

Oral graft *vs* host disease: An immune system disorder in hematopoietic cell transplantation

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Author contributions: da Silva Santos PS designed research; da Silva Santos PS, Rubira CMF, Antunes HS, and Coracin FL performed research and analyzed data; da Silva Santos PS, Rubira CMF, Antunes HS, Coracin FL and França CM wrote the paper.

Conflict-of-interest: We do not have any conflict of interest with this paper.

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Received: October 8, 2014

Peer-review started: October 10, 2014

First decision: December 3, 2014

Revised: December 17, 2014

Accepted: January 15, 2015

Article in press: January 19, 2015

Published online: May 20, 2015

National Institutes of Health in 2005 by Working Group on Diagnosis and Staging Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD (cGVHD) established 2 principal categories of oral GVHD, acute and chronic. The oral mucosa may be the first site of manifestation of the disease. Clinical diagnosis needs to be confirmed by a biopsy of oral mucosa and minor salivary glands. Microscopic results have played a major role in the diagnosis and management of acute and chronic oral GVHD. Development of second malignancies is the greatest risk of oral cGVHD patients, mostly regarding squamous cell carcinoma. The focus of oral GVHD therapy is to improve symptoms and maintain oral function. The aim of this review article is to update the information on the oral GVHD in its clinical, microscopic features and their complications.

Key words: Stem cell transplantation; Graft *vs* host disease; Mouth mucosa; Diagnosis; Oral; Salivary glands

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Core tip: Graft *vs* host disease (GVHD) patients are susceptible to recurrent and deadly infections due to immune system harm. Chemotherapy treatment may cause a range of complications, such as neuropathic pain resulting from vincristine adverse effects, overgrowth of gingival due to cyclosporine and effects on bones and teeth growth and development during childhood and youth. Oral GVHD patients must have follow-ups due to risks of oral infections, bleeding, and cancerous developments.

Abstract

Graft *vs* host disease (GVHD) is a complication of patients who are treated by hematopoietic cell transplantation.

da Silva Santos PS, Rubira CMF, Antunes HS, Coracin FL, França CM. Oral graft *vs* host disease: An immune system disorder in hematopoietic cell transplantation. *World J Stomatol* 2015; 4(2): 96-102 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v4/i2/96.htm> DOI: <http://dx.doi.org/10.5321/wjs.v4.i2.96>

INTRODUCTION

Graft vs host disease (GVHD) is a complication of patients who are treated by Hematopoietic Cell Transplantation (HCT). GVHD has immunoregulatory characteristics when donor T cells react against histocompatibility antigens of the host. National Institutes of Health (NIH) in 2005^[1] by Working Group on Diagnosis and Staging Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD (cGVHD) established 2 principal categories of GVHD, acute and chronic, and each of the categories has 2 subcategories. The acute stage occurs with the absence of diagnostic or distinctive features of chronic GVHD. This stage also involves (1) classic acute GVHD that occurs within 100 d after transplantation; and (2) persistent, recurrent, or late acute GVHD (features of acute GVHD that occur beyond 100 d, often during withdrawal of immune suppression). The wide category is chronic GVHD, which involves (1) classic chronic GVHD (without features or characteristics of acute GVHD); and (2) an overlap syndrome, in which diagnostic or distinctive features of chronic GVHD and acute GVHD appear together^[1,2].

Both forms, acute and chronic, may affect oral cavities and be highly morbid. Skin rash, mucosal ulcerations, elevated liver enzymes, and diarrhea indicate the acute form. Sjögren's syndrome, scleroderma, thickening and lichenoid lesions of the skin and mucosa, xerostomia, mucositis, and dysphagia indicate the chronic form^[3,4].

GVHD patients are susceptible to recurrent and deadly infections due to immune system harm. Chemotherapy treatment may cause a range of complications, such as neuropathic pain resulting from vincristine adverse effects, overgrowth of gingival due to cyclosporine, and effects on bones and teeth growth and development during childhood and youth. Oral GVHD patients must have follow-ups due to risks of oral infections, bleeding, and cancerous developments.

INCIDENCE OF ORAL GVHD

Ion *et al.*^[5] in a retrospective study characterized a cohort of patients treated with HCT over 15 years (total 2578 patients). The study found that only 21 patients had developed acute GVHD (aGVHD), but 5 demonstrated only oral manifestations. Acute GVHD occurred in a median time of 22 d (8 to 154 d), and oral aGVHD occurred in a median time of 35 d (11 to 159 d). Oral features included an erythema and ulcerations of buccal mucosa (19 of 21; 90%), tongue (18 of 21; 86%; dorsum in 8), labial mucosa (16 of 21; 76%), palatal mucosa (15 of 21; 71%; hard palate in 7), and floor of mouth (7 of 21; 33%). Eight cases (38%) presented lip ulceration and crusting^[5].

Some risk factors were tissue incompatibility (HLA

and "minor" non-HLA antigens) between donor and recipient, advanced donor's age and patient's age, and the intensity of the conditioning therapy used for HCT preparations^[6].

Chronic GVHD occurs more frequently (40% to 70%) in allogeneic bone marrow transplantation patients (allo-BMT), but is not necessarily related to a prior history of aGVHD manifestations^[7]. Risk factors for cGVHD were related to donor, graft, and transplant-related older patient age, history of aGVHD, genders of donor and patient, certain underlying diagnoses (*e.g.*, chronic myelogenous leukemia or aplastic anemia), the use of mismatched or unrelated donors, infusion of donor lymphocytes, use of peripheral blood stem cells instead of bone marrow, and lack of T-cell depletion^[6].

CLINICAL FEATURES

The oral mucosa may be the first site of the manifestation of the disease, which suggests that other organs should be investigated^[8]. The signs and symptoms are divided by direct and indirect effects of cGVHD. The direct signs and symptoms are distributed in the areas^[9,10]: (1) Mucosa - Lichenoid striation, plaque, papule, erythema, ulceration, atrophic glossitis (Figure 1); (2) Salivary glands - Dryness, mucocele (multiple); (3) Musculoskeletal - Limitation of mouth opening, limited tongue mobility; (4) Taste buds - Taste alteration; and (5) Gingiva - Desquamative gingivitis, lichenoid.

The indirect effects are dental decay, loss of attachment of periodontium, osteonecrosis of the jaw, candidiasis, and malignant transformation of oral mucosa and salivary glands^[9,10].

The NIH Consensus Development Project defined 4 different types of manifestations of oral cGVHD that should be used to assess the severity of oral cGVHD (Figure 2). In the 0- to 15-point system, clinical evidences are assessed globally to reflect the severity and extent of oral involvement^[11].

Clinical diagnosis needs to be confirmed by a biopsy of oral mucosa and minor salivary glands. The criteria for obtaining these specimens are an incisional biopsy of a nonulcerated site to include underlying gland lobules^[12] (5 to 10 lobules is recommended) and the site of preference as the lower lip mucosa, which is the clinical manifestation in this area of the mouth. The orientation regarding characteristics of the biopsy and the sequence of observation for microscopic structures facilitate the process of the histological diagnosis^[13].

MICROSCOPIC FEATURES

Chronic GVHD is a multifactorial disease with clinical and histopathologic features that can often confuse the pathologist. Horn *et al.*^[14] published the first study about the significance of oral mucosa and salivary glands after allogeneic HCT. It was based on the lichen planus-like lesions in association with xerostomia in

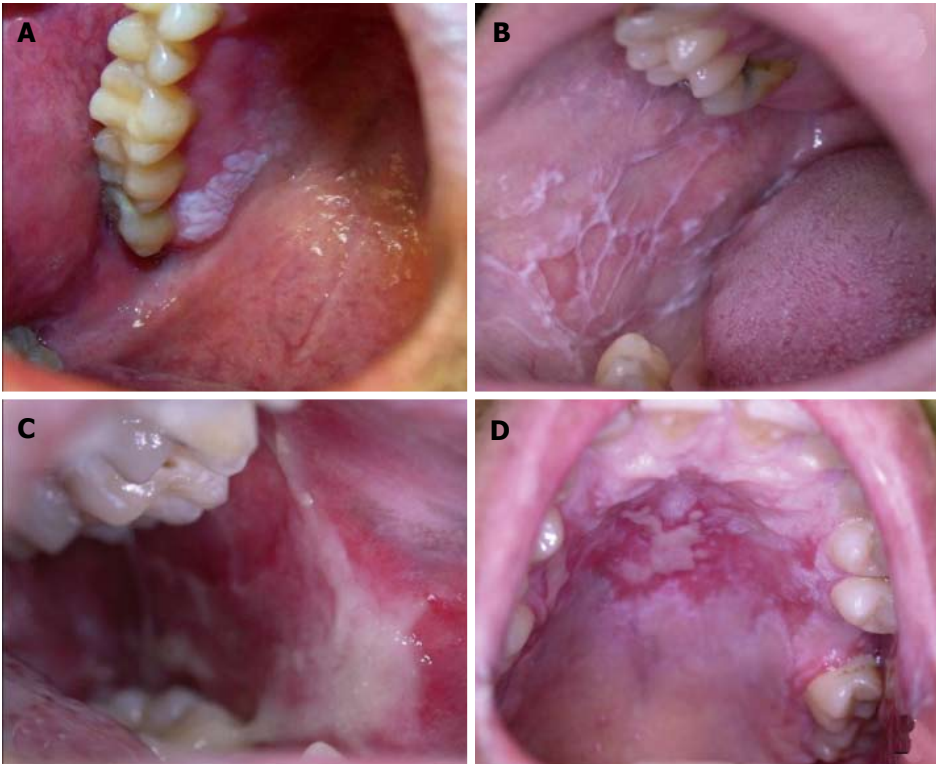


Figure 1 Clinical features of oral chronic graft vs host disease. A: Plaque; B: Lichenoid striae; C: Papule ulceration; D: Erythema ulceration.

<div>Mouth</div> <div><div>Mouth</div><div><div>Hard palate</div><div>Soft palate</div><div>pharynx</div><div>Uvula</div><div>Tongue</div></div></div>	Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
	Erythema	None	0	Mild erythema or moderate erythema (< 25%)	1	Moderate (\geq 25%) or severe erythema (< 25%)	2	Severe erythema (\geq 25%)	3
	Lichenoid	None	0	Hyperkeratotic changes (< 25%)	1	Hyperkeratotic changes (25%-50%)	2	Hyperkeratotic changes (> 50%)	3
	Ulcers	None	0	None	0	Ulcers involving (\leq 20%)	3	Severe ulcerations (> 20%)	6
	Mucocoeles ¹	None	0	1-5 mucocoeles	1	6-10 scattered mucocoeles	2	Over 10 mucocoeles	3
				¹ Mucocales scored for lower labial and soft palate only				Total score for all mucosal changes	

Figure 2 NIH's oral chronic graft vs host disease clinical scoring instrument. Adapt from Treister *et al*^[37].

59 transplanted patients^[14]. The study established that the histopathological criteria for oral GVHD should include both oral mucosa and salivary glands features (Table 1)^[14]. The histopathological features of oral cGVHD in epithelium and lamina propria included basal vacuolization, exocytosis, and interstitial inflammation (Figure 3). Salivary glands features included mild to severe destruction of ducts and acini (Figure 4)^[14].

Histopathology has played a major role in the diagnosis and management of acute and chronic GVHD^[12]. However, histological observations of cGVHD lesions are not specific. The changes may vary, depending on time between HCT and biopsy, biopsy size, number of serial sections, presence of ulceration area, insufficient depth, and the coexistence of other inflammatory processes at the site^[15]. Histopathological changes can be more apparent after 60 d post-HCT and may be represented by nonspecific inflammation that leads to false-negative GHVD diagnosis^[12,16]. Therefore, the NIH consensus of the

Working Group highlighted the importance of considering the clinical features, such as lichen planus-like lesions and xerostomia, to define the diagnosis of oral cGVHD^[12].

The NIH consensus presented the minimal criteria necessary to diagnose GVHD (whether acute or chronic) and the diagnostic features for chronic GVHD in each involved organ system (Tables 2 and 3). The minimal histological criteria for oral cGVHD follows basic criteria; this includes localized or generalized epithelial changes comprising lichenoid-like inflammation, exocytosis, apoptosis, the presence of intralobular, periductal lymphocytes with or without plasma cells, and exocytosis of lymphocytes into intralobular ducts and acini^[13]. Apoptotic bodies in both epithelium and salivary glands can be seen in oral cGVHD^[12].

The most frequent microscopic features in the epithelium include acanthosis, lymphocyte exocytosis, and the thickening of basal lamina. In the lamina propria, the most frequent features include interstitial

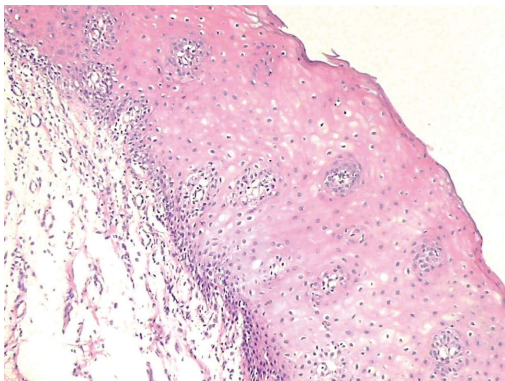
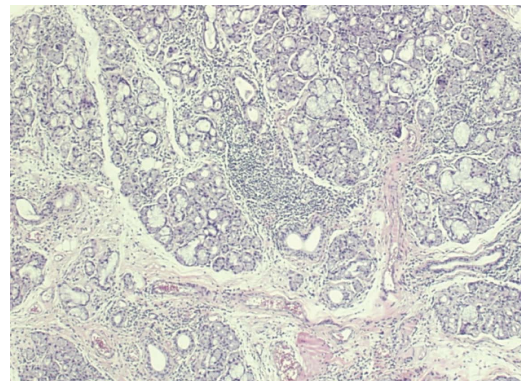
Table 1 Histological grading of oral mucosa and salivary glands according to Horn *et al*^[14]

Grade	Definition
Grade I	Mucosa: Vacuolization of basal cells, moderate lymphocytic infiltrate, moderate epithelial exocytosis Salivary glands: Mild interstitial inflammation
Grade II	Mucosa: Epithelial cells with basal vacuolization and dyskeratotic, necrotic keratinocytes with satellitosis, moderate to heavy lymphocytic infiltrate in the submucosa and moderate epithelial exocytosis Salivary glands: Mild acinar destruction, ductal dilation, squamous metaplasia, mucous pooling, mild fibrosis, duct cell proliferation, periductal lymphocytic infiltrate
Grade III	Mucosa: Focal cleavage between the epithelium and connective tissue, intense lymphocytic infiltrate in the connective tissue, dyskeratotic epithelial cells, lymphocyte exocytosis Salivary glands: Marked interstitial lymphocytic infiltrate. Diffuse destruction of ducts and acini
Grade IV	Mucosa: Separation of epithelium and the connective tissue Salivary glands: Nearly complete loss of acini, dilated ducts, interstitial fibrosis with or without inflammation

Table 2 Minimal criteria for diagnosis of oral chronic graft *vs* host disease and categories

Category	Definition
Not GVHD	No evidence for GVHD
Possible GVHD	Evidence of GVHD but other possible explanations (<i>e.g.</i> , Clinical features that suggest or favor a drug reaction)
Consistent with GVHD	Clear evidence of GVHD with mitigating factors (<i>e.g.</i> , Unequivocal evidence of CMV yet abundant apoptotic epithelial changes that are not associated with CMV- infected cells by immunostaining)
GVHD	Unequivocal evidence of GVHD and no further comment necessary (<i>e.g.</i> , Inflammation may be minimal despite extensive destruction of the targeted epithelia)

Adapt from Shulman *et al*^[12]. GVHD: Graft *vs* host disease; CMV: Cytomegalovirus.

**Figure 3** Epithelium and lamina propria showing basal vacuolization, exocytosis and interstitial inflammation.**Figure 4** Salivary glands features included mild to severe destruction of ducts and acini.

lymphocytes infiltration. In minor salivary glands, they include periductal fibrosis and inflammatory infiltrate both in acini and periductal sites. Salivary glands analysis must be done carefully because they can be affected, even before the development of mucosal injury. Major salivary glands can reflect the same features of inflammatory infiltration and fibrosis^[17].

Horn's criteria^[14] and the NIH Consensus^[12] are different in objectives and subjective features (Tables 1-3). In fact, any correlation between clinical and histopathological severity of oral GVHD leads to a nonsynchronous understanding of the epithelium and salivary gland disease. The absence of clinical and histopathological correlation does not diminish the importance of histological analysis of cGVHD. A comparison of the NIH Consensus^[12] and the

Horn criteria^[14] for histopathological diagnosis of cGVHD shows that they are related in a certain way. This suggests that the use of the NIH Consensus^[12] for oral mucosa and salivary glands may be better to characterize the extent of cGVHD^[13]. Moreover, a differential diagnosis is possible with infectious lesions and drug reactions^[13,18,19].

COMPLICATIONS OF THE ORAL CGVHD

Viral, fungal, and bacterial infections of the oral mucosa are frequently superimposed in patients with cGVHD. Mainly due to the dryness and immunosuppression^[9].

Related to fungal infections acute pseudomembranous candidiasis is the most frequent presentation^[20], but all clinical forms: erythematous, pseudomembranous,

Table 3 Shulman *et al.*^[12] chronic graft-vs-host disease histologic classification of oral mucosa and salivary glands, according to National Institutes of Health Consensus

Epithelium	Epithelial thickness (normal, atrophic, hyperkeratosis and acanthosis), presence of vacuolization, apoptosis, spongiosis, atypical keratinocytes, exocytosis of lymphocytes, presence of other inflammatory cells and thickening of basal lamina
Lamina propria	Predominant cell type in the inflammatory infiltrate and their distribution in relation to the salivary duct and epithelium
Salivary glands	Lymphocytes within the duct, periductal mixed infiltrate, presence of lymphocytes within the acini, apoptosis in the ducts and acini, periductal fibrosis, acinar cell degeneration, interstitial fibrosis, duct ectasia and loss of polarity of epithelial cells of the duct

hyperplastic, and angular cheilitis can be seen at some point in the course of the disease. To prevent and treat candidiasis nystatin and chlorhexidine mouth washes may be prescribed^[20,21]. When multiple areas of the mouth are affected and there are risk of invasive candidiasis, the systemic fluconazole is indicated.

When patients with oral cGVHD are thrombocytopenic, there is a risk for bleeding mouth, gums and also primarily associated with ulcers of the mucosa^[22]. In these cases, careful and effective oral hygiene in biofilm reduction are important.

SECOND MALIGNANCIES AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

The biggest concern regarding late complications, with patients who underwent HCT, is the development of second malignancies. These patients have a higher risk of developing hematological malignancies, lymphoproliferative disease, and solid tumors (lung, esophagus, skin, oral mucosa, colon, melanoma, glioblastoma, sarcoma, and other organs), owing to various risk factors, including total body irradiation, chemotherapy, and cGVHD^[23,24].

Besides the cellular mechanisms that link to chronic inflammation of GVHD with malignant transformation of the affected sites, there are other possible mechanisms of malignant transformation that are related to the prolonged use of immunosuppressive therapy, performed for the treatment of chronic GVHD. Such suppression can facilitate infections with oncogenic viruses, such as Human Papilloma virus or Epstein-Barr virus, which would normally be controlled by the immune system^[23,25,26]. In young patients with cGVHD reached the peak of development of oral squamous cell carcinoma (SCC) occurs 8 to 9 years after HCT^[24].

Studies that evaluated the risk of cancer in patients after HCT showed an increased risk of developing secondary malignancies in comparison to the general population^[25,27,28]. It is noteworthy that in patients with Fanconi anemia, the risk of developing a second tumor is even higher^[29,30] being observed an increased risk of 10 to 15 times, a difference that may be related to chromosomal instability and deficiency in the repair process of the disease^[26]. Chronic GVHD is associated with risks of developing oral SCC^[26,28,31].

In a retrospective study, Atsuta *et al.*^[28] evaluated 17,545 patients who underwent HCT. The researchers

concluded that in recipients of allogeneic HCT (myeloablative conditioning), extensive-type chronic GVHD was an important risk factor for the development of secondary solid cancers (RR = 1.9, $P < 0.001$); it was an independent risk factor for cancers in the oral cavity/pharynx and esophagus. In a cohort study, Majhail *et al.*^[32] evaluated 4318 patients who underwent HCT (Acute Myeloid Leukemia 1742, Chronic Myeloid Leukemia 2576) and found that out of cancer patients, 72% had a diagnosis of cGVHD. In this study, cGVHD was the only significant risk factor associated with oral cavity cancer. Chen *et al.*^[33] evaluated 170 patients who underwent allogeneic HCT over twenty years with a median follow-up of 14.1 years (range 5.1-23.3 years). Eight (4.7%) patients developed secondary carcinoma: 5 developed squamous cell carcinomas in the oral cavity, 1 in the esophagus, 1 ovarian adenocarcinoma, and 1 breast. In this group, 7 patients (87.5%) were subjected to treatment for cGVHD with a median time post-transplant diagnosis of 10 years. Patients who had cGVHD after HCT were at risk of developing secondary carcinomas (RR = 15.374; 95%CI: 2.168-59.875). In this study, before the development of oral squamous cell carcinoma, all 5 patients had signs and symptoms of recurrent oral ulcers, warts, and white lesions in the regions of developing cancer. It is important to note that HPV was not associated with carcinogenesis in these patients with oral SCC.

While oral cancer is represented mostly by squamous cell carcinoma and very aggressive-type behavior, it is important to emphasize that this particular type represents about 50% of all solid tumors in patients who undergo HCT^[23,25,31-36]. Abdelsayed *et al.*^[34] mentioned that oral cancer in patients with GVHD might have more aggressive biologic potential with a higher tendency for recurrence and the development of new lesions. Mawardi *et al.*^[37] evaluated 26 post-HCT patients who had developed verrucous hyperplastic hyperplasia (12%), dysplasia (19%), and invasive carcinoma (69%). Twenty-four patients (96%) had cGVHD, and of these patients, 96% (23/24) presented oral features.

Due to the increased amount of patients who survive HCT and remain free of the original disease, attention should be paid to the presence of potentially cancerous lesions or tumors that already exist. Studies reported that after HCT, patients had an increased risk of developing secondary tumors in comparison to the general population^[25,27]. Therefore, there is concern about the early detection of a second primary

tumor in these patients. Currently, the consensus on screening guidelines and long-term follow-ups of HCT complications is that oral mucosa and dental status should be examined during the annual examination of patients with GVHD and every 6 mo for patients with Fanconi's anemia^[23,29,38].

TREATMENT

Oral cGVHD management focuses on ameliorating symptoms, maintaining oral function, and restoring mucosal integrity by treating symptomatic oral abnormalities and ulcerative lesions^[9].

The first-line therapy for cGVHD in other areas beside oral mucosa, involves systemic corticosteroids. When the oral cavity is the only site involved, the topical management of oral cGVHD may be indicated^[10]. Therapy is indicated based on corticosteroid with presentations on solutions^[10] such as Dexamethasone, Budesonide, Prednisolone, Triamcinolone, and Betamethasone^[37]. The corticosteroids with presentation gel, creams, and ointments are Fluocinonide, Clobetasol, Betamethasone, and Triamcinolone. The nonsteroidal immunosuppressive solution and ointment is Tacrolimus^[10].

CONCLUSION

GVHD is a common sequela of patients who are treated by HCT. Diagnosing oral complications and manifestations of GVHD disease is fundamental for dental management during medical therapy.

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P- Reviewer: Cho SY, Mishima, K, Shimauchi H, Vieyra J

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