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Characterization of Oral Involvement in Acute Graft-versus-Host Disease



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ABSTRACT

Acute graft-versus-host-disease (aGVHD) is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT). The purpose of this study was to characterize the oral features associated with aGVHD in patients who underwent HSCT between 1995 and 2010 and developed prominent oral aGVHD. Data was collected from patient medical records and analyzed descriptively. Twenty-one cases were identified, of which 5 (24%) demonstrated only oral features; the remaining 16 had variable involvement of skin ($n = 14$), liver ($n = 7$), and gut ($n = 5$). The median time to onset of any sign of aGVHD was 22 days (range, 8 to 154 days), and that for onset of oral aGVHD was 35 days (range, 11 to 159 days). Sites affected by nonspecific erythema and ulcerations included buccal mucosa (19 of 21; 90%) tongue (18 of 21; 86%; dorsum in 8), labial mucosa (16 of 21; 76%), palatal mucosa (15 of 21; 71%; hard palate in 7), and floor of mouth (7 of 21; 33%). Eight cases (38%) presented with lip ulceration and crusting. In addition to systemic therapies, topical solutions of dexamethasone, tacrolimus, and morphine were used for ancillary support. Oral features of aGVHD may be the initial manifestation and include nonspecific erythema and ulcerations of keratinized and non-keratinized mucosa and lips. Intensive topical therapies may help reduce symptoms and promote healing.

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INTRODUCTION

Acute graft-versus-host disease (aGVHD) is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT) that develops when transplanted donor T cells mount an alloimmune response against recipient (host) tissues, resulting in tissue damage, morbidity, and, in severe cases, death [1]. Based on the National Institutes of Health consensus criteria, aGVHD is defined as either classical aGVHD, occurring within 100 days after transplantation, or persistent, recurrent, or late aGVHD, typically occurring beyond day +100 during withdrawal of immune suppression and associated with poorer outcomes [2]. The incidence, timing, and severity of aGVHD are influenced by several clinical factors, including donor–recipient HLA matching, stem cell source, number of T cells in the donor graft,

conditioning regimen intensity, and GVHD prophylaxis regimen [3,4]. Despite prophylaxis, aGVHD develops in up to 30% to 50% of allogeneic HSCTs [4,5].

Oral features developing in the context of aGVHD have been reported infrequently [6–13]. This is in stark contrast to conditioning regimen–associated oral mucositis and oral chronic GVHD (cGVHD), both of which are commonly encountered in the context of allogeneic HSCT and have been extensively characterized in the literature [12,14,15]. Clinical characteristics of the oral features attributed to aGVHD have been reported as generalized mucosal erythema and pseudo-membranous ulcerations, but also with features more suggestive of cGVHD, such as lichenoid hyperkeratotic striations [1,11,16]. The objective of the present study was to characterize a cohort of patients with oral features associated with aGVHD with respect to clinical findings, management, and outcomes.

METHODS

A retrospective medical records review was conducted of patients who underwent allogeneic HSCT at Dana-Farber/Brigham and Women's Cancer Center between 1995 and 2010 and were subsequently diagnosed with oral

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Table 1
Diagnostic Criteria for Oral aGVHD

Clinical Feature	Description
Oral mucosa	Nonspecific erythema and ulcerations that can affect nonkeratinized and keratinized oral mucosa as well as the lip vermillion
Systemic aGVHD	Oral lesions typically developing in association with classical aGVHD features (eg, skin, liver, gut)
Mucositis	Complete resolution of oral ulcerations secondary to conditioning regimen, if present, before onset of oral aGVHD lesions
HSV	Viral culture negative, ongoing acyclovir prophylaxis
Engraftment	Two consecutive days with ANC >500

aGVHD. All patients were evaluated by the Oral Medicine and Dentistry consultation service at Dana-Farber/Brigham and Women's Cancer Center. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. Owing to the study's retrospective nature, patient consent was not obtained.

Transplantation-related data collected included primary diagnosis for HSCT, donor information (including age and sex), graft source, conditioning regimen, GVHD prophylaxis regimen, and mucositis history. With respect to GVHD, data collected included day of onset of aGVHD, day of onset of oral lesions, target organ involvement, highest aGVHD grade, systemic immunosuppressive therapy, oral ancillary therapy, subsequent development of oral cGVHD, and survival at day +100 post-transplantation.

aGVHD was graded clinically according to consensus or the International Bone Marrow Transplant Registry (IBMTR) Severity Index Systems scale [17,18]. Each target organ was staged from 0 to 4, and an overall aGVHD grade of 0 to IV was determined. Patients with aGVHD limited to the oral cavity were considered grade 0, because the consensus and IBMTR scales do not recognize the oral cavity as a target organ. aGVHD was further classified according to the National Institutes of Health criteria [2].

Oral aGVHD was defined as the onset of oral mucosal erythema and ulcerations in the context of engraftment (defined as 2 consecutive days with an absolute neutrophil count [ANC] >500) and aGVHD involvement of classical target organs (Table 1). Biopsy analysis of the involved oral mucosa was not performed in all cases, typically when the diagnosis of aGVHD was not already established. All patients were started on standard acyclovir prophylaxis on admission for HSCT, and viral cultures were obtained from all patients at the time of onset of oral aGVHD lesions. In patients who had developed conditioning regimen-associated oral mucositis during HSCT, all ulcerations were required to be completely resolved before the onset of oral aGVHD lesions. Clinical intraoral photographs were reviewed to confirm objective findings collected from the medical records.

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). Progression-free survival was defined as the time from the date of HSCT until the date of disease relapse, progression, or death and was censored at the time of last contact. Overall survival was defined as the time from the date of HSCT until the date of death and was censored at the time of last contact.

RESULTS

Patient Characteristics

Among the 2578 recipients of allogeneic HSCT during the 15-year study period, 21 developed oral aGVHD (Table 2). The median age of these 21 patients was 49 years (range, 21 to 65 years), and two-thirds were male. Approximately one-third of the patients received a reduced-intensity conditioning regimen, and the majority received methotrexate and a calcineurin inhibitor for GVHD prophylaxis. The median time from HSCT to diagnosis of aGVHD (based on any diagnostic feature) was 22 days (range, 8 to 154 days), with 95% of recipients presenting with typical clinical features within the first 100 days.

Classical features of aGVHD were observed in the majority of patients, including skin (n = 14), liver (n = 7), and gastrointestinal (n = 5) involvement, with the majority (14 of 21; 67%) classified as grade III-IV. Five patients (24%) presented with oral features only and thus were

Table 2
Characteristics of the 21 Patients with Oral aGVHD

Characteristic	Value
Median age (range)	49 (21-65)
Male sex, n (%)	14 (67)
Disease, n (%)	
Acute myelogenous leukemia	7 (33)
Acute lymphoblastic leukemia	4 (19)
Chronic myelogenous leukemia	4 (19)
Myelodysplastic syndrome	3 (14)
Myeloproliferative disorder	2 (10)
Multiple myeloma	1 (5)
Donor type, n (%)	
Matched related donor	11 (52)
Matched unrelated donor	9 (43)
Mismatched unrelated donor	1 (5)
Conditioning regimen intensity, n (%)	
Myeloablative	15 (71)
Reduced intensity	6 (29)
Graft source, n (%)	
Peripheral blood stem cells	14 (67)
Bone marrow	7 (33)
GVHD prophylaxis, n (%)	
Tacrolimus/methotrexate	6 (33)
Methotrexate/cyclosporine A	6 (33)
Sirolimus/tacrolimus/methotrexate	2 (12)
Sirolimus/mycophenolate mofetil	1 (6)
Sirolimus/tacrolimus	1 (6)
Bortezomib/tacrolimus/methotrexate	1 (6)
T cell depleted	1 (6)
Not available	3 (14)
Days to ANC >500, median (range)	14 (11-50)

considered to have grade 0 aGVHD. Of the patients presenting with multisystem involvement, in 3 cases the initial site was the oral cavity (followed in each case by skin). Except for these 3 patients, and the 5 patients with oral features only, all other patients developed oral features after being diagnosed with aGVHD and started on systemic corticosteroid therapy (see below). Oral mucositis preceded the onset of aGVHD in approximately one-half of the patients (11 of 21; 52%), with complete resolution of oral ulcerations in all cases before the onset of aGVHD. All patients received acyclovir prophylaxis, and all viral cultures for herpes simplex virus (HSV) were negative (data not shown). No patient had any other identified infection (eg, cytomegalovirus reactivation, oropharyngeal candidiasis).

Oral aGVHD Features

The median time from HSCT to diagnosis of oral aGVHD was 35 days (range, 11 to 159 days). Oral lesions were generally characterized as extensive, irregular nonspecific erythema and ulcerations of the keratinized and nonkeratinized mucosa (Figure 1). Lichenoid striations typical of cGVHD were not observed. Taking all cases into consideration, the buccal mucosa, tongue (ventrolateral and dorsum), labial mucosa, and hard and soft palates were variably affected; no gingival involvement was noted (Table 3). Eight patients presented with prominent lip ulceration with crusting that typically extended beyond the vermillion border (Figure 2). Except for 1 patient who experienced xerostomia and severe salivary gland hypofunction, xerostomia was not reported by any other patient. One patient developed asymptomatic palatal superficial mucoceles.

Oral mucosal biopsy specimens were obtained in 4 patients. Three of these biopsy specimens showed mucosal

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