1083-8791/05/1109-0009$30.00/0
doi:10.1016/j.bbmt.2005.06.002

Oral Chronic Graft-versus-Host Disease in Pediatric Patients after Hematopoietic Stem Cell Transplantation

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Received March 14, 2005; accepted June 13, 2005

ABSTRACT

Chronic graft-versus-host disease (cGVHD) is a serious and potentially life-threatening complication of hematopoietic stem cell transplantation. This study, which is the largest single-center series of oral disease in pediatric patients with cGVHD, describes the oral findings in 49 consecutive patients seen in a pediatric multidisciplinary cGVHD clinic. All consecutive patients seen at the multidisciplinary pediatric hematopoietic stem cell transplantation/cGVHD clinic at the Dana-Farber Cancer Institute (Boston, MA) from July 2001 through October 2003 were included in this study. Subjective and objective assessments of mucosal, salivary gland, and sclerotic pathology were performed for each patient, and specific therapy was initiated when indicated. Oral mucosal cGVHD was identified in 22 (45%) of 49 patients. Only 4 (8%) of 49 patients reported mouth pain, and all patients reported being able to eat well. All patients who required specific therapy for their oral mucosal cGVHD (45%) were already taking at least 1 immunomodulatory agent; however, efficacy of treatment was difficult to assess because of inconsistent follow-up periods. Subjective and objective salivary gland and sclerotic disease were observed far less often. Oral mucosal pathology is common in these patients, and appropriate diagnosis and management of oral lesions is critical to reduce patient morbidity and to improve quality of life. The apparent lack of salivary gland involvement was notable. Developing validated age-appropriate evaluation strategies and identifying effective treatment guidelines will be invaluable in the future management of these patients.

KEY WORDS

Graft-versus-host disease • Hematopoietic stem cell transplantation • Pediatric patients • Oral lesions

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a serious and potentially life-threatening complication of hematopoietic stem cell transplantation (HSCT). Many patients with benign and malignant hematologic diseases now undergo HSCT. With continually improving survival rates, cGVHD has become one of the leading long-term complications that causes both morbidity and mortality in these patients [1].

The skin, liver, and gastrointestinal tract (including the oral cavity) are the primary organs classically affected by cGVHD, although other systems may be involved, such as the pulmonary system, depending on the course and severity of disease. Oral involvement primarily affects the mucosa and salivary glands. Mucosal lesions are similar to those of oral lichen planus and are characterized by reticular, erythematous, or ulcerative involvement [2]. Sclerotic changes resulting in trismus and reduced mobility of the stomatognathic complex may develop secondary to fibrosis from chronic and severe mucosal disease or may represent a primary process in the skin and muscles [3,4]. Salivary

gland involvement is characterized by a decrease in salivary gland output that potentially results in oral discomfort, an increased incidence of caries, candidiasis, and difficulties in eating, speaking, and swallowing [5].

Although oral cGVHD has been characterized in adult patients [6], the literature describing this condition in pediatric patients is scarce [7-12]. This study, which represents the largest single-center series of oral disease in pediatric patients with cGVHD, describes the oral findings in 49 consecutive patients seen in a pediatric multidisciplinary cGVHD clinic.

METHODS

All consecutive patients seen at the multidisciplinary pediatric HSCT/cGVHD clinic at the Dana-Farber Cancer Institute (Boston, MA) from July 2001 through October 2003 were included in this study. This is a long-term follow-up clinic that focuses on patients with active issues, including but not limited to cGVHD. A standardized evaluation form designed by the authors specifically for this clinic was completed for every patient visit. A complete extraoral and intraoral clinical examination was performed for all patients, including subjective and objective assessments of mucosal, salivary gland, and sclerodermatous pathology. In addition, parents were permitted to assist by encouraging the child and/or helping him or her remember symptoms, and parental assessments were used as surrogates for children who were preverbal.

Oral mucosal cGVHD was classified as reticular (generally least symptomatic or asymptomatic), erythematous (generally more symptomatic), or ulcerative (generally most symptomatic), with lesions potentially described as having all 3 presentations. All ulcerative lesions were cultured for herpes simplex virus. Pain and discomfort associated with mucosal disease were assessed by using subjective questions. Assessment of salivary gland involvement was based on targeted questions and evaluation of saliva consistency, mucosal dryness, presence or absence of floor-of-mouth pooling, and the modified Schirmer test [13]. Sclerotic disease was assessed clinically and through subjective questions. Other oral lesions were documented primarily by clinical examination, although a histologic diagnosis was obtained when excision was indicated or the diagnosis was unclear. Select cases were photographed after receiving permission from the patients and their parents or guardians. When necessary, specific therapy for the management of oral lesions was initiated. Institutional review board approval was obtained for retrospective review of charts and the HSCT database of all of the patients included in this study.

Table 1. *Pre-HSCT Diagnoses of Patients Included in the Study (n = 49)*

Diagnosis	n
Acute lymphoblastic leukemia	9
Acute myelogenous leukemia	9
Aplastic anemia*	8
Congenital marrow failure syndrome	6
Myelodysplasia	6
Chronic myelogenous leukemia	3
Congenital immunodeficiency	3
Hemoglobinopathy	2
Non-Hodgkins lymphoma	2

*One of the patients with aplastic anemia was subsequently diagnosed as having dyskeratosis congenita and has been reported separately [15].

Table 2. *Conditioning and Acute GVHD Prophylaxis Regimens for Patients before HSCT*

Treatment	No. Patients
Conditioning regimen	
CY, TBI	28
CY, ATG, TBI	5
CY, BU	3
CY, BU, FL, PRD	2
CY, Ara-C	1
CY, ATG	1
CY, VP-16	1
CY, BU, FL	1
CY, topotecan, TBI	1
CY, Ara-C, TBI	1
CY, ATG, procarbazine	1
BU, ATG, melphalan	1
CY, Ara-C, VP-16, TBI	1
Acute GVHD prophylaxis	
CSA, MTX, PRD	25
CSA, MTX	15
CSA	2
MTX	2
Tacrolimus, PRD	1
MTX, PRD	1
CSA, leucovorin, MTX, PRD	1
CSA, tacrolimus, MTX, PRD	1

Several patients underwent more than 1 transplantation (included in the table) and there were incomplete data for 2 patients.

CY indicates cyclophosphamide; TBI, total body irradiation; VP-16, etoposide; ATG, antithymocyte globulin; BU, busulfan; FL, fludarabine; PRD, prednisone/methylprednisolone; Ara-C, cytosine arabinoside; CSA, cyclosporine; MTX, methotrexate.

RESULTS

General Findings

Forty-nine patients who had been treated with HSCT for a variety of conditions were examined from July 2001 through October 2003 (Tables 1 and 2). The age at the first visit, age at transplantation, sex distribution, time elapsed since transplantation, average number of medications (immunomodulatory drugs or drugs to treat symptoms related to cGVHD), presence of oral cGVHD, salivary gland involvement, and oral lesions requiring treatment are summarized

Table 3. *Descriptive Statistics for All Patients*

Variable	Data
No. patients	49 (male, n = 29; female, n = 20)
Patient visits	71
Median no. visits (range)	1 (1-4)
Age at first visit, median (range)	11 (2-22)
Age at transplantation, y, median (range)	8.5 (1-20)
Time since transplantation, y, median (range)	2 (0.3-9)
No. medications,* median (range)	3 (0-21)
Patients with oral mucosal cGVHD†	22/49 (45%)
Patients requiring specific treatment for oral mucosal cGVHD	10/22 (45%)
Patients with salivary gland hypofunction‡	2/49 (4%)
Patients requiring treatment of oral lesions§	22/49 (45%)

*Includes all medications (eg, topical, systemic, prescription, and nonprescription); calculated as the greatest number of medications at any visit if the patient was seen more than once.

†Oral mucosal cGVHD was considered present if lesions were identified at any visit if the patient was seen more than once.

‡Salivary gland involvement was not assessed by minor salivary gland biopsy or sialometry and may be affected by certain medications.

§This includes treatment of any oral lesions (eg, soft tissue hyperplasia), including but not limited to oral mucosal cGVHD.

in Table 3. There were 71 patient visits; most patients (67%) were evaluated only once (Figure 1). A history of skin, gastrointestinal, or liver cGVHD involvement was present in most patients (Table 4). Most patients (59%) were taking 1 or more of the following immunomodulatory medications: prednisone, cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus, hydroxychloroquine, azathioprine, or intravenous immunoglobulin. Only 9 patients were receiving prophylactic antifungal medications (fluconazole or nystatin), 5 patients were receiving prophylactic antiviral medications (acyclovir, valacyclovir, or famciclovir), and 27 patients were receiving prophylactic antibiotics (trimethoprim/sulfamethoxazole, amoxicillin, penicillin, or cephalexin).

Table 4. *History of cGVHD of the Skin, Liver, and Gastrointestinal Tract*

Organ Involved	No. Patients (n = 49)	%
Skin	32	65
Gastrointestinal tract	31	63
Liver	18	37
Other	9	18
None	7	14

Individual patients may have had multiple visits and variable involvement over time. Other was defined as involvement of other sites with cGVHD (eg, eyes, lungs, or joints).

Subjective Findings

Subjective data pertaining to mucosal disease, salivary gland function, presence of fibrosis, and changes in taste are detailed in Table 5. Whereas only 4 patients (8%) out of 49 reported mouth pain and all patients reported being able to eat well, 10 patients (20%) admitted to avoiding certain foods because they hurt their mouths. Spicy and acidic foods and drinks were commonly cited irritants. Five patients (10%) reported that their mouths were dry, although no patient complained of difficulty swallowing. Four patients reported that their mouth or tongue felt tight. Only 1 of these patients upon examination actually

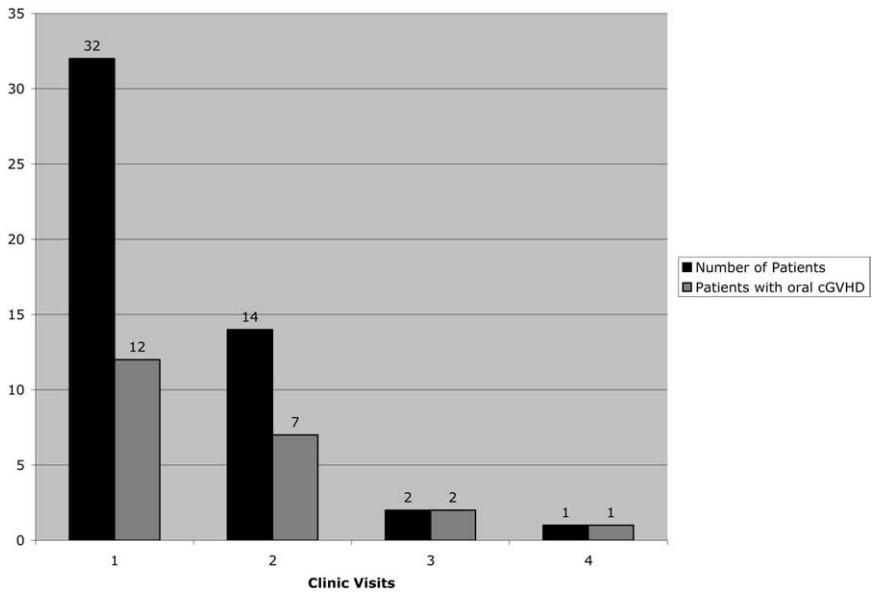

Figure 1. Number of visits (n = 71) and number of patients with oral cGVHD for the 49 patients.

Table 5. *Subjective Data*

Question	Percentage Responding "Yes"
Mucosal disease	
Does your mouth hurt?	13%
Do you avoid any foods because they make your mouth hurt?	23%
Sclerodermatous changes	
Does your mouth or tongue feel tight?	8%
Salivary gland involvement	
Does your mouth feel dry?	13%
Can you swallow food without difficulty?	100%
Taste	
Does food taste the same now as it did before transplantation?	90%

There were 5 instances in which the answers changed from one visit to the next in patients who were seen more than once. In most of these cases, the changes in subjective responses reflected changes in their objective findings as well. For those who responded "no" to the taste question, the changes in taste were not uniform and were often very specific to one or two foods.

had clinical signs of soft tissue fibrosis with limited mobility, as evidenced by obvious restricted mobility of the tongue and labial mucosa (Figure 2). Regarding changes in taste perception before and after transplantation, only 5 patients out of 49 reported that certain foods tasted different after HSCT. It is interesting to note that these sensory changes were not uniformly positive or negative, but rather were described overwhelmingly as "different" for various foods.

Objective Findings

Oral mucosal cGVHD was identified in 22 (45%) of 49 patients (Table 6). Most (42%) lesions were erythematous, followed by reticular (36%) and ulcerative (21%) forms. Eight of 22 patients (36% of patients with oral mucosal cGVHD) presented simultaneously with a combination of 2 or more forms of mucosal disease: reticular, erythematous, or ulcerative (Figure 3). Of the patients who were seen more than once (n = 17), 6 (35%) were found to have different forms of mucosal cGVHD at subsequent visits. This is indicative of the dynamic nature of this condition.

There were only 2 cases of putative salivary gland

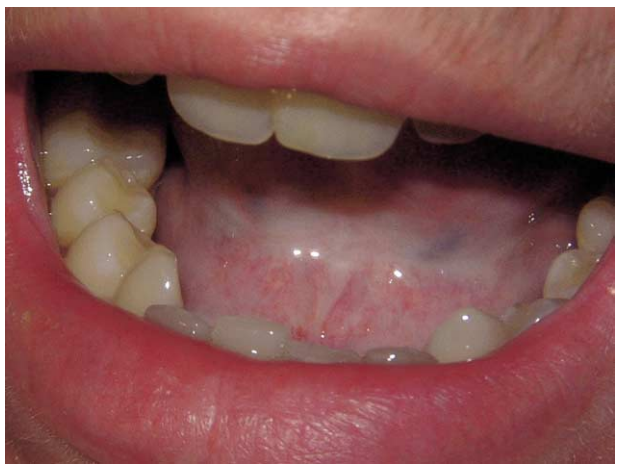

Figure 2. Soft tissue fibrosis of the tongue resulting in restricted mobility. The tissue appeared pale and was somewhat firm to palpation.

Table 6. *Oral Mucosal cGVHD Lesions*

Type	No. Patients Affected	%
Reticular	12	36
Erythematous	14	42
Ulcerative	7	21
Total	33	100

Patients could have more than 1 lesion per visit, and each lesion could have reticular, erythematous, and/or ulcerative components. For example, a patient who was seen twice, with reticulation of the right and left buccal mucosa and tongue dorsum with a single ulcer on the right lateral tongue, would be counted once for both reticular and ulcerative. Eight patients presented with 2 or more forms, 5 patients presented with different forms at different visits, and 1 patient first presented with no mucosal disease then subsequently developed reticulation.

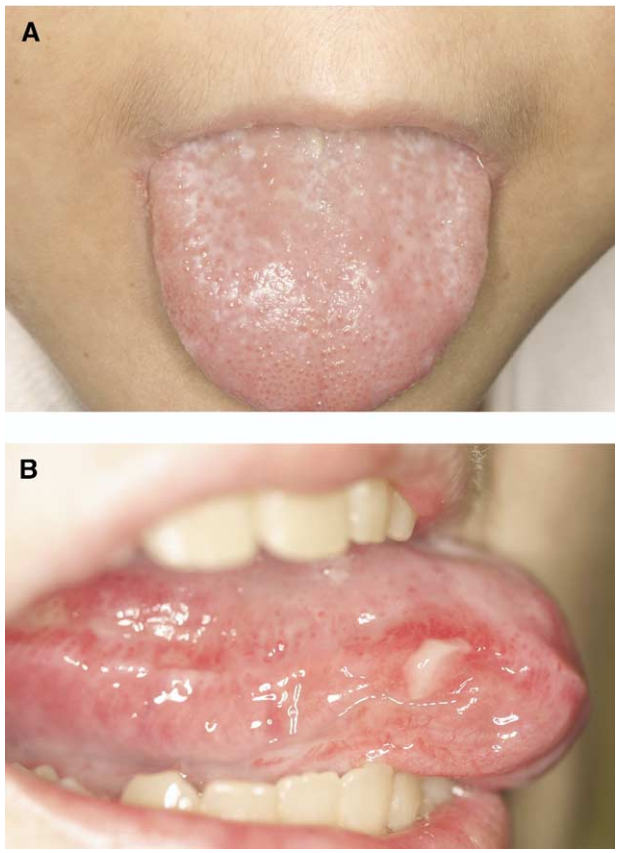

Figure 3. Oral mucosal cGVHD. A, Extensive reticulation of the tongue dorsum. B, In a different patient, a solitary ulcerative lesion of the right lateral tongue with associated erythema and reticulation extending posteriorly.

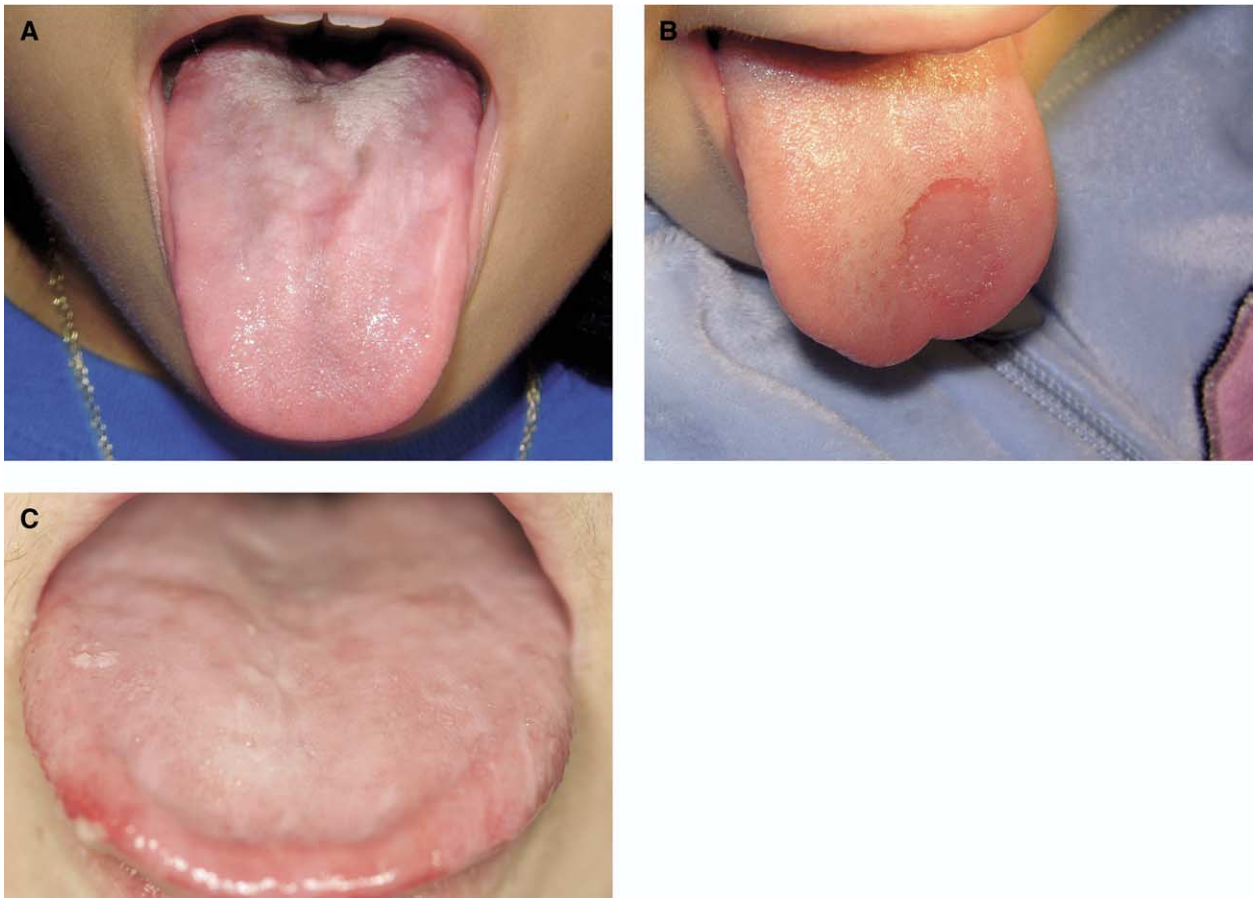

Figure 4. Atrophic glossitis in the setting of cGVHD. A, Smooth and depapillated tongue dorsum: unaffected areas appear completely normal. B, Distinct well-defined area of partially depapillated tongue dorsum. C, Generalized atrophy of the tongue dorsum with unaffected areas appearing as small islands of normal papillation. The border of an ulcerative lesion extending from the ventral aspect of the right tongue can be seen.

cGVHD. In the first case, the patient had both subjective complaints of oral dryness and objective findings of minimal salivary flow and dryness, as evidenced by an absence of floor-of-mouth pooling and generalized dry, atrophic, and pale mucosa. In the second case, there were no subjective complaints, but objectively there was minimal resting salivary flow and dryness, and there were rampant caries. The modified Schirmer test [13] was initially included as part of the salivary function assessment, but it was discontinued because of abundant salivary flow in nearly all patients ($\geq$15 mm at 1 minute in the first 10 patients evaluated; data not shown), as well as difficulties in performing the test accurately in very young children.

The most frequently encountered lesions other than mucosal (reticular, erythematous, and ulcerative) cGVHD were atrophic glossitis (Figure 4A, B, and C), gross caries, and soft tissue fibrosis presenting as either limited opening due to sclerosis (Figure 5) of the facial skin or limited mobility of soft tissue structures (Table 7). The patient with fibrosis and limitation in opening had undergone transplantation 2 years previously. No ulcerative lesions were culture positive for herpes simplex virus regardless of the presence or absence of prophylactic antiviral medications, and only 2 infectious lesions were identified. Both were presentations of pseudomembranous candidiasis (Figure 6), angular cheilitis, or both. One was in an indi-

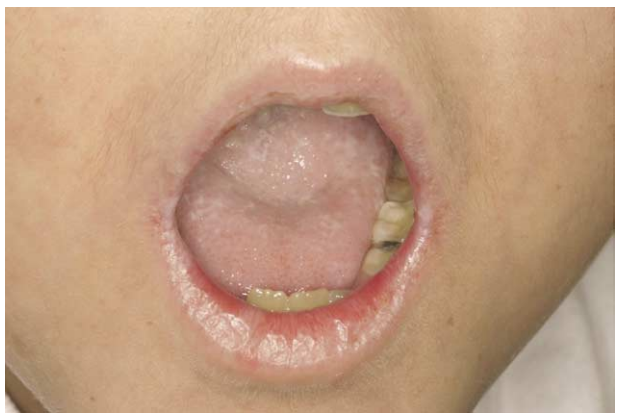

Figure 5. Sclerotic cGVHD of the lips and facial skin, mucosa, or both, resulting in marked limited opening of the mouth. This is the same patient seen in Figure 3A.

Table 7. *Other Oral Lesions Identified Clinically or Histologically*

Variable	n
Other primary lesions	
Atrophic glossitis	9
Sclerosis/band formation	3
Commissural plaques*	3
Postinflammatory hyperpigmentation†	2
Secondary lesions	
Candidiasis/angular cheilitis‡	2
Mucoceles (single or multiple)	2
Soft tissue hyperplasia§	2
Coated tongue	1
Verruciform xanthoma	1
Incidental lesions	
Gross caries	4
Papilloma/condyloma	2
Bite injury	2
Fibroma	1
Parulis	1

"Other primary lesions" were defined as being attributed directly to cGVHD; "secondary lesions," to treatment and immunosuppression; and "incidental lesions" were not considered to be associated with cGVHD, HSCT, or treatment.

*These white, plaquelike lesions resembled leukoplakias clinically. However, histopathologic evaluation of identically appearing lesions in adults was consistent with cGVHD (data not shown).

†Pigmented lesions in the location of a cGVHD mucosal lesion were assumed to be postinflammatory pigmentation.

‡One of these patients was taking nystatin, and neither was taking topical steroids intraorally.

§In one patient, soft tissue hyperplasia lesions of the buccal mucosa and tongue were removed surgically and completely recurred (Figure 8). In this case, this was counted only once.

vidual who was not taking nystatin, and one was in another who was, although nystatin compliance was difficult to ascertain.

Other lesions were noted in smaller numbers of patients. Mucoceles were noted in 2 individuals. One lesion was in the lower labial mucosa, and the other consisted of several superficial lesions on the palate

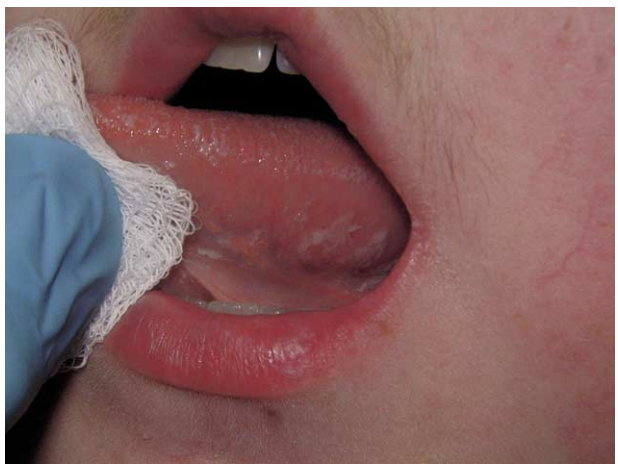

Figure 6. Pseudomembranous candidiasis of the left ventral tongue that easily wiped away with gauze, revealing an erythematous base.

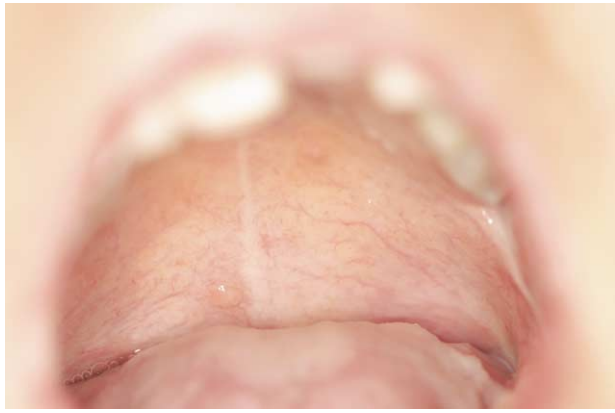

Figure 7. Superficial mucocele of the soft palate.

(Figure 7). A papillary tongue lesion in an 11-year-old African American girl appeared clinically to be a squamous papilloma, but it was diagnosed histopathologically as a verruciform xanthoma (Figure 8). In another case, extensive soft tissue hyperplasia of the buccal mucosa and lateral tongue bilaterally was noted and hypothesized to be associated with tacrolimus use [14]. It was surgically excised in the operating room under general anesthesia (Figure 9). After a rapid recurrence, the lesions were excised a second time 6 weeks after the first operation, and tacrolimus use was minimized. Since the second excision, the lesions have not recurred at nearly 2 years of follow-up. Another patient presented with a tongue leukoplakia that was diagnosed histopathologically as dysplasia; this patient, reported previously, initially underwent transplantation for aplastic anemia, but the ultimate diagnosis was dyskeratosis congenita [15].

Treatment

Any patient with gross caries was advised to see a dentist as soon as possible. Incisional biopsy was rec-

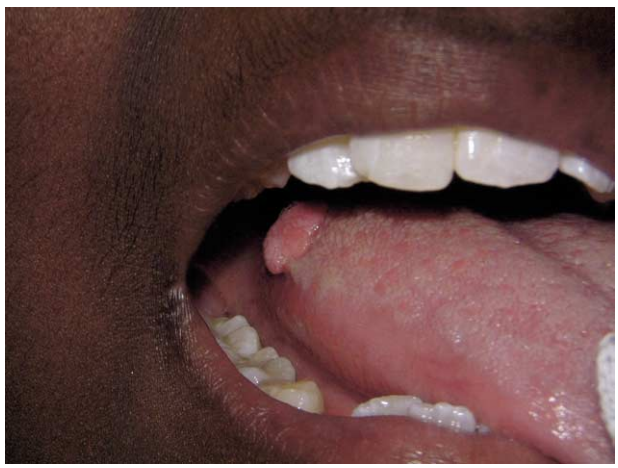

Figure 8. Exophytic papillary pink lesion of the right posterior lateral tongue that was histopathologically diagnosed as verruciform xanthoma.

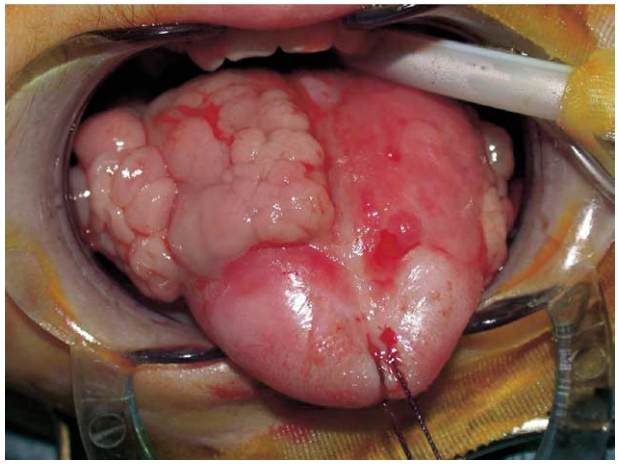

Figure 9. Extensive lobulated tissue hyperplasia of the tongue, putatively associated with use of tacrolimus. There was also an underlying atrophic glossitis.

ommended for all leukoplakias, and excisional biopsy was recommended for all soft tissue nodules or masses. Treatment of oral mucosal cGVHD was initiated with fluocinonide or clobetasol 0.05% gel, tacrolimus 0.1% ointment, dexamethasone elixir (0.5 mg/5 mL), and intralesional triamcinolone (40 mg/mL) injections used singly or in combination. All patients who required specific therapy for their oral mucosal cGVHD (45%) were already taking at least 1 immunomodulatory agent (except for 1 patient who was taking only trimethoprim/sulfamethoxazole). Response to therapy was difficult to assess because of inconsistent follow-up, different lengths of time between visits, and variations in doses of systemic immune suppression. Both cases of putative salivary gland cGVHD were treated conservatively with home fluoride applications and increased hydration. In the second case, the patient was also referred to an oral surgeon for extractions of nonrestorable carious teeth. Only 1 mucocele was recommended for excision because it had been present for several months and was located deep in the labial mucosa. The cases of candidiasis responded to either nystatin or fluconazole treatment.

DISCUSSION

Graft-versus-host disease (GVHD) is classified as either acute or chronic. Acute GVHD occurs within the first 100 days after allogeneic HSCT, and cGVHD occurs thereafter. The clinical manifestations of cGVHD are similar to those of a wide range of autoimmune diseases, such as Sjögren syndrome and systemic sclerosis [16,17]. Tissue damage seems to be mediated largely by activated donor T cells that recognize host antigens as foreign and attack target organs such as the skin, liver, and gastrointestinal tract [16]. Chronic GVHD is associated with significant immunodeficiency due to impaired T- and B-cell production and function that is further exacerbated by treatment with immunosuppressant medications [5,16]. In patients undergoing HSCT from matched related donors, the incidence of cGVHD (in those who survive HSCT) has been reported as 13% in patients younger than 10 years, 28% in patients 10 to 19 years, and >40% in patients older than 20 years [18]. The overall numbers after matched unrelated donor HSCT are significantly higher [19]. Risk factors for cGVHD in the pediatric population include diagnosis, donor and recipient age, female donor for male recipient, history of acute GVHD, and use of total body irradiation, although none is specific for oral involvement [20]. Overall, cGVHD is estimated to affect 50% of surviving adults and 20% of surviving children [12]. Approximately one half of affected patients have limited involvement. Of patients with more extensive disease, approximately 60% respond well to immunosuppressive therapy. However, the other 40% require prolonged immunosuppressive therapy and may die from opportunistic infections or advanced organ involvement [5].

In this study, we report the oral findings from 49 children who underwent HSCT for a variety of benign and malignant disorders and who were seen in a long-term follow-up clinic that specialized in evaluating patients with cGVHD. Accordingly, approximately 90% of patients had a history of any cGVHD. Almost 50% were found to have oral cGVHD. Despite systemic management of cGVHD, 10 patients required additional topical and/or intralesional treatment specifically directed toward their oral mucosal lesions (predominately erythematous and ulcerative forms).

To date, only 3 large-scale studies have described the oral findings in pediatric patients with cGVHD after HSCT (Table 8) [7-9,12]. Comparing our results with the findings of these studies is difficult because of differences in demographics, genetic disparities, conditioning regimens, cell sources, transplantation and GVHD prophylaxis protocols, study design, length of follow-up, and techniques, criteria, and terminology for evaluating oral involvement. In the prior reports, approximately 20% of patients were found to have oral cGVHD. In this study, 45% of subjects were affected. This is likely due to selection bias. We were more likely to see patients with more extensive disease because this follow-up clinic favored scheduling of patients with known or suspected HSCT-related complications. Our distribution of reticular, erythematous, and ulcerative lesions was more or less consistent with previous findings (to the extent that these classifications were used in prior reports), although we seemed to have a slightly higher proportion of ulcerative lesions. This classification of lesions is important because reticular lesions rarely require intervention,

Table 8. *Previous Reports of Pediatric Oral cGVHD in Large-scale Studies*

Study	No. of Patients	Patients with Oral cGVHD	% M/F	Age, y (range)	Time Since Transplantation	Method of Evaluation	Findings	Treatments
Berkowitz et al. (1987) [7]	41 (prospective study; patients observed before HSCT)	8/41 (20%)	63% M 37% F	9.3 (7 mo to 7 y)	Not specified	Mucosal disease assessed by clinical and histologic examination Salivary gland hypofunction assessed clinically	Lichenoid: 1/8 Erythema: 7/8 Xerostomia: 4/8 Hyposalivation resolved in 2/4 patients within 6 mo and persisted in 2/4 for 1 y; however, none developed caries	Anesthetic mouth rinse, systemic steroids, saliva substitutes, topical fluoride
Dahllof et al. (1988, 1989) [8, 9]	54 (prospective study; all patients observed before HSCT)	9/45 (20%) patients observed for >6 mo. Three patients died within the first year; 6 were long-term survivors	57% M 43% F	7 (1-12)	6 mo to 7 y (median, 3.9 y)	Mucosal disease assessed by clinical and histologic examination Salivary gland hypofunction assessed by sialometry	Skin and oral involvement in all cases Of the 6 long-term survivors: Up to 1 y after HSCT: Erythema: 3/6 Erosive lichenoid: 2/6 Atrophic lichenoid: 1/6 Beyond 1 y after HSCT: Atrophic lichenoid: 5/6 Erythema: 1/6 Average salivary flow rate 1 y after HSCT was 0.7 mL/min. Average salivary flow rate after the first year was 1.1 mL/min	Sugar-free chewing gum, fluoride varnish, treatment of mucosal disease not specified
Nicolatou-Galitis et al. (2001) [12]	90 patients were screened for evidence of cGVHD; 11 were included in the study	8/11 (73%) or 8/90 (9%)	73% M 27% F	10.7 (1.5-15)	172 d (range, 81-360)	Mucosal disease assessed by clinical and histologic examination Salivary gland hypofunction assessed clinically	Lichenoid: 4/8 Ulcerative: 2/8 Hyposalivation: 7/8 Mucoceles: 3/8	Systemic and topical steroids, cyclosporin A

whereas erythematous and ulcerative lesions typically demand aggressive therapy.

The prevalence of sclerotic oral cGVHD (clinically) seemed very low. This is consistent with the findings of others that sclerotic cGVHD is rare and tends to occur as a late event [21]. The apparent lack of salivary gland involvement—only 5 patients complained of xerostomia (subjective oral dryness), and only 2 (4%) patients had any clinical evidence of hyposalivation (by visual assessment)—was notable, especially because this was a designated cGVHD clinic. Nicolatou-Galitis et al. [12] reported 7 of 8 patients with cGVHD (in part diagnosed by minor salivary gland biopsy) and clinically obvious xerostomia; this is a much higher percentage than observed in our study. However, there was no description of how xerostomia or hyposalivation was assessed in the aforementioned study, so it is unclear to what extent our findings are significantly different. Our findings also seem to be in contrast to those in the adult population with cGVHD, in which salivary gland involvement is reported to be much more prevalent, with approximately 60% developing xerostomia, 40% to 90% demonstrating hyposecretion, and 0% to 50% showing clinical signs of dryness [6,22,23]; this differential involvement in the 2 populations warrants further investigation. Furthermore, improved understanding of the relationship between objective and subjective measures of salivary gland involvement, especially with respect to age, is critical in this patient population.

Mucoceles were reported infrequently by Nicolatou-Galitis et al. [12], and we similarly found only 2 patients with mucoceles. Mucoceles in these patients may be attributable to low-level cGVHD of the salivary gland acini and ducts (causing increased viscosity, decreased flow, and weakening and/or leakiness of the ductal epithelium) or to local extension and involvement of mucosal cGVHD into underlying salivary ducts [24,25]. We did not observe clinically evident salivary gland or local (ie, in the area of the mucocele) oral mucosal cGVHD in our 2 patients; however, the 3 superficial mucoceles observed by Nicolatou-Galitis et al. were seen in the setting of mild to heavy salivary gland cGVHD (histologically) in 2 patients and prominent lichenoid mucosal lesions in the other.

Diagnosis of oral symptoms and findings in this pediatric patient population is frequently a more complex undertaking than in adults, because procedures such as biopsies (and, in some cases, even clinical examination) present unique challenges. For example, it is not entirely possible to rule out candidiasis in the differential diagnosis of erythematous cGVHD lesions clinically (although they can be easily cultured if candidiasis is suspected). However, no cases of assumed erythematous cGVHD worsened with topical steroid treatment (in most cases, this follow-up was assessed by the transplant specialists and not the oral medicine specialists), thus suggesting that treatment on the basis of clinical findings alone is reasonable in this population. The young age of the patient population also influenced the subjective assessment of xerostomia because it was not clear whether all patients truly understood what the question ("Does your mouth feel dry?") meant. However, the failure of patients (or their parental surrogates) to report difficulty with eating and swallowing food (which is a more common complaint in the adult population [6]) supports the inference that the prevalence of putative salivary gland hypofunction was very low in this population. Furthermore, it is possible that some positive responses to the targeted subjective questions regarding oral tightness reflected the sensation of facial fullness related to long-term prednisone treatment rather than actual tissue fibrosis. It is not yet clear what the most reliable evaluation should consist of for the youngest patients.

Oral evaluations contributed to the establishment of systemic diagnoses [15] and also resulted in recognition of novel pathologies other than oral cGVHD. The diagnosis for the patient with dyskeratosis congenita was in part based on the oral findings of leukoplakia rather than cGVHD and tongue biopsy. Although a single case of verruciform xanthoma has been reported in the young adult cGVHD population [26], it is exceedingly rare in children and has never been reported in the pediatric cGVHD population. The precise etiology of the soft tissue hyperplasia in the patient taking tacrolimus is unclear [27]. However, similar lesions have been reported to occur in patients taking cyclosporine (another calcineurin inhibitor). Our case suggests that this complication may be seen with other members of this class of drug and thereby suggests that the shared mechanism of action may be related to the development of these lesions. A relationship to the drug is suggested by the nearly complete recurrence after the first excision, followed by resolution when the drug dose was minimized after the second excision.

Thus, careful oral examination is likely to make significant contributions to understanding and managing the increasing number of children who survive HSCT. Oral mucosal pathology is common in these patients, and appropriate diagnosis and management of oral lesions is critical to reduce patient morbidity and to improve quality of life. Although efficacy could not be determined with certainty, patients seemed to benefit from treatment regimens; however, future studies are needed to establish optimal approaches. Age-related issues such as the ease and acceptability of biopsy and the reliability and availability of self-assessment of subjective symptoms need to be considered in the development of evaluation and treatment strategies. This cross-sectional analysis suggests that cGVHD findings are similar to those seen in adults,

although hyposalivation is not a common complication in these younger patients. The absence of severe ulcerative oral mucosal cGVHD and, apparently, a very low prevalence of oral pain (both of which are often seen in the adult population) further emphasize the importance of describing and investigating the apparent age-related differences in the presentation of oral cGVHD.

Identifying treatment strategies for this condition will be an invaluable advance in the effective management of these patients. Development of validated age-appropriate evaluation strategies is critical. In addition, the study suggests that active participation of oral medicine practitioners in the long-term follow-up of these patients is likely to significantly affect not only the proper management of oral cGVHD, but also the establishment of other diagnoses and treatment strategies. For example, the observation of impaired dental growth and development that seems to be due to effects from HSCT conditioning regimens may have major significance for ongoing management of oral health, including restorative and orthodontic treatments [11]. Establishment of additional long-term follow-up data is paramount to guide clinicians in the treatment of pediatric oral cGVHD and to minimize comorbidities such as infection, impaired dental growth, and development of secondary oral malignancies, which these patients may be at especially high risk for developing [28,29].

ACKNOWLEDGMENTS

We gratefully acknowledge the support of the Frank J. Hanna Jr Research Fund and National Institutes of Health/National Institute of Dental and Craniofacial Research grant no. K16 DE00275.

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