Lichenoid sialadenitis in chronic graft versus host disease

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Abstract

Chronic graft versus host disease (cGVHD) remains the principal long-term life-threatening complication in hematopoietic stem cell transplant recipients. We present a case of lichenoid sialadenitis in a 23-year-old-man with systemic cGVHD. The histological examination showed a lymphocytic inflammatory infiltrate adjacent to the salivary gland duct, similar to the histological aspects described in the typical manifestations of oral lichen planus and lichen planopilaris. This consists of a band-like inflammatory infiltrate not only targeting the cutaneous epithelium but also adnexal structures, such as hair follicles and salivary gland ducts. It is well described that the oral lesions in cGVHD share most of morphological and clinical manifestations with those described in oral lichen planus. The mechanisms of lichenoid salivary gland ducts destruction might be similar, although xerostomy appears to be specific to cGVHD, which may represent a clinical sign of massive salivary gland impairment related to ductal lichenoid destruction in patients with cGVHD.

Keywords: chronic graft versus host disease, cGVHD, salivary glands, xerostomia, lichen planus pilaris, oral lichen planus

Introduction

The use of hematopoietic stem cell transplant (HSCT) as standard treatment for hematological disorders has increased markedly in the past 50 years. Despite the improvements in conditioning regimens, donor matching, and post-HSCT complication prophylaxis, graft versus host disease remains the principal long-term life-threatening complication affecting 30 to 70% of HSCT recipients [1,2].

The clinical symptoms of chronic graft versus host disease (cGVHD) are heterogeneous; most patients develop manifestations in skin (75%), oral mucosa (51-63%), liver (29-51%), and eye (22-33%), [3,4]. The most common skin clinical features include sclerotic or erythematous/violaceous lichen-planus-like lesions, which may also be present in oral tissues. Oral mucosal lichenoid lesions are considered a classic cGVHD characteristic. Additionally, other oral cavity alterations, such as salivary gland impairment (manifested through xerostomia symptoms), mucoceles, mucosal atrophy, ulcers, and pseudomembranes may be present in many cases [5,6].

There is no pathognomonic feature for skin histological diagnosis. However, the NIH consensus specific criteria for cGVHD is the presence of lichen planus-like features such as epidermal orthohyperkeratosis, hypergranulosis, and acanthosis along with lichenoid inflammation and/or vacuolar changes of eccrine units. In cases of lichen sclerosus-like manifestations, the presence of sclerosis and homogenization of papillary dermal collagen are reported, together with interface changes such as melanophages in the papillary dermis and sparse lymphocytic infiltrate [5]. The oral mucosal histological features are similar to those found in skin, comprising a lymphocytic lichenoid interface along the basal keratinocyte layer of epithelial tissue, which shows signs of hyperkeratosis. The inflammatory infiltrate often reveals lymphocyte exocytosis and apoptosis [5,7].

The clinical and histological manifestations in salivary glands from patients with cGVHD are hardly ever analyzed; periductal lymphocytic infiltrate, damaged intralobular ducts, vacuolar changes, lymphocyte exocytosis, apoptosis, periductal fibroplasia, and lymphoplasmacytic inflammatory infiltrate are some of the features histologically associated with cGVHD of the salivary gland [8]. This case report associates clinical and histological features of salivary gland cGVHD and compares these characteristics with salivary gland lichen planus and lichen planopilaris.

Case Synopsis

A 23-year-old man, diagnosed with cGVHD after a full-match related allogenic bone-marrow HSCT, for severe aplastic anemia presented with oral symptoms. The patient underwent myeloablative conditioning with busulfan and cyclophosphamide and GVHD prophylaxis consisted of cyclosporine and methotrexate. The patient also received a prophylactic regimen of acyclovir, nystatin, betamethasone, and eye lubricant. The patient was diagnosed with moderate cGVHD by the assessment of clinical manifestations using the NIH global severity score; the diagnostic alterations are described and scored in **Table 1** [5].

Clinical examination showed scattered cutaneous violaceous papules intermingled with scarring and depigmentation; similar lesions were also observed in the lip vermilion. Oral manifestations included mucosal erosions, scarring, and depapillation of the tongue (**Figure 1A)**. The patient also complained of xerostomia; sialometry test showed a 0.24ml/min salivary flow (reference values of 0.29-0.41ml/min).

A biopsy of the labial mucosa was performed for harvesting salivary glands for the evaluation of salivary gland cGVHD compromise. The histological analysis showed hyperkeratosis, acanthosis, spongiosis, and basal keratinocytes with vacuolar degeneration. A lymphocytic inflammatory infiltrate was observed adjacent to the excretory salivary gland duct, in a lichenoid sialadenitis pattern; an intense hydropic degeneration of the excretory ductal epithelium was observed associated with the inflammatory infiltrate. The associated salivary glands showed an interstitial lymphoplasmocytic infiltrate without parenchymal aggression (**Figure 1B-D**).

Case Discussion

The present case showed full manifestations of oral cGVHD with salivary gland alterations, resulting in xerostomia. This symptom, significantly adds to the

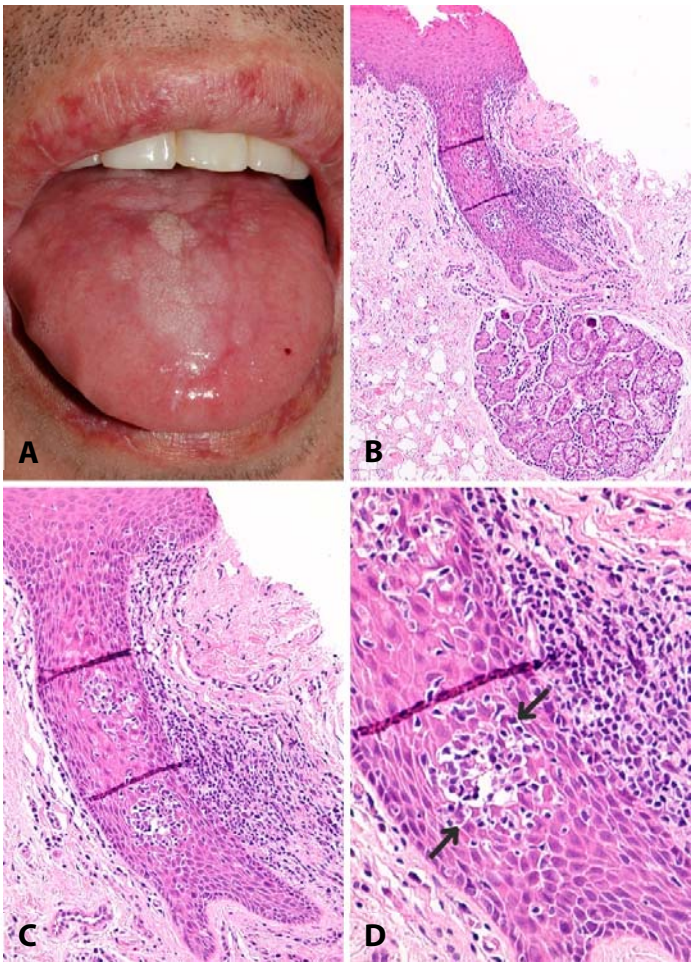

Figure 1. ***A)*** *Clinical aspects of chronic graft versus host disease (cGVHD) comprise lichenoid alterations on lips and tongue. Note a depapillated dorsum of the tongue the dry and dull aspect of the mucosa. Histopathological aspects of salivary glands in this cGVHC case, H&E:* ***B)*** *fragment of lip mucosa showing a salivary gland lobule with moderate lymphocytic sialadenitis and mild atrophy, associated with excretory duct tract that extends to the mucosa covering epithelium, 40×;* ***C)*** *the excretory duct is associated with an intense lymphocytic inflammatory infiltrate with lichenoid architecture, 250×;* ***D)*** *note the lymphocytic exocytosis with destruction of the ductal epithelium associated with apoptotic bodies (arrows), 400×.*

Table 1. *NIH consensus criteria for global severity score assessment of clinical manifestations of chronic graft versus host disease*

Organ or site	cGVHD diagnostic clinical manifestation	cGVHD distinctive clinical manifestation	Common alterations seen in GVHD	Score
Skin	Poikiloderma in the cervical region; Lichen planus-like features	Depigmentation		2
Oral Cavity	Lichen-planus like hyperkeratotic lesions in lips, tongue dorsum and buccal mucosa	Xerostomia; Mucosal atrophy; Oropharyngeal ulcers	Erythema	2
Muscles, fascia, joints	No alterations			0
Lungs	No alterations			0
Liver			Increased ALT and GGT	1
GI tract	No alterations			0
Eyes		Hyperemia; KCS; Loss of visual acuity (cataract)		2
Genital tract	No alterations			0
GLOBAL SEVERITY SCORE		Moderate cGVHD		

Abbreviations: cGVHD, chronic graft versus host disease; ALT, alanine aminotransferase; GGT, gamma glutamiltransferase; KCS, keratoconjunctivitis sicca.

other oral mucosal symptoms of cGVHD and severely impacts quality of life.

The management of patients with cGVHD is challenging, owing to the multiple manifestations of the disease with variable severity and outcomes. Oral cGVHD has been described separately as three distinct diseases—oral mucosa manifestations, salivary dysfunction, and limited mouth opening [9,10]. Bassim et al. have demonstrated pathogenesis interdependence among these manifestations; one must consider all these signs and symptoms to plan an effective multidisciplinary therapeutic approach to control the disease and improve the patients' life quality [11]. Thus, salivary gland dysfunction in cGVHD patients contribute to oral infections, periodontal disease, and increased caries risk. In addition, salivary dysfunction worsens the mucosal status already altered by the lichenoid lesions, leading to pain and limited capacity of mouth opening.

Oral lesions in cGVHD are identical to oral lichen planus (OLP), [12]. Lesions consist of symmetrically-distributed papules, bullae, erosions, ulcers, and atrophy [13]. Nonetheless, xerostomia in not observed in OLP.

Histological analysis of OLP is mainly characterized by hyperkeratosis, acanthosis, vacuolar degeneration of basal layer keratinocytes, Civatte bodies, "saw-tooth" rete ridge formations, and the dense, band-like interface inflammatory infiltrate. The lichenoid interface infiltrate adjacent to a salivary gland duct has been previously discussed by Lourenço et al. in 2010, in a patient with typical manifestations of OLP [14]. The histological aspects of the salivary gland lichen planus present similar features to the salivary gland changes examined in the present case: a lymphocytic infiltrate in juxtaposition to the salivary gland duct associated with vacuolar alterations and colloid bodies. This band-like inflammatory infiltrate may also be observed in skin manifestations of lichen planus (LP), not only targeting the cutaneous epithelium but also adnexal structures, such as hair follicles, as observed in lichen planopilaris (LPP). The latter corresponds to salivary gland lichen planus [14]. According to the National Institutes of Health (NIH) consensus, the minimal histologic criteria for oral cGVHD depends on lichenoid epithelial changes or the presence of intralobular, periductal lymphocytes in lobular ducts and acini, pointing out the importance of salivary gland analysis for the disease diagnosis. The present

description of a lichenoid band-like inflammatory infiltrate adjacent to salivary gland excretory ducts as a manifestation of cGVHD highlights the similar features to those lichenoid patterns well-described in other adnexal lichenoid alterations.

Clinical oral examination and salivary gland biopsy were previously proposed as active screening tools for cGVHD diagnosis 100 days after transplantation. This screening includes the microscopic analysis of mucosal salivary glands, which may be useful in predicting and diagnosing a possible systemic extension of the disease, especially hepatic compromise [15].

The development of cGVHD can be divided into three phases: inflammatory, immunological dysregulation, and fibrotic/sclerotic. The inability to regulate and maintain the immunological homeostasis leads to unresolved inflammation with exacerbated repair mechanisms leading to the fibrosis and eventual dysfunction of the targeted organ [16].

Conclusion

To our knowledge, there is no previous description of a lichenoid band-like inflammatory infiltrate adjacent to salivary glands excretory ducts as a manifestation of cGVHD; the mechanisms of this alteration might be similar to those described in the LPP, as the physiological mechanisms in cGVHD, OLP, and LPP share some similarities.

These diseases result from a complex interaction between cellular mediation and cytokine secretion, leading to a clinical and histological similar pattern, that ultimately results in the sclerosis and scarring of the affected tissue. However, the mechanisms of these alterations in salivary glands are still to be unraveled and this finding may represent an additional explanation for salivary gland impairment and xerostomia in patients with cGVHD.

Potential conflicts of interest

The authors declare no conflicts of interests.

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