

GRAFT VERSUS HOST DISEASE

Definition

Graft-versus-host disease (GVHD) is the most common complication of allogeneic hematopoietic stem cell transplantation (HSCT). In HSCT, the patient's bone marrow is destroyed with chemotherapy and/or radiation and replaced by donor hematopoietic stem cells. In allogeneic HSCT the donor is usually a close family member or occasionally someone outside the family who has been found to be a "match".

GVHD occurs when transplanted donor's immune cells (graft) react to patient's tissues (host) and tries to destroy them. As a consequence of this action, the patient's organs impair their ability to function, and increase the patient's susceptibility to infection.

GVHD is generally divided into two syndromes - acute and chronic. Acute GVHD (aGVHD), is that occurring within three months after transplantation, and chronic GVHD (cGVHD), usually develops after the third month post-HSCT. Patients may develop one, both or neither reaction.

Acute and chronic GVHD differ in their symptoms, clinical signs and time of onset. Acute GVHD primarily involves the skin, liver, oral mucosa, and gastrointestinal tract. In contrast, cGVHD presents a far more varied clinical picture including liver dysfunction, pulmonary fibrosis, sclerodermatous skin changes, oral and gastrointestinal mucosa changes, and a reduced production of tears and saliva.

Epidemiology

The incidence of GVHD varies considerably according to immunologic risk factors such as degree of histocompatibility transplantation antigen disparity between donor and recipient, age of recipient and donor, sex and parity of donor, type of GVHD prophylaxis, and history of recipient herpes virus infection. The range of incidence of acute GVHD is 30% to 75% and of chronic GVHD is 25% to 70%.

With the lack of clearly defined criteria for diagnosing *oral* aGVHD, it has not been possible to accurately determine the incidence rates. Oral involvement occurs in 80% of patients suffering from cGVHD and the oral cavity may, in some instances, be the primary or even the only site of cGVHD involvement.

Clinical presentation

Because of the several potential causes of oral mucosal changes during the first period post HSCT, it is difficult to distinguish changes due to aGVHD from those due to other conditions (i.e. mucositis). The majority of reports have attributed to aGVHD punctate or generalized mucosal erythema, white striae or papules on the oral mucosa and lips (in patterns similar to

those seen in oral lichen planus), mucosal erosion-desquamation-ulceration, xerostomia, and pain. However, many of these changes can also be caused by pre HSCT chemoradiotherapy conditioning, post-HSCT drugs, or infections.

Generally, the oral manifestations of cGVHD are clinically similar to those of aGVHD, although in the case of the former they may be more readily recognized with the resolution of conditioning-regimen oral toxic effects and decreased risk of oral infections.

Lichen planus-like lesions are the most distinctive oral change of cGVHD: hyperkeratotic striae, patches, plaques, and papules may affect oral and perioral tissues and severe atrophy and ulcerations, resembling erosive lichen planus, can be noted in patients with severe extensive cGVHD. The ulcerations are often covered with a heavy pseudomembranous clot that is grayish white to yellowish. In addition, mucosal surfaces appear erythematous and atrophic, aspects attributed to a relative loss of keratinization or loss of surface structures as filiform papillae or gingival stippling. Oral pain is often reported by patients with cGVHD and is either continuous or elicited by eating, drinking or oral hygiene procedures.

Patients with cGVHD usually experience xerostomia resulting in subjective suffering and disturbances in chewing, swallowing and speaking, along with increased levels of dental caries and oral candidiasis.

Aetiopathogenesis

GVHD occurs when donor graft T cells recognize antigenic disparities between donor and recipient tissues. T cells are special white blood cells that are able to recognize foreign matter in the body. Usually, T cells orchestrate attacks on bacteria, viruses and other foreign substances. They can also distinguish "self" from "non-self" human cells. In fact, on the surface of many human cells there is an inherited set of genetic markers called "human leukocyte antigens" (HLA). Like a fingerprint, no two persons' set of HLA markers are exactly the same (except for identical twins). The T cells use these HLA markers to distinguish "self" from "non-self." If a "non self" human cell is encountered in the body, the T cells quickly activate the immune system to destroy it. Greater is disparity between the foreign organ's HLA markers or "tissue type" and that of the T cells, swifter and more vigorous will be the attack. Based on this mechanism, T cells can induce rejection of a transplant organ such as liver or kidney. The ability of the immune system's T cells to distinguish "self" from "non self" can create a serious problem after allogeneic HSCT. In this case, the transplanted organ are the T cells; as a consequence, the donor's T cells may identify the patient's tissues as "non-self" and attack them. In oral GVHD the target tissue ("non self") are the oral mucosa and minor salivary glands.

Diagnosis

Currently, the diagnosis of oral GVHD depends on the demonstration of systemic signs and symptoms of GVHD and the exclusion of other causes of oral lesions.

Oral lichenoid lesions are statistically related to cGVHD. Oral lichenoid lesions in cGVHD however, cannot be distinguished either clinically or histologically from conventional oral lichen planus. A past history of HSCT is the key element to differentiate oral lichen planus from oral GVHD. Xerostomia and decreased whole saliva flow have a low specificity in the diagnosis of cGVHD and might also be caused by drugs.

Histopathologic criteria for both acute and chronic GVHD are similar, although there have been no large studies on the histopathology of oral aGVHD, since it is difficult to obtain oral biopsies during the immediate post-HSCT period, when the patient is at high risk for infections and bleeding complications.

The histopathological changes of the oral mucosa in cGVHD include epithelial atrophy, with apoptotic bodies, hydropic degeneration of the basal cells, and a mononuclear sub-epithelial cell infiltrate with lymphocyte invasion. The minor salivary glands may show periductal lymphocytic or lymphoplasmacytic infiltration of both intralobular and major excretory ducts, with more pronounced ductal damage leading to necrosis of ductal epithelium, resulting in obstruction and eventual acinar damage and fibrosis.

Treatment

Management of oral aGVHD consists of systemic treatment, pain control, and local, usually palliative, measures. In general, oral lesions of aGVHD will respond to systemic immunosuppression, and patients need opiates for pain control. For local comfort and symptomatic relief, saline rinses, topical anaesthetics such as viscous lidocaine or dyclonine hydrochloride, and combinations of lidocaine and/or diphenhydramine hydrochloride can be helpful. Topical corticosteroid rinses (dexamethasone) and gels (flucinonide, clobetasol, or triamcinolone) have been used with some success.

Management of oral cGVHD consists of appropriate systemic therapy combined with proper oral hygiene and use of topical drugs. In general, topical steroid preparations, such as flucinonide and clobetasol gel, and steroid elixirs (dexamethasone or betamethasone) are the mainstay of local treatment for cGVHD. Also immunosuppressants such as ciclosporin and azathioprine have been used as topical therapy in oral GVHD. The administration of the photosensitizing drug psoralen, followed by skin and oral exposure to ultraviolet A irradiation is successfully used in the treatment of cutaneous and oral GVHD. Some evidence suggests that patients who do not respond to systemic and/or topical steroids may benefit from the use of thalidomide. There are only isolated reports of the use of tacrolimus for cutaneous GVHD, but no data on its use in oral lesions.

In patients with xerostomia, the available treatment options, such as salivary substitutes, are largely palliative and usually offer only short-term relief. Pilocarpine, a cholinergic agonist, has been long known to stimulate salivary secretion.

Additionally, careful diagnosis and appropriate treatment can reduce the oral pain caused by superimposed oral infections due to herpes simplex virus and *Candida* species. Good oral hygiene and prevention of tissue trauma are imperative to minimize the risk of infection, pain, periodontal changes and caries. Topical fluorides are indicated in cases of severe xerostomia to prevent rampant caries.

Prognosis and complication

In patients with oral manifestation of aGVHD, oral infections, due to *Candida* species and herpes simplex virus can occur simultaneously, exacerbating the symptoms and making recognition of aGVHD more difficult. Chronic GVHD may be associated with altered or reduced taste; in this case xerostomia can have an impact on speech, deglutition, and when present, use of oral prostheses, apart dental demineralization and caries.

Moreover, oral cGVHD might be a predisposing factor in the development of oral squamous cell carcinoma.

Prevention

There are no reported clinical trials that have evaluated prevention or treatment of oral GVHD. Clearly, the best means of preventing or managing oral GVHD is the successful systemic prevention or management of systemic disease (ciclosporin, prednisone).

Recommended prophylactic regimens to prevent or minimize the oral manifestations of GVHD include removal of all appliances and compromised teeth with definitive dental restoration before HSCT. In the post-HSCT period, frequent oral rinsing with weak sodium peroxide and bicarbonate solution is useful. Infections prophylaxis can be achieved with topical nystatin or azoles (*Candida*), chlorhexidine (bacteria), and aciclovir (herpes simplex).

Further reading

- 1 Demarosi F et al. Oral involvement in chronic graft-vs-host disease following allogeneic bone marrow transplantation. Arch Dermatol 2002; 138:842-3
- 2 Hiroki A et al. Significance of oral examination in chronic graft-versus-host disease. J Oral Pathol Med 1994; 23:209-15
- 3 Nakamura S et al. Oral involvement in chronic graft-versus-host disease after allogeneic bone marrow transplantation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996; 82:556-63.
- 4 Schubert MM et al. Recognition, incidence, and management of oral graft-versus-host disease. NCI Monogr 1990; 9:135-43
- 5 Woo SB et al. Graft-vs-host disease. Crit Rev Oral Biol Med 1997; 8:201-16

Links

http://www.medicalistes.org/gvhd/us/general_us/frameset1_us.html



Figure 1. Oral GVHD, lesions of the oral mucosa



Figure 2. Oral GVHD, lesions of the palate



Figure 3. Oral GVHD, lesions of the tongue

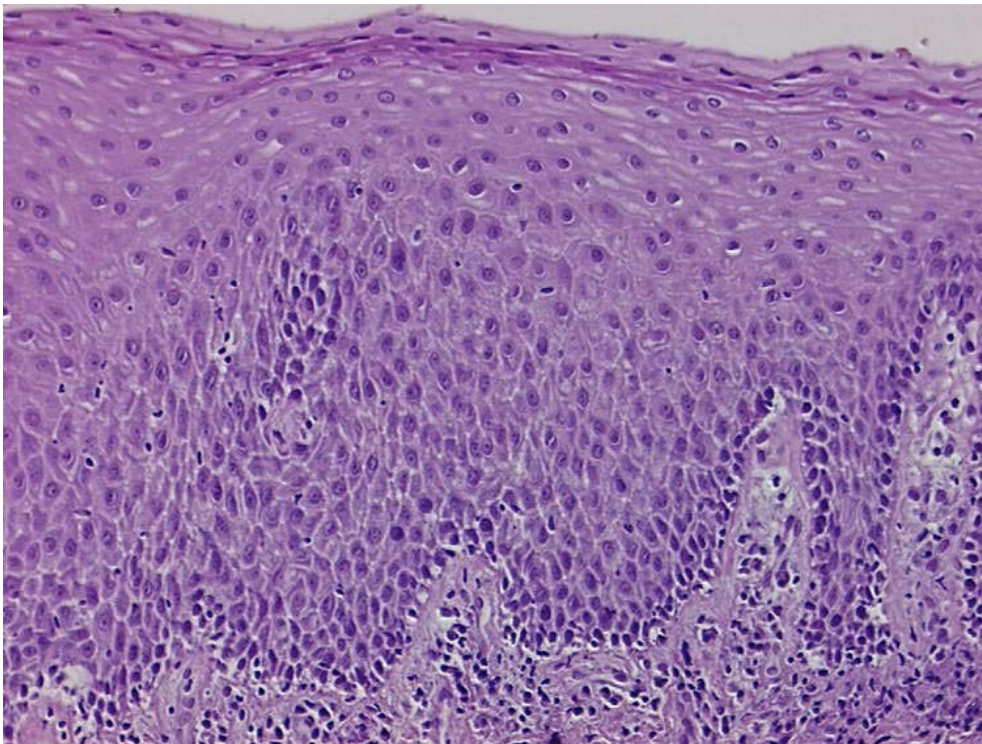


Figure 4. Oral GVHD, histological aspect