



Revista Brasileira de Hematologia e Hemoterapia Brazilian Journal of Hematology and Hemotherapy

www.rbhh.org



Scientific comment

Oral features of graft-versus-host disease[☆]

Sandra Regina Torres*

Faculdade de Odontologia, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil

Chronic graft-versus-host disease (cGVHD) is a late complication of allogeneic hematopoietic stem cell transplant (HSCT), occurring in 18% to 70% of recipients.¹⁻³ The oral tissues may be involved in up to 90% of the patients that present cGVHD in other organs.⁴⁻¹⁰ Oral mucosa lesions and salivary gland dysfunction are the main manifestations of oral cGVHD, but a reduction of the mouth opening due to the perioral deposition of collagen may also occur.¹⁰

Patients with oral involvement of cGVHD may present sensitivity, pain, xerostomia, and dysgeusia,¹⁰⁻¹² and the severity of the oral manifestations may be associated to the severity of the disease.⁵ The sites of the oral mucosa most commonly involved by the lesions are the buccal mucosa and the tongue.^{10,13-15} The diagnosis of the oral lesions is based on clinical aspects. However, a biopsy of the oral mucosa and/or minor salivary glands may be requested when oral and systemic signs and symptoms are not sufficient for the diagnosis of cGVHD.⁵

According to the National Institutes of Health (NIH), the oral features of cGVHD may be classified as diagnostic (lichen planus-like changes, hyperkeratotic plaques, and reduction in mouth opening), distinctive (xerostomia, mucocelles, mucosal atrophy, pseudomembranes, and ulcers), and common to both acute graft-versus-host disease and cGVHD (gingivitis, mucositis, erythema, and pain).¹⁶⁻¹⁸ The NIH criteria consider certain subjective data, such as xerostomia and reduction of mouth opening. However, some patients with reduced salivary flow rates and reduced range of mouth opening do not present these symptoms.¹⁰ Thus, a definition of hyposalivation and the

expected loss in the range of mouth opening would be more valuable for the clinician.

Oral lesions may persist even after the resolution of cGVHD in other organs.² Topical treatment is required in most cases, since oral cGVHD lesions do not completely respond to systemic therapies.¹⁹ Some publications on case series reported good responses of oral lesions to topical treatment with cyclosporin,²⁰⁻²¹ azathioprine,²²⁻²³ budesonide,¹⁹ tacrolimus,⁹ and psoralen/ultraviolet light (PUVA).^{4,24} Few clinical trials have studied the topical treatment of oral cGVHD lesions with dexamethasone, budesonide, and PUVA.²⁴⁻²⁶ Therefore, evidence-based studies on the topical treatment of oral cGVHD lesions with other drugs are needed.

Patients with oral cGVHD lesions frequently have secondary infections, mainly candidiasis. The higher susceptibility to fungal infections is due to factors such as the presence of oral mucosa lesions,²⁷ the immunosuppressive therapy,^{2,4,28} and the reduced salivary flow rates.^{1,8,29-35}

The salivary glands represent an important cGVHD target,^{1,6,8,29-36} and the antimicrobial and buffer properties of the saliva are important for oral homeostasis.³⁷ However, individuals are able to distinguish xerostomia only when the salivary flow rates are very low.³⁸ Salivary gland dysfunction may be detected by scintigraphy and histopathology, but non-invasive exams such as sialometry and sialochemistry may detect quantitative and qualitative alterations, respectively.^{37,39,40}

Reduced salivary flow rates may lead to discomfort, dysphagia, dysphasia, dysgeusia, halitosis, and consequent

[☆]See paper by Gomes AO et al. on pages 43-9.

*Corresponding author at: Faculdade de Odontologia, Universidade Federal do Rio de Janeiro, Avenida Carlos Chagas Filho 373, Prédio do CCS, Bloco K, 2º andar, Sala 56, Ilha da Cidade Universitária 21.941-902 Rio de Janeiro, RJ, Brazil.

E-mail address: sandratorres@ufrj.br (S.R. Torres).

1516-8484/\$ - see front matter © 2014 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. All rights reserved.

DOI: 10.5581/1516-8484.20140005

infections, including dental decay and candidiasis.^{41,42} The early diagnosis of salivary gland dysfunction related to cGVHD is important for the management of dry mouth complications. Moreover, it will help the clinician with the investigation of the cGVHD in other organs. The management of hyposalivation has been extensively addressed, but only few clinical studies verified the improvement of salivary flow rates in a population of cGVHD patients.^{1,29,39,43}

Scleroderma may be observed in cGVHD patients, and is characterized by cutaneous sclerosis, but may also involve oral tissues. An increased deposition of collagen may occur in cGVHD patients and lead to a reduction in the mouth opening, limited tongue movement, and dysphagia.^{44,45} This will make oral hygiene procedures difficult and may be another factor contributing to infections.

In conclusion, oral features are frequently present in cGVHD patients. Health care professionals should be aware of early oral manifestations of cGVHD in order to manage the complications of these conditions.

In this issue of the *Revista Brasileira de Hematologia e Hemoterapia* Gomes et al. evaluate oral cGVHD manifestations in less than one year compared to over one year after hematopoietic cell transplantation.⁴⁶

Conflicts of interest

The author declares no conflicts of interest.

REFERENCES

- Nagler RM, Nagler A. Pilocarpine hydrochloride relieves xerostomia in chronic graft-versus-host disease: a sialometrical study. *Bone Marrow Transplantation*. 1999;23(10):1007-11.
- Schubert MM, Sullivan KM. Recognition, incidence, and management of oral graft-versus-host disease. *NCI Monographs*. 1990(9):135-43.
- Woo SB, Lee SJ, Schubert MM. Graft-vs.-host disease. *Crit Rev Oral Biol Med*. 1997;8(2):201-16.
- Redding SW, Callander NS, Haveman CW, Leonard DL. Treatment of oral chronic graft-versus-host disease with PUVA therapy. Case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;86(2):183-87.
- Schubert MM, Sullivan KM, Morton TM, Izutsu KT, Peterson DE, Flournoy N, et al. Oral manifestations of chronic graft-versus-host disease. *Arch Intern Med*. 1984;144(8):1591-5.
- Nagler R, Marmary Y, Krausz Y, Chisin R, Markitziu A, Nagler A. Major salivary gland dysfunction in human acute and chronic graft-versus-host disease (GVHD). *Bone Marrow Transplant*. 1996;17(2):219-24.
- Flowers ME, Parker PM, Johnston LJ, Matos AV, Storer B, Bensinger WI, et al. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood*. 2002;100(2):415-19.
- Nicolatou-Galitis O, Kitra V, Vliet-Constantinidou CV, Peristeri J, Goussetis E, Petropoulos D, et al. The oral manifestations of chronic graft-versus-host disease (cGVHD) in paediatric allogeneic bone marrow transplant recipients. *J Oral Pathol Med*. 2001;30(3):148-53.
- Eckardt A, Starkea O, Stadlerb M, Reuterb C, Hertensteinb B. Severe oral chronic graft-versus-host disease following allogeneic bone marrow transplantation: highly effective treatment with topical tacrolimus. *Oral Oncol*. 2004;40(8):811-4.
- Noce CW, Gomes A, Copello A, Barbosa RD, Sant'anna S, Moreira MC, et al. Oral involvement of chronic graft-versus-host disease in hematopoietic stem cell transplant recipients. *Gen Dent*. 2011;59(6):458-62; quiz 463-4.
- Inamoto Y, Martin PJ, Chai X, Jagasia M, Palmer J, Pidala J, et al; Chronic GVHD Consortium. Clinical benefit of response in chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2012;18(10):1517-24.
- Boer CC, Correa ME, Miranda EC, de Souza CA. Taste disorders and oral evaluation in patients undergoing allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2010;45(4):705-11.
- Pavletic SZ, Lee SJ, Socie G, Vogelsang G. Chronic graft-versus-host disease: implications of the National Institutes of Health consensus development project on criteria for clinical trials. *Bone Marrow Transplant*. 2006;38(10):645-51.
- Pavletic SZ, Martin P, Lee SJ, Mitchell S, Jacobsohn D, Cowen EW, et al; Response Criteria Working Group. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. *Biol Blood Marrow Transplant* 2006;12(3):252-66.
- Pereira CM, de Almeida OP, Correa ME, Souza CA, Barjas-Castro ML. Oral involvement in chronic graft versus host disease: a prospective study of 19 Brazilian patients. *Gen Dent*. 2007;55(1):48-51.
- Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant*. 2005;11(12):945-56.
- Shulman HM, Kleiner D, Lee SJ, Morton T, Pavletic SZ, Farmer E, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: II. Pathology Working Group Report 12. *Biol Blood Marrow Transplant*. 2006 Jan;12(1):31-47.
- Martin PJ, Weisdorf D, Przepiorcka D, Hirschfeld S, Farrell A, Rizzo JD, et al; Design of Clinical Trials Working Group. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: VI. Design of Clinical Trials. *Biol Blood Marrow Transplant*. 2006;12(5):491-505.
- Elad S, Or R, Garfunkel AA, Shapira MY. Budesonide: A novel treatment for oral chronic graft versus host disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;95(3):308-11.

20. Epstein JB, Reece DE. Topical cyclosporin A for treatment of oral chronic graft-versus-host disease. *Bone Marrow Transplant.* 1994;13(1):81-86.
21. Epstein JB, Truelove EL. Topical cyclosporine in a bioadhesive for treatment of oral lichenoid mucosal reactions: an open label clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1996;82(5):532-6.
22. Epstein JB, Gorsky M, Epstein MS, Nantel S. Topical azathioprine in the treatment of immune-mediated chronic oral inflammatory conditions: a series of cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;91(1):56-61.
23. Epstein JB, Nantel S, Sheoltch SM. Topical azathioprine in the combined treatment of chronic oral graft-versus-host disease. *Bone Marrow Transplant.* 2000;25(6):683-87.
24. Wolff D, Anders V, Corio R, Horn T, Morison WL, Farmer E, et al. Oral PUVA and topical steroids for treatment of oral manifestations of chronic graft-vs.-host disease. *Photodermatol Photoimmunol Photomed.* 2004;20(4):184-90.
25. Sari I, Altuntas F, Kocyigit I, Sisman Y, Eser B, Unal A, et al. The effect of budesonide mouthwash on oral chronic graft versus host disease. *Am J Hematol.* 2007 May;82(5):349-56.
26. Elad S, Zeevi I, Finke J, Koldehoff M, Schwerdtfeger R, Wolff D, et al. Improvement in oral chronic graft-versus-host disease with the administration of effervescent tablets of topical budesonide-an open, randomized, multicenter study. *Biol Blood Marrow Transplant.* 2012;18(1):134-40.
27. Torres SR, Nikitakis NG, Anjum S, Black S, Meiller TF. Candida colonization in oral lichen planus lesions. In: 2006 North American Workshop on Systematic Review; 2006; Baltimore, MD, USA.
28. Imanguli MM, Pavletic SZ, Guadagnini J-P, Brahim JS, Atkinson JC. Chronic graft versus host disease of oral mucosa: review of available therapies. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006;101(2):175-83.
29. Nagler RM, Nagler A. The effect of pilocarpine on salivary constituents in patients with chronic graft-versus-host disease. *Arch Oral Biol.* 2001;46(8):689-95.
30. Nagler RM, Nagler A. Sialometrical and sialochemical analysis of patients with chronic graft-versus-host disease — a prolonged study. *Cancer Investigation.* 2003;21(1):34-40.
31. Izutsu KT, Menard TW, Schubert MM, Ensign WY, Sullivan K, Truelove EL, et al. Graft versus host disease-related secretory immunoglobulin A deficiency in bone marrow transplant recipients. Findings in labial saliva. *Lab Invest.* 1985;52(3):292-97.
32. Nagler R, Barness-Hadar L, Lieba M, Nagler A. Salivary antioxidant capacity in graft versus host disease. *Cancer Invest.* 2006;24(3):269-77.
33. Singhal S, Mehta J, Rattenbury H, Treleaven J, Powles R. Oral pilocarpine hydrochloride for the treatment of refractory xerostomia associated with chronic graft-versus-host disease. *Blood.* 1995;85(4):1147-48.
34. Singhal S, Powles R, Treleaven J, Rattenbury H, Mehta J. Pilocarpine hydrochloride for symptomatic relief of xerostomia due to chronic graft-versus-host disease or total-body irradiation after bone-marrow transplantation for hematologic malignancies. *Leuk Lymphoma.* 1997;24(5-6):539-43.
35. Souza LN, Carneiro MA, Azevedo WM, Gomez RS. Vascular endothelial growth factor (VEGF) and chronic graft-versus-host disease (cGVHD) in salivary glands of bone marrow transplant (BMT) recipients. *J Oral Pathol Med.* 2004;33(1):13-16.
36. Nagler RM, Nagler A. The molecular basis of salivary gland involvement in graft-vs-host disease. *J Dent Res.* 2004;83(2):98-103.
37. Torres SR, Lotti RS, Peixoto CB, Graça PAC, Lima MEP, Pina CC, et al. Evaluation of the efficacy of a questionnaire to detect hyposalivation. *Rev Assoc Paul Cir Dent.* 2002;56(3):227-31
38. Dawes C. Physiological factors affecting salivary flow rate, oral sugar, clearance, and the sensation of dry mouth in man. *J Dent Res.* 1987;66:648-53.
39. Nagler RM, Nagler A. Sialometrical and sialochemical analysis of patients with chronic graft-versus-host disease - a prolonged study. *Cancer Invest.* 2003;21(1):34-40.
40. Jensen SB, Pedersen AM, Reibel J, Nauntofte B. Xerostomia and hypofunction of the salivary glands in cancer therapy. *Support Care Cancer.* 2003;11(4):207-25. Comment in: *Support Care Cancer.* 2003;11(4):199-200.
41. Torres SR, Peixoto CB, Caldas DM, Silva LR, Akiti T, Nucci M, et al. Relationship between salivary flow rates and Candida counts in subjects with xerostomia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2002 Feb;93(2):149-54.
42. Torres SR. Xerostomia: clinical consequences and treatment. *Pro-Odonto Prevenção. Programa de Atualização em Odontologia Preventiva e Saúde Coletiva.* 1st ed. Porto Alegre: Artmed/Panamericana; 2008. p. 165-96.
43. Singhal S, Powles R, Treleaven J, Rattenbury H, Mehta J. Pilocarpine hydrochloride for symptomatic relief of xerostomia due to chronic graft-versus-host disease or total-body irradiation after bone-marrow transplantation for hematologic malignancies. *Leuk Lymphoma.* 1997;24(5-6):539-43.
44. Silva MM, Bouzas LFS, Filgueira AL. Tegumentary manifestations of graft-versus-host disease in bone marrow transplantation recipients. *An Bras Dermatol.* 2005;80(1):69-80.
45. Schubert MM, Correa ME. Oral graft-versus-host disease. *Dent Clin North Am.* 2008;52(1):79-109, viii-ix.
46. Gomes AO, Torres SR, Maiolino A, dos Santos CW, Silva Junior A, Pizzigatti CM, et al. Early and late oral features of chronic graft-versus-host disease. *Rev Bras Hematol Hemoter.* 2014;36(1):43-9.