Abstract

Allogeneic hematopoietic stem cell transplantation is considered the standard of care for hematological and lymphoid malignancies. One of the complications associated to this therapy is an immune-mediated reaction known as graft versus host disease with repercussions towards many organs and tissues. In this article, ocular complications of graft versus host disease will be reviewed.

**Keywords:** bone marrow transplantation; graft versus host disease; dry eye.

Introduction

Bone marrow and peripheral blood stem cells transplantation, also known as allogeneic hematopoietic stem cell transplantation (AHSCT), are procedures largely performed around the world to treat hematological disorders and some metabolic diseases.1-3 Besides its clinical efficacy, AHSCT is associated to a serious complication known as Graft versus Host Disease (GvHD), which can be fatal or affecting quality of life of long-term survivors suffering of this immune reaction.

Patients submitted to allogeneic bone marrow or peripheral blood stem cell transplantation may present an immune T-cell mediated reaction against skin, eyes or gastrointestinal tract few weeks after the allogeneic transplantation. This immune reaction is result of a very complex interaction between donor and recipient adaptive immunity. This complication occurs when genetically defined proteins of the recipient cells such as HLA (Human Leukocyte Antigen) respond to donor T cells starting the immunerreactive process.4

Historically, GvHD developing within 100 days after allogeneic transplantation is considered acute (aGvHD) and describes a distinctive syndrome of dermatitis, hepatitis and enteritis.5 After this period of time, is considered chronic (cGvHD) and is associated to ocular, oral, gastrointestinal, pulmonary and neuromuscular manifestations.6

As the temporal classification of the disease is subjected to error due to overlapping signals and symptoms, in 2005, a group of experts, sponsored by the National Institute of Health, standardized the definition of aGvHD and cGvHD (Table 1).7

Clinical presentation

In the acute form, with estimated incidence of 40 to 60% among patients receiving HSCT from HLA-identical sibling donors and 75% in patients receiving HLA matched unrelated donors5, patients presenting the following signs and symptoms, two or three weeks after the allogeneic transplantation may be suspicious for aGvHD:

- **High fever;**
- **Dermatology:** Pruritic rash, maculopapular exanthema, thickening of skin;
- **Eyes:** Hemorrhagic conjunctivitis and pseudomembranes;
- **Gastrointestinal disorders** (diarrhea, intestinal bleeding, abdominal pain).

Anorexia and upper GI symptoms are common in older patients.
If not under clinical control, this form of GvHD can be lethal.\(^7\)

In the chronic form, manifestations can be widespread or present in a single organ or tissue:

- Ocular involvement (irritation, ocular burning and diminished or absent tear secretion, dry eye);
- Atrophy of oral mucosa leading to dry mouth, intolerance to spicy or acidic food, dysphagia;
- Anorexia and weight loss;
- Loss of hair (alopecia);
- Pulmonary symptoms (bronchiolitis obliterans) such as wheezing, dyspnea, chronic cough;
- Pericarditis;
- Weakness, muscle cramps and neuropathic pain.

### Risk factors for GvHD

Patients submitted to allogeneic stem cell transplantation are at risk for developing GvHD. In aGvHD, the most important associated risk factor is donor/recipient human leukocyte antigen (HLA) match.\(^7\) Perfect matched patients have low risk of developing GvHD. Other risk factors are advanced age of either the donor or the recipient and a female donor who has been pregnant in the past.\(^7\)

In cGvHD, there is a higher risk in patients who have received allogeneic hematological stem cells from HLA-mismatched related-donor or from HLA-matched unrelated-donor. Patients that may have experienced aGvHD and older recipients also are at risk.\(^9\)

Table 2 summarizes the procedures associated with high risk of GvHD.

### Ocular manifestations of GvHD

Can be present and affect 60 to 90% of patients with cGvHD, with similar symptoms and signals of an immune mediated inflammatory disease such as Sjögren syndrome. The onset of ocular GvHD after AHSCT is variable and is influenced by donor-recipient matching characteristics. In the majority of patients with GVHD, ocular involvement follows the occurrence of systemic manifestations; however, importantly, it can also precede or develop independently of systemic disease in a minority of patients.\(^11\)

GvHD usually affects the ocular surface, including primarily the conjunctiva, meibomian glands and lachrymal gland. The ocular surface disease induced by fibrosis of lachrymal gland\(^12,13\), dysfunction of meibomian glands\(^14-21\) and chronic inflammation of the conjunctiva\(^14-17\) affects the cornea secondarily. The induced secondary dry eye and ocular surface dysfunction leads to punctate keratopathy, larger erosions, keratolysis and even corneal perforation (Figure 1).\(^14-17,21\)
In patients developing ocular surface symptoms, assessment of disease status can be made by a thorough clinical evaluation. Clinical work-up may include the use of questionnaires such as McMonnies, OSDI and others, ocular surface vital staining (with fluorescein, rose bengal or lisamine green), tear break-up time evaluation (invasive or non-invasive with the Tearscope or similar), Schirmer test 1 and with anesthetic and nasal stimulation, impression cytology, meibiomicroscopy, tear evaporimetry, tear osmometry, among others.

### Management of ocular manifestations of GVHD

In addition to systemic therapy with steroids (pulsetherapy with methylprednisolone followed by short term oral 1 mg/Kg/day of prednisone) alone or combined with methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, daclizumab, thalidomide, anti-IL2 receptor, tacrolimus, mycophenolate mofetil, combined with methotrexate, cyclosporine, oral 1 mg/Kg/day of prednisone) alone or methylprednisolone followed by short term pulse therapy with steroids (pulsetherapy with methylprednisolone 1000 mg IV 2 times/day for 3 days), topical immunosuppressors2,15,17-22, when ocular anti-CD5-specific immunotoxin and others, ocular surface vital staining (with fluorescein, rose bengal or lisamine green), tear break-up time evaluation (invasive or non-invasive with the Tearscope or similar), Schirmer test 1 and with anesthetic and nasal stimulation, impression cytology, meibiomicroscopy, tear evaporimetry, tear osmometry, among others.

Preservative-free artificial tears and lubricants can be associated with topical steroids, as well as topical 0,05% to 0,1% cyclosporine A or 0,03% topical tacrolimus, 20% to 50% autologous serum drops and/or albumin serum eye drops.17,22

As accessory therapy, contact lenses can be used as bandage (in acute corneal erosions) or as reservoir of fluid as in scleral lens (Boston Scleral Lens23 or Jupiter Scleral Lens24) with variable results.

### Table 2: Procedures associated with a high risk of GVHD

<table>
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<th>Procedure</th>
<th>Groups at risk</th>
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| Allogeneic HCT | - Patients receiving no GVHD prophylaxis;  
- Older patients;  
- Recipients of HLA-nonidentical stem cells;  
- Recipients of graft from allosensitized donors;  
- Recipients of grafts from unrelated donors. |
| Solid-organ transplantation (organs containing lymphoid tissue) | - Recipient of small-bowel transplants |
| Transfusion of unirradiated blood products | - Neonates and fetuses;  
- Patients with congenital immunodeficiency syndrome;  
- Patients receiving immunosuppressive chemoradiotherapy;  
- Patient receiving directed blood donations from partially HLA-identical, HLA-homologous donors |

### REFERENCES