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Salivary Gland Involvement in Chronic Graft-Versus-Host Disease: Prevalence, Clinical Significance, and Recommendations for Evaluation

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Although xerostomia is a commonly reported complaint in patients with chronic graft-versus-host disease (cGVHD), criteria for evaluating the prevalence and characteristics of salivary gland involvement have not been well defined in this patient population. Previous studies also have made no distinction between salivary and mucosal oral cGVHD. We systematically evaluated signs and symptoms of sicca in a large cohort of patients with cGVHD (n = 101) using instruments widely used to study Sjogren's syndrome. Xerostomia was reported by 77% of the patients and was associated with xerophthalmia in all but 1 case. The salivary flow rate was ≤0.2 mL/min in 27%, and ≤0.1 mL/min in 16%. Histopathological changes, consisting of mononuclear infiltration and/or fibrosis/atrophy, were present in all patients with salivary dysfunction. Importantly, there was no correlation of salivary and oral mucosal involvement in cGVHD. Patients with cGVHD-associated salivary gland involvement had diminished oral cavity-specific quality of life and lower body mass index. Salivary gland involvement is a common and clinically distinct manifestation of cGVHD. Formal evaluation of salivary function using standardized criteria is needed, and this could be incorporated as an outcome measure in clinical trials of cGVHD.

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KEY WORDS: CGVHD, Sicca syndrome, Xerostomia, Xerophthalmia, Sjogren's syndrome

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is the single most important complication in long-term survivors after allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1]. Involvement of cGVHD of the salivary and lacrimal glands results in Sjogren's syndrome (SS)-like manifestations, including hyposecretion of saliva and tears.

Xerostomia can be a distressing symptom, and decreased salivary flow may lead to reduced food intake, dental caries, and oral mucosal infection with *Candida* species [2]. In addition, salivary dysfunction may be associated with other, more severe manifestations of cGVHD, such as pulmonary involvement [3]. Therefore, formal assessment of salivary gland dysfunction is important in an overall assessment of cGVHD. Salivary gland function can be assessed using noninvasive tests, and could be used as an outcome in clinical trials.

Whereas the prevalence of xerophthalmia after allo-HSCT has been estimated to range between 40% and 70% in various studies [4-6], the prevalence of salivary gland involvement has not been well described [7]. Oral dryness complaints in cGVHD are often reported as "oral" or "mouth" involvement, and are not distinguished from oral mucosal lesions [8]. This is in part because older literature implied that the pathologic changes of the minor salivary glands found in cGVHD represented a continuum of the oral mucosal lesions found in the disease. However, oral mucosal and salivary gland involvement in cGVHD bear close resemblance

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Table 1. Patient Characteristics (n = 101)

Diagnosis, n (%)	
Acute leukemia/myelodysplastic syndrome	42 (41)
Chronic leukemia	23 (23)
Lymphoma	21 (21)
Multiple myeloma	8 (8)
Aplastic anemia/myelofibrosis	5 (5)
Paroxysmal nocturnal hemoglobinuria	2 (2)
Conditioning, n (%)	
Myeloablative	59 (59)
Reduced intensity	42 (41)
Donor type, n (%)	
Matched sibling donor	73 (72)
Matched unrelated donor	28 (28)
Stem cell source, n (%)	
Bone marrow	19 (19)
Peripheral blood	80 (79)
Unknown	2 (2)
Karnofsky Performance Status score, mean (SD), range	81 (12), 30-100
Months since transplantation, mean (SD), range	43 (38), 4-201
Months since cGVHD diagnosis, mean (SD), range	36 (37), 1-196

cGVHD indicates chronic graft-versus-host disease.

to autoimmune disorders affecting these tissues, specifically oral lichen planus and SS, which occur independently of each other and affect distinct patient populations. Although guidelines for evaluation of lacrimal dysfunction in cGVHD were defined in the recent National Institutes of Health (NIH) consensus criteria [9,10], no recommendations have been provided for evaluation of salivary gland involvement. Therefore, the aim of this study was to systematically examine the characteristics and correlates of salivary gland function in cGVHD and to determine whether oral mucosal and salivary gland pathology in cGVHD occurred independently. We also developed preliminary guidelines that could be used to evaluate patients with cGVHD who report oral dryness.

PATIENTS AND METHODS

Patients

A total of 101 consecutive adult patients enrolled in a cGVHD cross-sectional study (clinicaltrials.gov #NCT00331968) were included in this study. The study was approved by the National Cancer Institute's Institutional Review Board, and informed consent was obtained from all participants. Patients underwent comprehensive multispecialty clinical evaluation, laboratory testing, and research sample collection, and they completed a series of patient-reported outcome measures. The diagnosis of cGVHD was established using NIH consensus criteria [9]. The sample had a mean patient age of 45.9 ± 12 years (range, 20-66 years), predominantly white (n = 92; 91%), and with approximately equal representation of males (n = 53; 52%) and females (n = 48; 48%). The median time from transplantation to cGVHD diagnosis was 5 months (range, 3-35 months). Most patients had active moderate or severe cGVHD requiring continuation of systemic immunosuppression. Transplant and cGVHD characteristics for the sample are presented in Tables 1–3.

Table 2. Characteristics of Patients with cGVHD (n = 101)

	Salivary Dysfunction	
	Present (n = 22)	Absent (n = 59)
Onset of cGVHD, n (%)		
De novo	10 (45)	21 (36)
Quiescent	2 (9)	13 (22)
Progressive	10 (45)	25 (42)
Platelet count ≤100,000, n (%)	5 (23)	4 (7)
Clinician global rating of cGVHD, n (%)		
Mild	0 (0)	2 (3)
Moderate	8 (36)	24 (41)
Severe	11 (50)	26 (44)
Missing	3 (14)	7 (12)
Change in cGVHD over previous month, n (%)		
Better	5 (23)	10 (17)
About the same	9 (41)	18 (31)
Worse	8 (36)	31 (53)
Intensity of current immunosuppression, n (%)		
None	3 (14)	5 (8)
Mild*	2 (9)	6 (10)
Moderate†	9 (41)	16 (27)
High‡	8 (36)	22 (59)
Chronic GVHD clinical severity score, mean (SD), range	37 (10), 19-56	30 (9), 7-48
Lee cGVHD symptom scale total score, mean (SD), range	34 (14), 11-69	25 (13), 1-60

cGVHD indicates chronic graft-versus-host disease.
*Single agent prednisone <0.5 mg/kg/day.
†Single agent prednisone ≥0.5 mg/kg/day or single agent/modality with and without prednisone ≥0.5 mg/kg/day.
‡Two or more agents/modalities with and without prednisone ≥0.5 mg/kg/day.

Clinical Evaluations

Salivary and lacrimal symptoms were evaluated using methods described by the American-European Consensus Group (AECG) for SS [11]. The presence of xerostomia and xerophthalmia were determined using the 3-item AECG screening questionnaire, which assesses both the presence and duration of symptoms. Patient-reported symptoms of dry mouth have been reported to not correlate well with objective measures of salivary function [12]. In addition, xerostomia severity was graded on a patient-reported scale of 0-10.

Evaluation of salivary gland function was performed by measuring the unstimulated salivary flow rate using 5-minute saliva collection into a preweighed 50-ml centrifuge tube in a modification of a procedure described previously [13]. Objective evaluation of lacrimal function included Schirmer's test (performed with local anesthesia) and evaluation of keratopathy and conjunctival involvement by fluorescein and lissamine green staining according to European-U.S. criteria for evaluation of SS [11]. A Schirmer's test score of ≤5 mm in 5 minutes was considered abnormal.