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Oral pyogenic granulomas: a rare manifestation of oral graft-versus-host-disease

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ABSTRACT

Background: Chronic graft-*versus*-host disease (cGVHD) is a frequent complication following allogeneic hematopoietic cell transplantation (allo-HCT) and commonly affects the oral cavity. Up to 80% of patients develop oral manifestations, which may significantly impair quality of life, especially in pediatric patients. **Objective:** To describe the diagnosis and management of a pyogenic granuloma in a pediatric patient with oral cGVHD. **Case report:** A 5-year-old male patient underwent a second haploidentical allo-HCT for severe aplastic anemia. On day +270 post-transplantation, he developed painful ulcerative lesions on the bilateral buccal mucosa and lateral borders of the tongue, which evolved into ulcerated nodular lesions. Initial conservative management with topical 0.1% clobetasol propionate was attempted, without clinical improvement. Due to lesion progression and persistent pain, the patient was referred to the surgical center for excision of the nodules. Histopathological examination was consistent with pyogenic granuloma. Seven days after surgery, recurrence was observed on the right buccal mucosa. Topical treatment with 0.1% clobetasol propionate ointment associated with acetate plates was prescribed, leading to regression of the recurrent lesion. **Conclusion:** Complete surgical excision associated with elimination of local traumatic factors remains the standard treatment, while adequate control of the underlying oral cGVHD may contribute to favorable clinical outcomes.

Keywords: Case Reports; Granuloma; Pyogenic; Graft vs Host Disease; Hematopoietic Stem Cell Transplantation.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is an effective therapeutic approach for oncological hematological disorders and bone marrow failure. In this transplantation method, the recipient receives hematopoietic precursor cells derived from the circulating blood or umbilical cord blood of a donor. Human leukocyte antigens (HLA) compatibility between the donor and recipient is essential to minimize the potential complications associated with the transplantation[1–3].

One of the primary complications associated with allo-HCT is graft-*versus*-host disease (GVHD). This alloimmune condition arises from donor T lymphocytes and is classified into three categories: acute, chronic, and overlap syndrome[4]. The oral cavity primarily exhibits chronic manifestations of the disease. Up to 80% of patients

undergoing allo-HCT present with manifestations of chronic oral GVHD (oral cGVHD)[5]. The predominant manifestations include lichenoid lesions, ulcers, and erythema, which primarily affect the buccal and labial mucosa, as well as the tongue and floor of the mouth[6]. Benign lesions, such as oral pyogenic granuloma (PG), rarely develop in cases of oral cGVHD.

PG is a vascular lesion that exhibits rapid growth in response to chronic trauma, typically presenting as a nodule or papule that may bleed upon contact and can potentially ulcerate[7]. Due to its characteristics, this type of lesion significantly impacts the quality of life of patients with oral cGVHD[8]. Diagnosis of PG requires histopathological examination, and differential diagnoses must be carefully considered to exclude malignant lesions or infectious processes. The differential diagnosis includes peripheral giant cell granuloma, peripheral ossifying fibroma, squamous cell carcinoma, and infectious lesions. Surgical excision and elimination of the underlying causative factor are considered the standard treatment for PG[3,7,9,10]. Atypical lesions such as PG associated with oral cGVHD warrant a dental professional's attention.

The manifestation of PG in post-allo-HCT patients has not been thoroughly characterized yet[8]. PG is an uncommon manifestation of oral cGVHD, and its true prevalence remains unknown because the available evidence is limited to isolated case reports and small case series. Literature data suggest that the inflammatory process induced by the lesion itself, in conjunction with the inflammatory response of GVHD and the use of calcineurin inhibitors administered to post-allo-HCT patients, may contribute to the development of PGs in an area exposed to trauma[3,9,10]. The adult population appears to be more significantly affected by PG in association with oral cGVHD. Reports documenting this association in pediatric patients following allo-HCT are scarce; three studies have reported the development of oral pyogenic granuloma following allogeneic transplantation in pediatric patients[3,11,12].

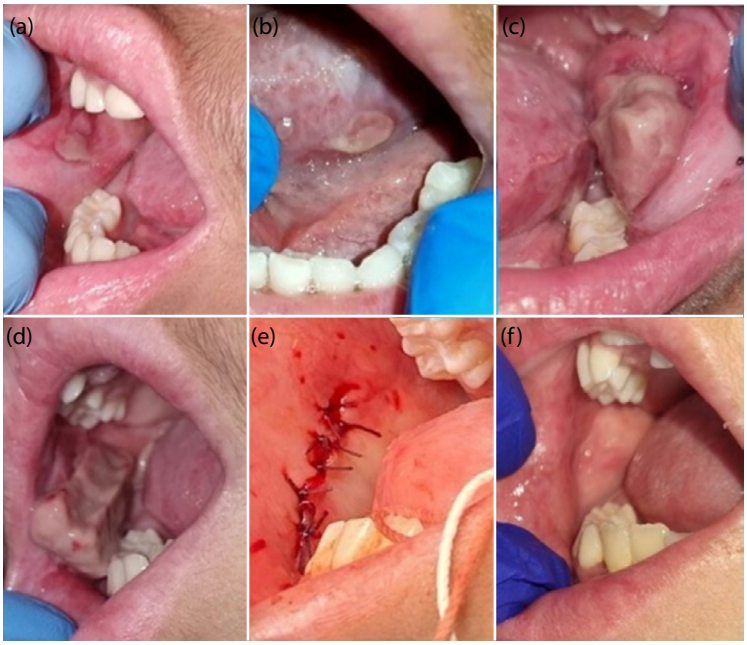
Therefore, the objective of this case report was to present the diagnosis and treatment of oral PG secondary to oral cGVHD in a pediatric patient undergoing allo-HCT.

CASE REPORT

A 5-year-old male patient underwent a second haploidentical transplant for severe aplastic anemia. The donor was his sister, and the cell source was peripheral blood. The patient received conditioning with fludarabine, cyclophosphamide, and total body irradiation (TBI), along with prophylaxis for GVHD using antithymocyte globulin (ATG). After 180 days post-transplantation, the patient was diagnosed with acute GVHD of the skin and initiated treatment with prednisolone at a dosage of 1 mg/kg/day.

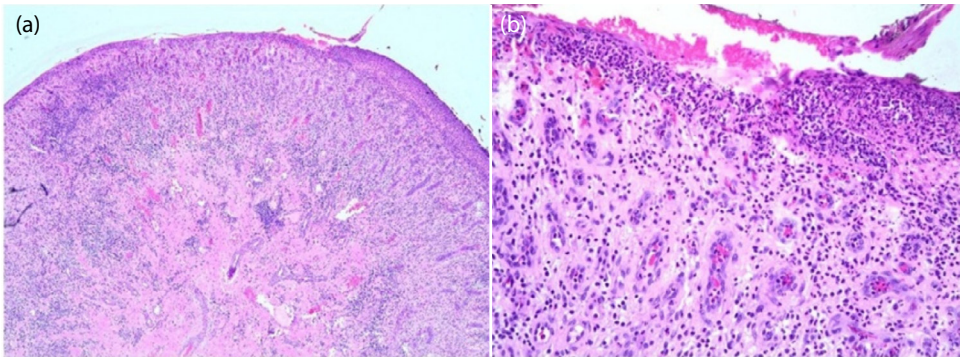
Approximately 250 days post-transplantation, the patient developed ulcerative lesions on the bilateral buccal mucosa and the lateral edges of the tongue, which rapidly progressed to ulcerated nodular lesions accompanied by pain (Figs. 1a–1d). He exhibited a Cushingoid facies and presented with teeth clenching. These features led to the development of a habit of sucking the buccal mucosa, which probably contributed to the exacerbation of the oral lesions. Furthermore, at the time of detection of the oral lesions, the patient was receiving cyclosporine to prevent transplant rejection. The dental team attempted to administer topical oral solution of 0.05% clobetasol propionate and tacrolimus ointment, but this intervention was unsuccessful.

The patient evaluated with significant pain and loss of appetite. Therefore, surgical excision of the lesions under general anesthesia and the application of acetate plates in the upper and lower arches were indicated to minimize trauma to the oral mucosa (Fig. 1e). The histopathological examination revealed extensive erosion of the epithelium associated with a mixed inflammatory process, fibrino-leukocyte crust, and capillary proliferation, supporting the diagnosis of PG (Figs. 2a and 2b). The nodular lesion on the right buccal mucosa recurred seven days post-excision. The application of 0.1% clobetasol propionate ointment, in conjunction with acetate plates, was prescribed, resulting in the regression of the lesion (Fig. 1f).



Source: Elaborated by the authors.

Figure 1. Full explanation of the figure. (a and b) Initial presentation of ulcerative lesions on the oral mucosa. (c and d) Subsequent development of nodular lesions. (e) Postoperative view immediately after surgical excision. (f) Clinical follow-up image obtained five months after excision.



Source: Elaborated by the authors.

Figure 2. Histological sections show a mucosal fragment with a prominent area exhibiting extensive surface epithelial erosion, accompanied by a mixed inflammatory infiltrate, a fibrino-leukocyte crust, and capillary proliferation. (a and b) Hematoxylin and eosin, 40× and 200×.

Ethical approval

This study was approved by the Human Research Ethics Committee of the Ribeirão Preto Clinical Hospital, Universidade de São Paulo (Ethical Clearance Certificate CAAE: 70464523.8.0000.5440), and was conducted in accordance with the ethical principles and good clinical research practices defined by the Declaration of Helsinki (2002 version). All patients provided written informed consent to participate in this study.

DISCUSSION

Allo-HCT is a treatment modality with high success rates in the oncohematological setting. However, despite recent advances, challenges following transplantation persist. GVHD represents the primary complication after allo-HCT, affecting multiple organs of the recipient and being associated with significant rates of morbidity

and mortality[5,13]. The oral cavity is one of the principal organs impacted by this condition[14]. Dentists should be vigilant regarding oral manifestations and consistently consider differential diagnoses to exclude infections or malignant diseases[3,11]. This case report presents an atypical manifestation of oral lesions associated with oral cGVHD, underscoring the importance of multidisciplinary monitoring for the diagnosis and management of these lesions.

The manifestations of oral cGVHD include diagnostic signs characterized by lichenoid lesions, deemed sufficient to establish a diagnosis of chronic GVHD in the oral cavity[15]. Additionally, distinctive signs such as xerostomia, mucoceles, pseudomembranous ulcers, and mucosal atrophy are considered insufficient for the diagnosis of oral cGVHD, and further testing is necessary. The occurrence of oral PG is infrequent in patients with oral cGVHD—only three cases have been described[3,11,12]—and this association raises the hypothesis that GVHD may facilitate PG development due to the chronic inflammatory response elicited by both conditions.

Oral PG is a benign vascular proliferation observed in young adults and children[9]. The most frequently affected sites are the gums—75% of oral PG cases are noted—, while the buccal mucosa, labial mucosa, and tongue are less commonly involved[3]. Some cases of oral PG have been reported in patients after allo-HCT, most of them occurring in association with oral cGVHD[3,9–12,16]. Although a direct causal relationship between cGVHD and PG has not been established, chronic inflammation, persistent mucosal injury, and dysregulated wound healing associated with cGVHD may create a microenvironment that favors the development of reactive vascular lesions such as PG[6,14,15]. Additional factors, including chronic local irritation, medications, poor oral hygiene, and repetitive trauma, such as habitual biting and contact with sharp tooth edges, are recognized contributors to oral PG development[7,9]. In the present case, prolonged corticosteroid therapy, reflected by the patient's Cushingoid facial appearance, together with bruxism and the habit of oral mucosal suction, may have acted as additional predisposing factors by promoting persistent local trauma and impaired tissue repair.

Surgical excision remains the standard PG treatment. Alternative approaches, including laser therapy, cryotherapy, sclerotherapy, and, in selected cases, intralesional corticosteroids, have also been described, depending on the lesion characteristics and the patient's clinical condition[3,9,10]. In immunosuppressed patients, surgical intervention should be reserved for cases that fail to respond to noninvasive treatment approaches. Although topical corticosteroids are widely used for the management of inflammatory manifestations of oral cGVHD, there are limited responses for PG[6,14]. In this case, the decision to proceed with surgical excision was based on the absence of clinical improvement following noninvasive therapeutic interventions, including topical corticosteroid therapy (clobetasol propionate) and topical tacrolimus, both associated with the use of protective oral appliances aimed at eliminating local traumatic factors.

In our patient, the acetate plate may also have contributed to lesion resolution by protecting the surgical site, minimizing mechanical trauma associated with the patient's oral mucosal suction habit, and facilitating tissue healing. Thus, the successful outcome was likely multifactorial, resulting from surgical excision combined with local protection and control of the underlying inflammatory condition.

The use of calcineurin inhibitors, such as cyclosporine, has been associated with the development of oral non-gingival soft tissue hyperplasia, including PG[17–19]. Cyclosporine is an immunosuppressive agent widely used for the prophylaxis of GVHD and the prevention of stem cell transplant rejection. Its mechanism involves the inhibition of calcineurin, leading to reduced interleukin-2 synthesis and T-cell activation suppression[19,20]. However, cyclosporine also promotes fibroblast proliferation and increases collagen synthesis, contributing to connective tissue overgrowth and hyperplasia[21]. The resulting excessive tissue growth can predispose patients, particularly those undergoing treatment for GVHD, to the oral PG development[22].

In cases of PG associated with bite trauma, the use of acetate protective splints can be justified, as they contribute to eliminate the traumatic etiologic factor, protect the surgically excised area, optimize the action of topical corticosteroids, and reduce the risk of recurrence[23]. In the present case report, recurrence of the lesion was observed seven days after surgical removal. However, the placement of the acetate splint, in combination with 0.1% clobetasol, resulted in complete regression of the residual lesion.

CONCLUSION

This case report highlights that oral manifestations of cGVHD may present with atypical reactive lesions, such as PG, even in pediatric patients. Since these lesions may mimic other inflammatory, infectious, or malignant conditions, careful diagnostic evaluation, including histopathological examination, is essential. Complete surgical excision associated with elimination of local traumatic factors remains the standard treatment, while adequate control of the underlying oral cGVHD may contribute to favorable clinical outcomes. Early recognition and appropriate management are crucial to relieve symptoms, prevent recurrence, and improve quality of life, emphasizing the importance of multidisciplinary care in patients with oral cGVHD.

CONFLICTS OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data are available from the corresponding author.

AUTHORS' CONTRIBUTIONS

Conception and design: Macedo LD and Pagliarone MJ; **Acquisition of data:** Pagliarone MJ, Reis TC and Romero GDA; **Analysis and interpretation of data:** Macedo LD, Pagliarone MJ, Grecco CES, Darrigo Junior LG, Faria JTB, Costa TCM and Stracieri ABPL; **Technical procedures:** Pagliarone MJ, Reis TC, Romero GDA and Ferrari TC; **Histopathological examinations:** Campos RB; **Manuscript writing:** Pagliarone MJ and Innocentini LMAR; **Critical revision:** Macedo LD, Innocentini LMAR and Ricz HMA; **Final approval:** Macedo LD.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

We declare that we did not use artificial intelligence tolls.

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