

Graft-versus-host disease, an eight case report and literature review

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ABSTRACT

Graft versus host disease (GVHD) is a common complication in bone marrow transplant (BMT) patients. It is characterized by systemic and oral cavity alterations. Depending on the timing of lesions, GVHD is classified as acute or chronic. Alterations in the oral cavity are lichenoid reticular lesions, erythema, ulcerations, and xerostomia. Sporadically, mucocele and pyogenic granulomas can be present. Aim: To describe GVHD oral manifestations in eight allogenic BMT patients, and discuss GVHD and drug-immunosuppression associated lesions diagnosis and treatment. Study design: For a year, we examined the oral mucosa of eight consecutive allogenic BMT patients attending the Dermatology outpatient clinic at the Instituto Nacional de Cancerología (National Institute of Oncology) in Mexico City, looking for oral mucosa lesions. Results: Patients were five men and three women, ages 24.8 ± 9.7 years. Four had a BMT because of chronic granulocytic-, two for acute myeloblastic-, one for acute lymphoblastic- leukemia, and one for aplastic anemia. Three patients developed acute GVHD, with reticular oral mucosa lesions, erythema and mucositis; and all eight developed chronic GVHD, with reticular oral lesions, erythema, and ulcerations. A Patient had tongue and cheek pyogenic granulomas. Six reported xerostomía. Other oral lesions, associated to drug-immunosuppression, were candidiasis and herpes simplex. Conclusions: Patients with GVHD frequently develop oral lesions, some of which interfere with normal feeding; timely diagnosis and treatment are therefore essential to improve the quality of life of affected patients. We propose an alternative treatment for pyogenic granulomas.

Key words: Graft-versus-host disease, bone marrow transplantation, pyogenic granulomas, xerostomia, candidiasis.

RESUMEN

La enfermedad de injerto contra huésped (EICH) es una complicación frecuente del paciente con trasplante de médula ósea (TMO). Es un síndrome caracterizado por enfermedad sistémica y bucal. Dependiendo del tiempo de aparición de las lesiones, se le divide en aguda y crónica. En la cavidad bucal se manifiesta con lesiones reticulares liquenoides, eritema, úlceras, xerostomía, ocasionalmente mucocelos y granulomas piógenos. Objetivos: Describir las manifestaciones bucales de EICH en 8 pacientes con TMO alogénico, y discutir el diagnóstico y tratamiento de las lesiones de la EICH y las asociadas al tratamiento inmunosupresor en estos pacientes. Diseño del estudio: En el transcurso de un año se examinó la mucosa bucal de ocho pacientes consecutivos con TMO alogénico en la consulta externa de dermatología del Instituto Nacional de Cancerología de la Ciudad de México para identificar la presencia de lesiones en la mucosa bucal. Resultados: Fueron cinco hombres y 3 mujeres, con edades de 24.8 ± 9.7 años. Cuatro recibieron TMO por leucemia granulocítica crónica, dos por leucemia mieloblástica aguda, uno por leucemia linfoblástica aguda, y uno por anemia aplásica. Tres pacientes desarrollaron EICH aguda, con lesiones en la mucosa bucal de aspecto reticular, eritema y mucositis, y los 8 pacientes

desarrollaron EICH crónica, con lesiones reticulares, eritema, y úlceras. Un paciente presentó granulomas piógenos en lengua y carrillos. Seis informaron xerostomía. Otras lesiones bucales, asociadas a inmunosupresión medicamentosa, fueron candidosis y herpes simple bucal. Conclusiones: Los pacientes con EICH frecuentemente desarrollan lesiones bucales, algunas de ellas impiden una alimentación normal, por lo que es fundamental su diagnóstico y tratamiento oportunos para mejorar la calidad de vida de los pacientes afectados. Se propone una forma alternativa de tratamiento para los granulomas piógenos.

Palabras clave: *Enfermedad injerto contra huésped, trasplante de médula ósea, granulomas piógenos, xerostomía, candidosis.*

INTRODUCTION

Allogenic bone marrow transplantation (BMT), when donor and recipient are not immunologically identical, is used for malignant hematopoietic neoplasias, some solid tumors, and some autoimmune diseases (1,2). Amongst the most frequent complications of this treatment is Graft-versus-Host Disease (GVHD) (1,2). GVHD is the outcome of donor's T-lymphocytes reacting against recipient's antigens, depending on type and number of histocompatibility mismatchings (1,2). GVHD occurs in 50 to 80% of patients receiving an allogenic BMT, and is a cause of high long-term morbidity and mortality in these patients (1-3). GVHD is characterized by dermatological, gastrointestinal, and hepatic lesions. The acute form (aGVHD), with lesions appearing during the first 100 days after BMT, is a high-mortality complication (1-4). Chronic form (cGVHD), developed more than 100 days after BMT, is an autoimmune disease with dermatosis, liver dysfunction, pulmonary fibrosis, alterations in oral and gastrointestinal mucosa, and decreased salivary and lachrymal flow (1-3). Some oral lesions are included in the clinical manifestations of GVHD, and their presence is highly predictive of this complication. These are very symptomatic, persistent lesions, occurring in 30 to 80% of BMT patients (3-6).

AIM

To describe oral manifestations of GVHD identified in eight BMT patients, and discuss diagnostic criteria and treatment of these lesions, as well as those oral lesions associated to immunosuppressive treatment.

PATIENTS AND METHODS

We describe the oral manifestations of acute and chronic GVHD, identified in eight ambulatory patients with allogenic bone marrow transplant examined at the Dermatology Service of the Instituto Nacional de Cancerología (National Institute of Oncology) in Mexico City. Dermatological and oral mucosa examinations were performed by a dermatology specialist and a specialist in oral pathology. Primary disease diagnosis, evolution time and treatment, as well as BMT protocol studies results and post BMT management information was obtained from clinical records. Management of primary disease went along established protocols for allogenic BMT: chemotherapy -depending on primary disease- with methotrexate, cyclophosphamide, busulfan or etoposide, and total body irradiation (1,7). The criteria used

for clinical diagnosis of oral lesions were those by Kolbinson et al. (6) for oral manifestations associated to BMT.

RESULTS

Five men and three women were studied, ages 24.8 ± 9.7 (14-43) years. Seven patients had a previous diagnosis of leukemia; four chronic granulocytic, two acute myeloblastic, and one acute lymphoblastic, and one had aplastic anemia. One patient (case 4) received two allogenic BMTs in a one-year period. Table 1 presents GVHD classification and the characteristics of the patients.

Three patients (cases 2,6,7) developed aGVHD with severe mucocutaneous lesions 12 to 45 days after BMT. Oral lesions were white, small papules with a reticular character in non-keratinized mucosa. Six patients (cases 1,2,3,4,5,7) had mucositis, probably associated to chemotherapy. Five (cases 1,2,4,5,7) developed pseudomembranous candidiasis, one of them (case 2) extended to esophagus, and three (cases 1,4,7) had intra-oral herpes simplex. The oral lesions co-existed with cutaneous hyper pigmented lesions, xeroderma, generalized maculopapular eruptions, and erythematous maculae. Two cases developed gastrointestinal and liver function alterations.

All eight patients developed cGVHD, with cutaneous and oral lesions appearing between days 117 and 507 after BMT. Chronic GVHD diagnosis was based on clinical manifestations and their timing, and confirmed by skin- and, in four patients, oral mucosa biopsies. The oral lesions were reticular-looking, raised striae on vestibular mucosa. Three patients had them also on hard palate and tongue. Seven patients had ulcers with diffuse, erythematous borders on buccal mucosa. Case 8, a man with a BMT because of aplastic anemia, developed three ulcerated firm mass on tongue dorsum and buccal mucosa, which lasted more than two months (Fig. 1). An incisional biopsy revealed pyogenic granulomas (PG). All patients informed severe pain on oral mucosa, six xerostomia -diagnosed when the mucosa was clearly dry and/or the patient reported dry mouth with difficult eating or talking; salivary flow was not measured. Four biopsies of lip mucosa revealed hyperparakeratosis, basal cell layer degeneration, subepithelial lymphocytic infiltration, lamina propria mucosa fibrosis, and sub mucous salivary glands atrophy (Fig. 2). Three patients (cases 1,2,4) developed intraoral herpes simplex. Four (1,3,4,5) developed herpes zoster. Other alterations were conjunctivitis, xerophthalmia, and blepharitis.

Table 1. Clinical characteristics of the eight BMT patients and acute and chronic GVHD

Case No	Gender	Age	Diagnosis	Time (days) of appearance of mucocutaneous lesions	Classification aGVHD	Classification cGVHD ⁽⁵⁾	Follow-up time (days)	Prognosis
No 1	M	34	LGC ¹	117	--	G11/1V	1773	Without GVHD
No 2	M	20	LMA ²	12	G1/1V	G111/1V	1345	Died
No 3	F	43	LGC	507	--	G11/1V	2555	Stable cGVHD
No 4	M	14	LGC	461	---	G11/1V	2765	Stable cGVHD
No 5	F	27	LGC	156	---	G11/1V	2611	Without GVHD
No 6	M	23	LGC	28	G11/1V	G1/1V	181	Died
No 7	F	16	LAL ³	45	G1/1V	G1/1V	1765	Stable cGVHD
No 8	M	21	AA ⁴	120	---	G11/111	750	Stable cGVHD

1 Chronic granulocytic leukemia, 2 acute myeloblastic leukemia, 3 acute lymphoblastic leukemia, 4 aplastic anemia, 5ref (1).



Fig. 1. Ulcerated, firm lobulated masses on the dorsum of the tongue and vestibular mucosa, diagnosed as pyogenic granulomas associated to reticular and ulcerated lesions.



Fig. 3. Remission of the lesion, after intralesional corticosteroid infiltration.

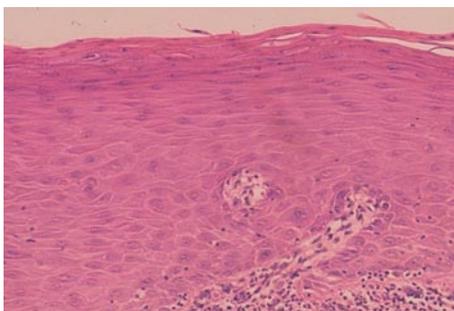


Fig. 2. Epithelium with hyperparakeratosis, basal cell layer degeneration, moderate chronic subepithelial inflammatory infiltrate, and fibrosis of the lamina propria.

Six cases had diarrhea and vomiting. Case 2 developed pulmonary tuberculosis and varicella, and case 6 presented severe liver complications; both died, at 181 (case 6) and 1345 (case 2) days after BMT.

Prescribed treatments for oral lesions were: diphenhydramine with kaolin and pectin or clobetasol gargles, topic fluocinonide, oral prednisone (20 to 50 mg/day) or thalidomide (50 to 200 mg/day) for lichenoid lesions, and nystatin gargles or oral fluconazole (100 to 200 mg/day) for mycotic lesions. In the patient with pyogenic granulomas surgical treatment was avoided because of neutropenia, and lesions were in-

filtrated twice a month with 5 mg triamcinolone, obtaining resolution after the third application (Fig. 3).

DISCUSSION

Oral mucosa was seriously affected both in acute and chronic forms of GVHD, by several progressive, weakening lesions. GVHD is an autoimmune alteration, where donor's T-lymphocytes play a key role in immunological assault on host tissues. Acute and chronic forms differing on clinical and immunological grounds (3,8), Acute GVHD represents an immunological alteration with a mostly TH1- type cytokine production pattern and skin, liver, and gastrointestinal tissue lesions caused by T-killer cells (1-3), while the chronic form (cGVHD) is a rather specific immuno-histocompatibility phenomenon with an autoimmune disease behaviour, a predominating TH2-type cytokine production pattern, and systemic manifestations (3,8). In GVHD, donor's T lymphocytes attack recipient tissues, particularly epithelia, resulting in apoptosis (2,9). T-lymphocytes release within assaulted cells protease granules known as granzymes, or they activate plasma membrane receptors such as TRAIL, from the TNF- α family. Both mechanisms activate cell's apoptotic machinery (10), even if T-lymphocytes are the main immune response effector cells, other cellular types have been identified in experimental models during the immunological response at the damaged site and in oral mucosa, such as plasma cells, macrophages, mastocytes, and Langerhans dendritic cells (10,11).

Identified risk factors for GVHD are increasing HLA disparity between recipient and donor (3), age -the syndrome being 80% more frequent in patients over 50 years- (1-3), donor type (unrelated), lacking of prophylactic acyclovir treatment for herpes virus infection or total body irradiation, and type of chemotherapy before BMT (1-3). Being of African-American origin has also been considered a possible risk factor (12).

Oral lesions are common sequelae in acute and chronic GVHD. Reported prevalence are 33 to 50% for aGVHD (4), and 60 to 80% for cGVHD (4,5). Three patients in this study developed raised interlacing white striae and diffuse oral mucosa ulcerations, xerostomia and diarrhea, matching the description of aGVHD. The oral lesions appear between days 21 and 43 after BMT (5); and whitish 1-mm papules with a reticular lichenoid pattern, oral mucosa exfoliation, and painful ulcerations have been described, that resolve before 60 days (4,6). A distinction must be made between oral lesions induced by aGVHD and those associated to pre-transplant chemotherapy. Chemotherapy-induced ulcerative mucositis presents as mucosal erythema and atrophy, pain, and xerostomia, and appear 7 to 14 days after treatment in 76.3% of the cases (13-15). Chemotherapy-associated mucositis is caused by drug cytotoxicity inhibiting epithelial cell division and maturation, resulting in atrophy and ulceration (15,16). The associated neutropenia predisposes, on the other hand, to opportunistic infections such as candidiasis (6,15,16). Irradiation of head and neck induce irreversible changes in major salivary glands, resulting in xerostomia (16).

Chronic GVHD can occur either as a non resolving acute form, which represents a bad prognosis, or de novo, more than a hundred days after BMT (2,3,8). It can be a limited disease affecting skin, oral cavity or liver, or a disseminated one, affecting two or more organs, i.e. skin and/or oral mucosa lesions combined with hepatic, ocular alterations, sicca syndrome, pulmonary and/or central nervous system disease (3-5). This is a high-mortality, systemic, progressive condition (3); two of the patients from this report died (cases 2 and 6), one from pulmonary tuberculosis and the other from liver disease.

An up to 80% prevalence of oral lesions has been reported in cGVHD (3-5,17-19). Reported lesions or oral manifestations are mucosal atrophy, mucositis, lichenoid lesions, ulcerations, severe oral pain, xerostomia, dysphagia and, occasionally, blister-type lesions resembling pemphigus (4,5,17-20). The most representative lesions are the lichenoid ones, both in pediatric (17,21) and adult (3-5,18-20) patients. Treister et al. (21) reported a 45% prevalence of oral lesions in children with cGVHD, erythema (42%) and reticular lesions (36%) being the most frequent ones. They also reported atrophic glossitis, superficial mucocele, verruciform xanthoma, and mucosal fibrosis, which limited mouth opening. Reticular lesions are generally symmetrically distributed in vestibular, labial, gum, and tongue mucosae (3-5,19,20). Differential diagnoses includes lichen planus (3,5,18-20), erythema multiforme, lupus erythematosus, pemphigus (5,19), scleroderma-systemic sclerosis (5,18-20), and chemotherapy-associated lesions (6,16). Even though lichen planus and the cGVHD oral lesions resemble each other, Hasséus et al. (22) reported different prevalence of cells with inflammatory response membrane markers between both diseases, with a larger amount of CD1, CD86, CD4, CD8, and CD25 positive immunocompetent cells in lichen planus as compared to cGVHD, implying a different regulation of the inflammatory response both conditions.

Suggested local measures for oral lesions treatment are medications such as diphenhydramine with kaolin and pectin or magnesium sulfate mouth washes, which reduce pain (16), topical steroids or azathioprine (23), budesonide gargles (24) and ultraviolet irradiation (25) or systemic medication such as prednisone, Cyclosporin-A (3,5), azathioprine (2,3), thalidomide (2,3), mophetyl mycophenolate, and tacrolimus (3).

Definitive cGVHD diagnosis depends on disease duration and evidence for end organ damage, and is confirmed by skin, oral mucosa -including salivary glands- or digestive tract biopsy. Oral mucosa biopsy shows epithelium hyperparakeratosis or atrophy, basal stratum hydropic degeneration, subepithelial clefting which occasionally form ampulae; on stratum spinosum isolated necrotic keratinocytes with pyknotic nuclei, intracellular epithelial edema, and apoptotic bodies. On connective tissue, slight or diffuse sub-epithelial lymphocyte infiltrate and fibrosis of the lamina propria (26). On lip and submaxillary salivary glands, apoptotic cells, lymphocyte infiltration, periductal fibrosis and conduct dilatation between acini (19,20,26,27). These histological

changes are usually associated to hyposalivation and xerostomia (20,27). Fujiwara et al. (11) and Soares et al. (26) identified by immunohistochemistry a high prevalence of positivity to CD68, CD45, and CD8 markers in biopsies of labial mucosa and minor salivary glands, and concluded that macrophages and T cells play a key role on disease pathogenesis. Histologically, GVHD must be distinguished from lichen planus, lupus erythematosus and Sjögren's syndrome (19,20).

Xerostomia is a frequent symptom in the GVHD patient (19,20,28). It causes mastication, swallowing and speaking difficulties, and predisposes to *Candida* infections (19,28), angular cheilitis (13), and rampant caries (17). Among causes for xerostomia are included head and neck irradiation, drugs used for malignant disease and GVHD treatment (16,19,20,27), decreased salivary flow, saliva chemical composition changes with increased sodium, magnesium, total proteins, epithelial growth factor, IgG and IgA concentrations (27,29). Six patients from this study informed dry mouth, diagnosed as xerostomia on the basis of symptoms, the finding of viscous saliva, and a dry oral mucosa. The clinical manifestations are similar to Sjögren's syndrome (SS), but there are some clinical and histological differences between these diseases (20,27,28); spontaneous pain and inflammation of the parotid glands are frequent in SS, but are not found in GVHD (29,30). Xerostomia management suggestions are sugar-free gum chewing, use of gels, toothpastes, saliva substitutes (28), and pilocarpine administration (29,31).

Pyogenic granuloma is another oral lesion occasionally reported in association with GVHD (32,33). It is a reactive-type entity with granulation tissue proliferation. Though it has not been described as a BMT complication proper, several reports in the literature do associate it with GVHD. It is described as a firm mass on buccal mucosa or ventral or dorsal tongue, irregular in shape, intensely red, with sessile or pedunculated base, frequently lobulated, generally ulcerated, single or multiple (32,33). In this study, one patient with a history of aplastic anemia presented these lesions on oral mucosa and tongue; the biopsy confirmed pyogenic granulomas (PG). The histopathological study shows hyperplastic granulation tissue with acute and chronic inflammatory infiltrate and variable fibrosis (32,33). Etiology of PG in GVHD is still unknown; it has been considered probably associated to Cyclosporine-A use, because of its known proliferative effect on oral mucosa fibroblasts (34). Differential diagnosis requires a biopsy, because drug immunosuppression is a risk factor for viral lymphoproliferative disease, which presents itself with swellings or ulcerations in the oral cavity (35). PGs are normally excised. In the informed case, because of neutropenia, and based on literature reports on treatment for other reactive lesions, a less invasive therapy was used, with intra-lesional infiltration of a corticosteroid (36). The mechanisms by which reactive lesions respond to corticosteroid infiltration are not yet known; a hypothesis stating it inhibits lysosomal proteins release into the extracellular environment (36). The

favorable evolution reported in the literature for similar lesions, and the low complications rate from this treatment led us to choose this procedure as a treatment alternative for pyogenic granulomas in immunocompromised or thrombocytopenic patients, to avoid bleeding and lower the risk of added bacterial infection.

In this study, no superficial mucoceles were found; their presence, however has been reported in children and adults with cGVHD (17,21,37), developing on labial, oral, and soft palate mucosa, occasionally in association with reticular lesions. These are small sialomucin collecting vesicles in the subepithelial connective tissue (17,21,37), their etiology still unknown. García et al. (37) proposed they are probably a manifestation of cGVHD in the glands, attributable to obstruction or rupture of the intraepithelial portion of the salivary conducts by increased ductal pressure -by mucous secretion- in salivary glands.

On the other hand, excessive drug-immunosuppression, radiotherapy, and chemotherapy used for primary disease treatment, predispose to opportunistic infections (15,16). The most frequent infections in BMT are those by *Candida*. (6,16). The risk for *Candida* infection increases as a result of decreased IgA concentration in saliva associated to xerostomia and neutropenia (16,28,38). Epstein et al. (38) reported a 31% prevalence for oral colonization by *Candida* in BMT patients, and 56% of those carriers had clinical candidiasis. Acute pseudomembranous candidiasis is the most frequent presentation in patients with compromised salivary glands (16,19), but all clinical forms: erythematous, pseudomembranous, hyperplastic, and angular cheilitis can be seen at some point in the course of the disease. Prophylaxis with fluconazole and chlorhexidine mouth washes reduces *Candida* colonization prevalence, lowering the risk for systemic dissemination (16,39). Topical treatment is done with nystatin suspension or cream, or clotrimazole lozenges dissolved in the oral cavity, and chlorhexidine mouth washes. First choice drugs for systemic treatment are fluconazole, ketoconazole, or itraconazole (14,38,39).

Another cause of oral morbidity in BMT patients is reactivation of virus from the herpes simplex (HS) family (6,16), with a reported incidence of 50-90% (40). It has been proposed that reactivation of latent virus in a sensorial ganglion is associated to decreased -through several mechanisms- local defenses, for instance through depletion of Langerhans cells or deterioration of their competence for antigen presentation and of immediate or late immunity to the virus; effects in which local production of prostaglandins seem to play a role (41). Viral reactivation is thus associated to recurrence of the lesions (41). Clinical presentation is one of severe, extensive, painful, slowly resolving ulcerated lesions, some times preceded by blisters occurring in gum, palate, and tongue, frequently confounded with mucositis or cGVHD lesions (16,19). Prognosis of the BMT patient has been considered pessimistic with recurring HS lesions and platelet counts below 100,000/mm³ (42). Sporadically, other lesions associated to the herpes virus family have been reported in BMT patients, such as extensive, long-lasting ulcerations on the lateral borders of the tongue, associated to cytomegalovirus

(43) and hairy leukoplakia on the lateral border of the tongue, associated to Epstein-Barr virus (EBV) (44). EBV is known for its association with lymphoproliferative disease and immunosuppression-induced lymphomas. Raut et al. (35) presented a case of gum non-Hodgkin lymphoma in a BMT patient. It has been demonstrated that prophylaxis with acyclovir, valacyclovir or valgancyclovir result in a lower incidence of lesions due to herpes simplex and cytomegalovirus (16,45).

Stomatologist involvement is pertinent in these patients. Before and after BMT, preventive measures must be taken to avoid opportunistic and bacterial infections, including dental infectious foci treatment, to avoid dissemination (46). It is suggested that dental care, with required surgical procedures as caries elimination, exodontias, periodontal treatment and topical application of fluorinated gel (46), be started 2-3 weeks before chemotherapy. It is also suggested that, prophylactic drugs be used before BMT, such as acyclovir, fluconazole, trimethoprim/sulfamethoxazole and chlorhexidine (39,45), against opportunistic microbes and, after BMT, artificial saliva or pilocarpine (28,31), as well as taking the necessary therapeutic measures to treat the multiple oral alterations in these patients.

CONCLUSIONS

GVHD is a frequent complication of BMT, with a high morbidity attributable to oral lesions that must be differentiated from other infectious and autoimmune conditions occurring in the oral mucosa. Interaction between hemato-oncology and stomatology is needed for timely diagnosis and treatment of oral complications, and preventive intervention programs. Intralesional corticosteroid infiltration for pyogenic granulomas is proposed as an alternative treatment in the immunosuppressed patient.

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