3	8
2/L	0	0	0	0	1	0	5	8	6	6
3/R	1	0	0	1	1	0	1	2	7	4
3/L	1	0	0	1	1	0	1	4	5	4
4/R	1	0	0	0	1	0	1	20	8	3
4/L	1	0	0	0	1	0	1	20	8	3
5/R	1	0	0	1	1	0	5	2	3	8
5/L	1	0	0	1	1	0	5	2	3	8
6/R	2	0	0	1	1	0	5	2	0	8
6/L	1	0	0	1	1	1	5	1	0	9
7/R	3	2	2	3	2	2	5	0	2	19
7/L	3	2	2	2	2	3	5	0	1	19

MGD = Meibomian gland dysfunction; CFS = Corneal fluorescein staining; BUT = Break-up time

cytologic signs of inflammation and dry eye, including reduction of Schirmer test and BUT values and decreased goblet cell number.

We found an increased conjunctival epithelial expression of ICAM-1 in GVHD patients. ICAM-1 is an intercellular adhesion molecule that regulates the interaction between cells and lymphocytes in immune cascades (19, 20). ICAM-1 and its ligand, lymphocyte-function associated antigen (LFA-1), have been shown to be up-regulated during chronic inflammation and in particular in GVHD reactions (21). The increased expression of ICAM-1 is particularly evident in tissues targeted by the disease such as skin and intestine in animal models of the disease (9, 10) and peripheral blood T cells, serum, liver, and skin of human GVHD (11-14). These findings suggest a role of ICAM-1 in the pathogenesis of GVHD, a role further confirmed by the improvement of disease symptoms after blocking of ICAM-1 and/or LFA-1 by monoclonal antibodies in animal models (15, 16).

Our data showed that increased conjunctival epithelial expression of ICAM-1 was associated with clinical and cytologic parameters of the disease. In particular, the expression of ICAM-1 was related to Schirmer test values and to goblet cell number reduction, highlighting the fundamental role of the immune reaction in the development of dry eye characteristics in GVHD patients.

The role of ICAM-1 in the pathogenesis of dry eye has been highlighted by other studies, both in patients with keratoconjunctivitis sicca and in animal models of the disease. ICAM-1 has been shown to be up-regulated in lachrymal acinar epithelial cells and conjunctival epithelial cells of the MRL/lpr mouse, an animal model of Sjögren-like keratoconjunctivitis sicca (22).

In addition, ICAM-1 is up-regulated in epithelial cells of the conjunctival and accessory lacrimal tissues in dry eye patients (22), and in particular both in Sjögren's syndrome keratoconjunctivitis sicca (SS-KCS) and non-Sjögren's keratoconjunctivitis sicca (NS-KCS) (23). The possibility that the clinical symptoms of KCS may be more dependent on T-cell activation and the resultant inflammation than previously believed has led to numerous clinical studies evaluating the use of topical anti-inflammatory drugs, such as cyclosporin A, in the treatment of dry eye (24-28) and, more specifically, has introduced the possibility of targeting the ICAM-1/LFA-1 inflammatory pathway by using monoclonal antibodies (22).

We found a different expression of ICAM-1 on the basis of clinical signs of the disease (total sign score), suggesting the possibility of utilizing it as a non-specific marker of disease severity. To our knowledge, there are no studies correlating ICAM-1 expression to disease severity in GVHD or dry eye. However, ICAM-1 expression has been considered as a parameter of disease severity and progression in Graves' ophthalmopathy (29) and as a negative prognostic factor in vitreoretinal proliferation (30).

In addition, ICAM-1 has been evaluated as parameter of response to anti-histamine therapy in allergic conjunctivitis (31) and glucocorticoid therapy in Graves' ophthalmopathy (29, 32). While ICAM-1 can certainly not be considered specific to any of these diseases, including GVHD, the fact that it can be rapidly and easily evaluated in patients makes it a potentially interesting non-specific marker to assess in the course of various ocular diseases.

Further studies are required in order to evaluate if ICAM-1 expression could represent a marker of disease progression or of response to therapy in patients with graft-versus-host disease. In addition, the characterization of the role of ICAM-1 in dry eye, and in particular in GVHD, could lead to the development of future potential targets of medical treatment.

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