J. Oral Diagn 2025;10:e322
https://doi.org/10.5327/2525-5711.322

ORIGINAL ARTICLE

# Profile of oral manifestations of graft versus host disease

Julia Rahal de Camargo[1], Halina Grossmann-Pereira[2], Rafael Zancan Mobile[2], Cassius Carvalho Torres-Pereira[1,2], Juliana Lucena Schussel[1,2]*

## Abstract

**Objective:** The objective of this cohort study was to evaluate patients previously diagnosed with oral lesions associated GVHD, aiming to characterize and describe the primary clinical presentations observed. **Methods:** A retrospective analysis of medical and dental records, alongside a photographic review, was conducted to assess the oral manifestations of GVHD in these patients. **Results:** The evaluation of medical records shows that GVHD affected more males (58.4%); The most affected age group was 21-50 years (55.6%); The most frequent lesion was hyperkeratotic plaque (76.4). The most common underlying disease was Fanconi Anemia (FA) representing 54.2%. Of these, 5.1% developed some malignant neoplasm, confirming the fact that patients with FA have a marked predisposition to carcinomas. **Conclusion:** It is evident that GVHD manifests itself in different ways in the oral cavity, therefore, knowing the clinical presentation of GVHD becomes important to determine the most appropriate treatment and to differentiate it from lesions with malignant potential.

**Keywords:** Hematopoietic stem cell transplantation; Graft-versus-host disease; Oral manifestations.

## INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is indicated for the treatment of several types of hematological diseases[1]. It involves the eradication of the individual's immune and hematopoietic system intending to correct a quantitative or qualitative defect in the bone marrow and its replacement by stem cells, either from the patient or from a donor[1,2].

A very common post-HSCT complication is the development of graft-versus-host disease (GVHD), which can decrease overall survival[2]. GVHD is characterized by a severe and, sometimes, lethal inflammatory condition in which the donor's T cells mediate an immune attack on the tissue cells of the graft host[3,4]. The manifestation of GVHD can be localized or systemic and the main sites of occurrence being the skin, liver and oral mucosa. It can be classified as acute GVHD (aGVHD) or chronic GVHD (cGVHD) according to the clinical characteristics and pathological signs of the diseases, regardless of the time of occurrence after HSCT[5].

Oral GVHD can occur in 45–83% of cases and is characterized by painful, hyperkeratotic, erythematous, ulcerative, atrophic inflammatory lesions and limited mouth opening[3,6,7]. According to the National Institutes of Health (NIH), the oral manifestations of cGVHD can be divided into: *diagnostic* represented by lichenoid lesions; *distinctive* represented by xerostomia, mucoceles, mucosal atrophy, pseudomembranes and ulcers; and alterations common to the acute form of GVHD, consisting of gingivitis, mucositis, erythema and pain, which are therefore important topics in the diagnosis of this clinical condition[5,8].

The variety of manifestations that oral GVHD can present might lead to a difficulty in the correct diagnosis. Differential diagnosis is important for the correct treatment and prevention of potentially malignant disorders. Thus, the objective of this study was to assess, through photographic images, the clinical variation of the oral

**Statement of Clinical Significance**
Hematopoietic stem cell transplantation (HSCT) treats hematological diseases but risks graft-versus-host disease (GVHD), often affecting the oral mucosa. Oral GVHD presents as hyperkeratotic or ulcerative lesions, complicating patient care. Understanding oral GVHD profiles improves management, reduces morbidity, and enhances long-term outcomes for HSCT recipients.

[1]Universidade Federal do Paraná, Department of Stomatology – Curitiba (PR), Brazil.
[2]Universidade Federal do Paraná, Post-Graduate Program in Dentistry – Curitiba (PR), Brazil.
***Correspondence to:** Email: juliana.schussel@ufpr.br
Received on February 21, 2025. Accepted on April 22, 2025.
https://doi.org/10.5327/2525-5711.322

GVHD lesions, as a way of better performing its diagnosis. This study aimed to assess patients with oral lesions associated with GVHD, characterizing their clinical presentations to improve diagnostic accuracy and guide management. Given the potential for these lesions to cause pain, dysfunction, and increased risk of infection, documenting their variability through photographic analysis provides a valuable tool for early recognition and tailored therapeutic interventions.

## MATERIALS AND METHODS

This retrospective cohort observational study analyzed the oral manifestations of GVHD in patients who underwent HSTC at a tertiary referral hospital in the southern of Brazil, between the years of 2015 and 2022, with aim to characterize the profile of oral GVHD lesions, favoring the early diagnosis and improve management. The present research was approved by the Ethical Research Board of the Hospital de Clinicas da Universidade Federal do Paraná, under the protocol CAAE 12019519.90000.0096, and, since it is a retrospective study involving the evaluation of medical records, the Informed Consent Form was exempted.

A retrospective evaluation of medical and dental information, in addition to photographic review from the hospital chart, was carried. Inclusion criteria were patients who underwent allogeneic HSCT, with complete medical and dental information with updated clinical evolution and photographic record of oral lesions, that developed oral GVHD.

For data analysis, information about clinical evolution, medical and dental history was assessed from the medical records such as: history of HSCT; medications in use, lymph node examination; blood count; oral health condition and details from oral manifestations: location of lesions, size, fundamental lesion, color, surface, consistency and time of evolution as well as clinical symptoms associated with oral GVHD.

Exclusion criteria comprised:

1. Autologous HSCT recipients,
2. Incomplete records or missing lesion photographs,
3. Oral lesions attributable to non-GVHD causes (e.g., herpes simplex or traumatic ulcers), and
4. Unavailable post-transplant follow-up data. These criteria aimed to isolate GVHD-specific manifestations while ensuring data reliability.

Lesions were classified as erythematous (erythema, ulcers, atrophic areas) or whitish (lichenoid features, hyperkeratotic plaques) for analysis. All patients had multifocal involvement, with heterogeneous presentations — individuals often demonstrated both erythematous and whitish lesions simultaneously at separate oral sites.

A descriptive statistical analysis was conducted to evaluate the frequency and percentage distribution of oral GVHD lesions. The study employed no inferential statistical methods, focusing on characterizing clinical presentations.

## RESULTS

The retrospective assessment of medical records was based on an active search for four variables: gender, age, fundamental lesion and underlying disease. A total of 1502 hospital charts were evaluated and 72 met the inclusion criteria.

Forty-two patients were male (58.4%) and 30 female patients (41.6%). The mean age of the sample was 37 years, ranging from 11 to 63 years old. To facilitate analysis, age was divided into four categories: 11–20 years; 21–50 years, 51–60 years and 61 years and over. In the 11-20 age category, a total of 25 (34.7%) patients were found. The highest percentage of the sample was found in the 21–50 age category with 40 patients (55.6%). Six (8.3%) patients were between 51–60 years old, and only 1 (1.4%) patient in the category 61 years old or more.

The most frequent presentation of oral lesions was lichenoid, erythematous, hyperkeratotic plaque, atrophy and ulcer (Figure 1). For matter of analysis, lesions were also divided as erythematous lesions and whitish lesions. All patients in the sample present more than one lesion, with different aspects. Thus, a single individual could present a red lesion (ulcer, atrophy and erythema) in one site of the oral cavity and a white lesion (lichenoid and hyperkeratosis) in a different site. The most recurrent lesion was the hyperkeratotic plaque, found in 55 patients, which corresponds to 76.4% of the sample. Subsequently, the lichenoid lesion was observed in 52 patients, corresponding to 72.2% of the sample. 39 patients had erythematous lesions, representing 54.2% of the sample. The ulcerated lesion was found in 36 patients, affecting 50% of the sample. Finally, the atrophic lesion was found in only 6 patients, representing 8.3% of the sample.

In the underlying disease variable, 14 diseases were evaluated, being them: Fanconi Anemia (FA) (54.2%); Chronic Myeloid Leukemia (CML)(9.7%); Acute Lymphoblastic Leukemia (ALL) and Severe Aplastic Anemia (SAA)(6.9%); Myelodysplasia (5.5%); Congenital

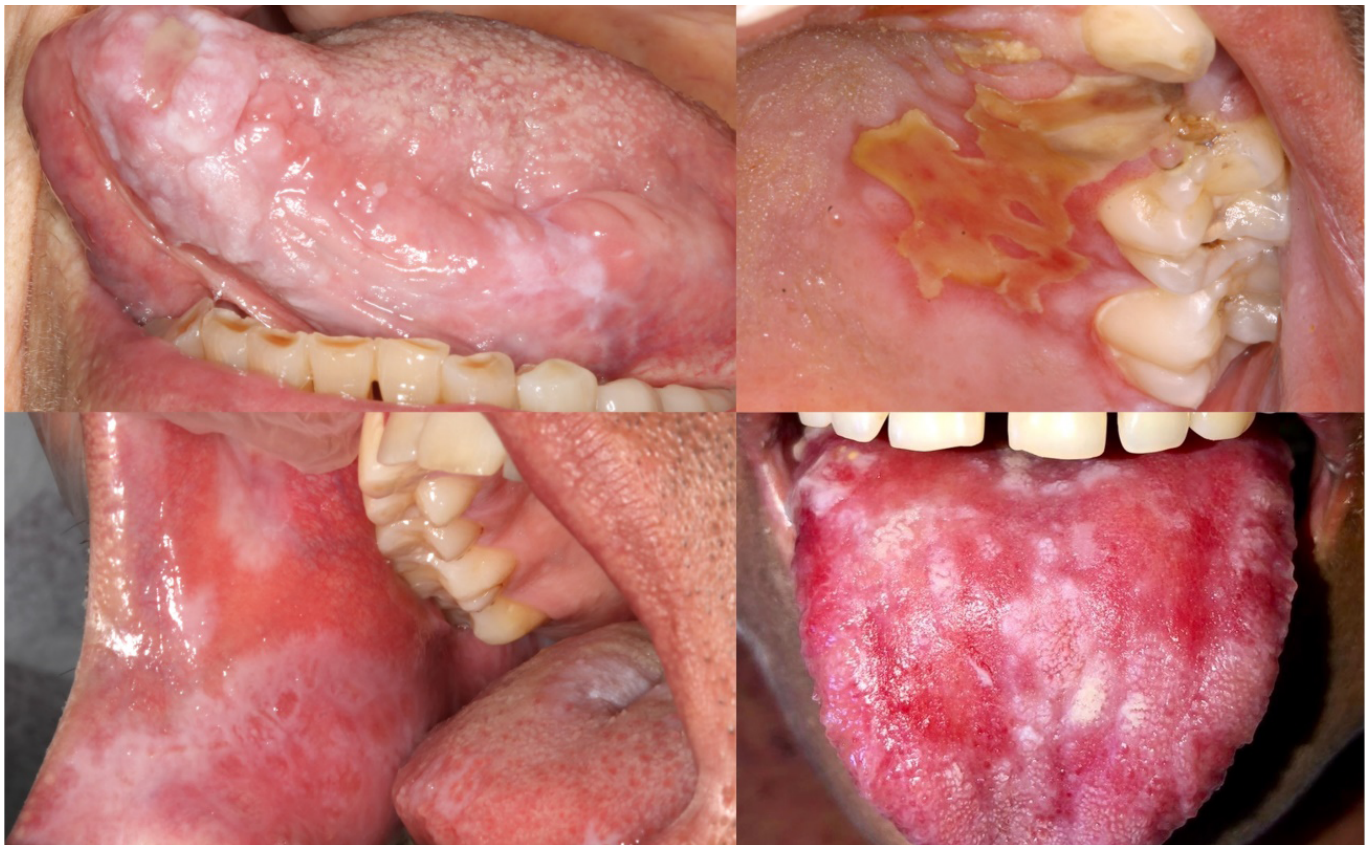

**Figure 1.** Clinical variation of graft-versus-host disease lesions: atrophic, ulcerated, leukoplasic, and lichenoid.

dyscreatosis (4.2%); Acute Myeloid Leukemia (AML) (2.8%); Wiskott Aldrich Syndrome (WAS); Leukemia; Myelofibrosis; Juvenile Myelomonocytic Leukemia (JMML); DOC 8 immunodeficiency; Medullary Aplasia (MA); and Chronic granulomatous disease (CGD) (1.4% each) (Table 1).

## DISCUSSION

GVHD is a common and important complication after HSCT and its prevalence varies from 25% to 80% in long-term follow-up[2]. cGVHD oral lesions can be painful and appear anywhere in the mouth. Patients with oral manifestations of cGVHD are at increased risk of developing rampant caries, candidiasis, gingivitis, and periodontitis, and it is also considered an oral potentially malignant disorder[9]. Pain, mucosal atrophy and limited mouth opening, or tongue mobility also cause swallowing and phonation difficulties[3,10].

In the present study 72 patients with oral GVHD were included, all of them had more than one lesion with different aspects, totalizing 188 oral lesions. Most lesions present as white plaques (107/57%) followed by 81 red lesions (81/43%). Nonetheless the authors observed a wide variety of clinical presentations.

Besides GVHD, patients under immunosuppression might present other oral lesions associated with inflammatory processes as well as opportunistic infections, that can present with varied clinical features leading to a difficulty for the definitive diagnosis[11]. The effects of the treatment itself combined with the different medications that are used during the recovery of the immune system, the opportunistic infections and other complications can also compromise the patient's evolution and make it difficult to establish the correct treatment, impacting the patient's quality of life, including speech and eating, in addition to the persistence of pain and discomfort[7,11].

Oral lesions may persist even after cGVHD cures in other organs. The control of such lesions, especially ulcerated ones, is essential since they can serve as a gateway for microorganisms present in the oral microbiota to reach the bloodstream, increasing the risk of septicemia[3].

While manifestations in other organs, such as the skin and liver, for example, can be confused with signs of other diseases; certain oral manifestations, such as lichenoid lesions, can be very useful in the diagnosis

**Table 1.** Epidemiological characteristics, main lesions, and underlying diseases.

| Variable/Category | n (%) |
|---|---|
| Gender | |
| Male | 42 (58.4) |
| Female | 30 (41.6) |
| Age group (years) | |
| 11–20 | 25 (34.7) |
| 21–50 | 40 (55.6) |
| 51–60 | 6 (8.3) |
| ≥61 | 1 (1.4) |
| Main lesions observed | |
| Hyperkeratotic plaque | 55 (76.4) |
| Lichenoid lesion | 52 (72.2) |
| Erythematous lesion | 39 (54.2) |
| Ulcer | 36 (50.0) |
| Atrophic lesion | 6 (8.3) |
| Underlying disease | |
| Fanconi Anemia | 39 (54.2) |
| Chronic Myeloid Leukemia | 7 (9.7) |
| Acute Lymphoblastic Leukemia | 5 (6.9) |
| Severe Aplastic Anemia | 5 (6.9) |
| Myelodysplasia | 4 (5.5) |
| Congenital Dyskeratosis | 3 (4.2) |
| Acute Myeloid Leukemia | 2 (2.8) |
| Wiskott-Aldrich Syndrome | 1 (1.4) |
| Leukemia (unspecified) | 1 (1.4) |
| Myelofibrosis | 1 (1.4) |
| Juvenile Myelomonocytic Leukemia | 1 (1.4) |
| DOC 8 Immunodeficiency | 1 (1.4) |
| Medullary Aplasia | 1 (1.4) |
| Chronic Granulomatous Disease | 1 (1.4) |

process, since oral involvement has been described as one of the initial alterations of cGVHD[12].

The high frequency of lichenoid lesions in patients undergoing HSCT was established by the 2014 NIH consensus as a sufficient clinical criterion, regardless of histopathological examination, for the diagnosis of cGVHD[5]. Ulcers, mucosal atrophy and mucocele are frequent features association with cGVHD[13].

Another important factor is the increased risk that patients with cGVHD have of developing a second neoplasm such as squamous cell carcinoma of the oral mucosa[9,14]. This factor must be considered, given that it is an aggressive disease that significantly influences both the quality of life and the overall survival of the patient, being described in the literature as a possible oral alteration associated with cGVHD[14]. Among the risk factors proposed to explain this high incidence are the inflammatory process associated with cGVHD, prolonged immunosuppression due to cGVHD treatment, immune dysfunction, Fanconi anemia, radiation-induced mutations and the carcinogenic and cytotoxic effects of various medications[12,15].

The Reference Hospital complex, where this study was carried out, is a pioneer in bone marrow transplantation (BMT), being the first service in Latin America to perform this type of transplant, in 1979. The vast experience acquired over the years made it possible to improve the treatment, and better understand the behavior of GVHD. Also, the large sample of FA patients is justified as it is a reference center in the treatment of this syndrome.

According to Furquim et al., after HSCT, FA patients have an estimated risk of 500 times of developing head and neck cancer compared to an unaffected one, and the oral cavity is affected in a third of those cases[16]. Through the results of this study, it was possible to observe that 7.7% of a sample of 39 patients with FA developed a malignant neoplasm during follow-up period.

For those reasons, after diagnosis, patients with FA need to seek longitudinal and comprehensive follow-up with a multidisciplinary team that includes hematologists, oncologists, dentists, otolaryngologists, endocrinologists, dermatologists, gastroenterologists, nephrologists and orthopedic surgeons[17].

## CONCLUSION

It is evident that GVHD manifests itself in different ways in the patient's oral cavity, varying the type of lesion, size, region, color and symptomatology, which makes early diagnosis of this disease difficult. Knowing well the clinical presentation of oral GVHD is important not only for determining the most appropriate prognosis and treatment, but also for distinguishing it from lesions with malignant potential.

Therefore, an early and accurate diagnosis is essential for the establishment of an effective treatment in the early stages of the disease. In addition, it is evident the importance of longitudinal follow-up with a multidisciplinary team after diagnosis.

## AUTHORS' CONTRIBUTIONS

JRC: Data curation, Investigation, Formal analysis, Writing – original draft. HGP: Data curation, Methodology, Validation, Writing – original draft. RZM: Data curation, Formal analysis, Methodology, Validation, Writing – original draft. CCTP: Conceptualization, Supervision, Validation, Writing – review and editing. JLS: Conceptualization, Methodology, Supervision, Project administration, Writing – review and editing.

## CONFLICT OF INTEREST STATEMENT

**Funding:** This work was supported by the Coordination of Higher Education Personnel (CAPES) and the National Council for Scientific and Technological Development (CNPq), through doctoral and scientific initiation scholarships, respectively.

**Competing interests:** The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval:** The study was approved by the Ethics Review Board of the Hospital de Clínicas under protocol number CAAE: 12019519.9.0000.0096.

## REFERENCES

1. Bazinet A, Popradi G. A general practitioner's guide to hematopoietic stem-cell transplantation. Curr Oncol. 2019;26(3):187-91. https://doi.org/10.3747/co.26.5033
2. Pinto GR, Sarmento VA, Carvalho-Filho PC, Fortuna VA, Costa RS, Conceição RR, et al. Gene expression profile of chronic oral graft-versus-host disease. PLoS One. 2022;17(4):e0267325. https://doi.org/10.1371/journal.pone.0267325
3. Scaraficci AC, Fernandes PM, Alves FA, Schimidt Filho J, Jaguar GC. Oral manifestations of graft-versus-host disease in patients submitted to allogeneic hematopoietic stem cell transplantation: the experience of a Brazilian Cancer Center. Support Care Cancer. 2022;30(1):567-73. https://doi.org/10.1007/s00520-021-06349-9
4. Kim EJ, Kim N, Cho SG. The potential use of mesenchymal stem cells in hematopoietic stem cell transplantation. Exp Mol Med. 2013;45(1):e2. https://doi.org/10.1038/emm.2013.2
5. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report. Biol Blood Marrow Transplant. 2015;21(3):389-401.e1. https://doi.org/10.1016/j.bbmt.2014.12.001
6. Piccin A, Tagnin M, Vecchiato C, Al-Khaffaf A, Beqiri L, Kaiser C, et al. Graft-versus-host disease (GvHD) of the tongue and of the oral cavity: a large retrospective study. Int J Hematol. 2018;108(6):615-21. https://doi.org/10.1007/s12185-018-2520-5
7. Margaix-Munoz M, Bagán JV, Jiménez Y, Sarrión MG, Poveda-Roda R. Graft-versus-host disease affecting oral cavity. A review. J Clin Exp Dent. 2015;7(1):e138-45. https://doi.org/10.4317/jced.51975
8. Lee SJ, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia M, et al. 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. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant. 2015;21(6):984-99. https://doi.org/10.1016/j.bbmt.2015.02.025
9. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, González-Moles MA, Kerr AR, et al. Oral potentially malignant disorders: a consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. Oral Dis. 2021;27(8):1862-80. https://doi.org/10.1111/odi.13704
10. Meier JKH, Wolff D, Pavletic S, Greinix H, Gosau M, Bertz H, et al. Oral chronic graft-versus-host disease: report from the International Consensus Conference on clinical practice in cGVHD. Clin Oral Investig. 2011;15(2):127-39. https://doi.org/10.1007/s00784-010-0450-6
11. Leidens N, Ballardin BS, Leal GA, Araújo AMM, Sessenta-Junior CF, Torres-Pereira CC, et al. Graft-versus-host disease and herpes simplex virus oral injuries in onco-hematological patient: case report. Spec Care Dentist. 2022;42(1):91-6. https://doi.org/10.1111/scd.12640
12. Mays JW, Fassil H, Edwards DA, Pavletic SZ, Bassim CW. Oral chronic graft-versus-host disease: current pathogenesis, therapy, and research. Oral Dis. 2013;19(4):327-46. https://doi.org/10.1111/odi.12028
13. Dean D, Sroussi H. Oral chronic graft-versus-host disease. Front Oral Health. 2022;3:903154. https://doi.org/10.3389/froh.2022.903154
14. Janowiak-Majeranowska A, Osowski J, Mikaszewski B, Majeranowski A. Secondary oral cancer after systemic treatment of hematological malignancies and oral GVHD: a systematic review. Cancers (Basel). 2022;14(9):2175. https://doi.org/10.3390/cancers14092175
15. Kutler DI, Patel KR, Auerbach AD, Kennedy J, Lach FP, Sanborn E, et al. Natural history and management of Fanconi anemia patients with head and neck cancer: a 10-year follow-up. Laryngoscope. 2016;126(4):870-9. https://doi.org/10.1002/lary.25726
16. Furquim CP, Pivovar A, Amenábar JM, Bonfim C, Torres-Pereira CC. Oral cancer in Fanconi anemia: review of 121 cases. Crit Rev Oncol Hematol. 2018;125:35-40. https://doi.org/10.1016/j.critrevonc.2018.02.013
17. Amenábar JM, Torres-Pereira CC, Tang KD, Punyadeera C. Two enemies, one fight: an update of oral cancer in patients with Fanconi anemia. Cancer. 2019;125(22):3936-46. https://doi.org/10.1002/cncr.32435