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Oral Manifestations Compatible with Chronic Graft-versus-Host Disease in Patients with Fanconi Anemia

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A B S T R A C T

Fanconi anemia (FA) is a genetic disease that is characterized by several congenital abnormalities and progressive bone marrow failure and is associated with an increased susceptibility to malignant disorders. Currently, the only potential cure for hematological disorders is hematopoietic stem cell transplantation (HSCT). However, 1 of the most common complications after HSCT is the development of oral chronic graft-versus-host disease (cGVHD), which is also a risk factor for the development of cancer, particularly oral squamous cell carcinoma. Therefore, the purpose of this study was to describe the prevalence and characteristics of oral manifestations compatible with cGVHD in patients diagnosed with FA according to the National Institutes of Health (NIH) consensus criteria. A total of 96 patients (51 females, 45 males; median age, 16 years) with FA, who were in medical follow-up after HSCT at the outpatient clinic of the bone marrow transplantation unit (Hospital de Clínicas from the Universidade Federal do Paraná) underwent an oral evaluation between January 2013 and December 2013. Post-HSCT periods varied from 1 to 261 months and were divided into 3 periods: immediate post-HSCT period; intermediate post-HSC period, and late post-HSCT period. Among the evaluated patients, 40 of 96 (42%) presented with oral manifestations of cGVHD, with 29 of 40 (73%) of these patients in the late post-HSCT period. NIH scale scores varied from 0 to 10, and lichenoid and hyperkeratotic lesions were the abnormalities most frequently observed (100%). Overall, a high prevalence of oral manifestations was observed for cGVHD patients with FA. These data highlight the importance of monitoring oral manifestations compatible with cGVHD to identify and treat individuals with a higher risk of developing oral cancer.

INTRODUCTION

Fanconi anemia (FA) is a rare genetic disease that is related to chromosomal instability and the defective repair of DNA damage [1,2]. FA is also characterized by congenital malformations, progressive bone marrow failure, and a 700-fold increase in the risk for head and neck squamous cell carcinoma (SCC) [1-3].

Currently, hematopoietic stem cell transplantation (HSCT) is the only potential cure for hematologic disorders related to FA [3,4]. However, after this procedure, patients have an additional 4-fold higher risk for head and neck SCC [5]. Moreover, patients subjected to HSCT are susceptible to chronic graft-versus-host disease (cGVHD), which is a common alloimmune and autoimmune complication [6]. Individuals with cGVHD can present with hyperkeratotic and lichenoid lesions in the mouth, erythema, ulcers, atrophy, and pain [7]. Patients with cGVHD also have an increased risk of developing malignancies [8-10].

Therefore, the purpose of this study was to evaluate the prevalence of oral manifestations of cGVHD in FA patients who underwent allogeneic HSCT, according to the National Institutes of Health (NIH) consensus criteria [7], and to describe the characteristics and distribution of these manifestations in the mouth.

MATERIALS AND METHODS

This cross-sectional study was performed between January 2013 and December 2013. Patients, regardless of age, with a confirmed FA diagnosis (positive diepoxy-butane test), who were subjected to allogeneic HSCT and underwent follow-up at the outpatient clinic of the bone marrow transplantation unit of the Hospital de Clínicas (Universidade Federal do Paraná) were evaluated. Patients' gender and age, time since HSCT, donor's

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Table 1
Demographic Data and Information Related to HSCT and Post-HSCT Periods for Patients with FA

Characteristic	Patients with Oral Manifestations of cGVHD	Patients without Oral Manifestations of cGVHD	Total
No. of patients	40 (42%)	56 (58%)	96 (100%)
Age, median (range), yr*	18 (5-32)	13 (6-42)	16 (5-42)
Gender			
Male	22 (55%)	23 (41%)	45 (47%)
Female	18 (45%)	33 (59%)	51 (53%)
Conditioning regimen			
Cyclophosphamide	20 (50%)	24 (43%)	44 (46%)
Combination chemotherapy	14 (35%)	28 (50%)	42 (44%)
Chemotherapy + total body irradiation	6 (15%)	4 (7%)	10 (10%)
Stem cell source and donor			
Related bone marrow	19 (48%)	24 (43%)	43 (45%)
Unrelated bone marrow	11 (28%)	16 (29%)	27 (28%)
Related cord blood	0 (0%)	1 (2%)	1 (1%)
Unrelated cord blood	3 (7%)	7 (12%)	10 (10%)
Unrelated peripheral blood	1 (2%)	0 (0%)	1 (1%)
Haploidentical	6 (15%)	8 (14%)	14 (15%)
Donor age, median (range), yr	19 (0-60)	13.5 (0-64)	17 (0-64)
Donor gender × patient gender			
Male × male	10 (25%)	17 (30%)	27 (28%)
Male × female	11 (28%)	12 (21%)	23 (24%)
Female × female	12 (30%)	16 (29%)	28 (29%)
Female × male	7 (17%)	11 (20%)	18 (19%)
Time after HSCT, median (range), mo	103 (3-211)	41.5 (1-261)	62.5 (1-261)
Post-HSCT period*			
Immediate (within 12 mo after HSCT)	3 (7%)	16 (29%)	19 (20%)
Intermediate (13-47 mo after HSCT)	8 (20%)	14 (25%)	22 (23%)
Late (>48 mo after HSCT)	29 (73%)	26 (46%)	55 (57%)
History of aGVHD†	10 (25%)	10 (18%)	20 (21%)
History of cGVHD*,†,‡	27 (68%)	15 (27%)	42 (44%)

aGVHD indicates acute graft-versus-host disease.
* $P < .05$.
† Data collected from medical records.
‡ cGVHD in different organs, besides the mouth.

characteristics, stem cell source, history of acute GVHD, and current medications were collected from each patient's medical records. Oral examinations were performed in the dental unit under reflective light by a dentist with experience applying the NIH scale (intrarater intraclass correlation coefficient, .969; inter-rater intraclass correlation coefficient, .934). Oral mucosa was dried with gauze and then observed for any alterations. Oral manifestations of cGVHD were scored based on diagnostics and distinctive signs according to the oral cGVHD activity assessment criteria published by the NIH [7]. The type and distribution of the lesions compatible with cGVHD were also assessed and registered in a clinical record specifically developed for this study.

Patients were excluded if they had undergone more than 1 HSCT, if the oral examination was prevented because of discomfort caused by oral cancer, or if their medical data were incomplete.

There is no standard criteria used to distinguish patients according to the time after transplantation. Based on the outpatient care standards adopted at this center and on the major complications observed after transplantation, periods in the present study were separated into 3 categories: (1) immediate post-HSCT period (up to 12 months after transplantation), the stage in which many individuals are stabilizing their immunity and blood cell count and are under immunosuppressive therapy; (2) intermediate post-HSCT period (13 to 47 months after transplantation), the stage in which most of the complications were either detected or resolved, as cGVHD often occurs in the first 3 years after the transplantation; and (3) late post-HSCT (>47 months after transplantation) period, in which patients commonly do not use any medication, and when they are usually released to their home town and came less frequently to the clinical evaluations.

Descriptive and analytic statistical analyses were performed. The chi-squared test, Fisher's exact test, and the linear trend chi-squared test were used to evaluate the association between the presence of oral manifestations of cGVHD, demographic data, and variables related to HSCT. It was considered a statistical significant association whenever $P \leq .05$. This study was approved by the ethics committee in research of the Universidade Federal do Paraná and each patient, or his/her guardian, signed an informed consent form.

RESULTS

A total of 103 individuals with FA who underwent allogeneic HSCT were evaluated. Seven patients were excluded based on the criteria described in the Materials and Methods, including 2 individuals with oral cancer. The final cohort included 96 patients (51 [53%] females and 45 [47%] males) with a median age of 16 years. Demographic data, HSCT characteristics, and GVHD data for this cohort are listed in Table 1.

Approximately 25% of the patients evaluated were receiving immunomodulatory prophylaxis or treatment for GVHD. In most cases, systemic medication was administered exclusively, and this included cyclosporine, mycophenolate mofetil, sirolimus, and prednisone alone or in combination. Five (5%) patients were applying a topical corticosteroid rinse to their oral mucosa. However, only 1 of these patients was using the topical medication exclusively.

Based on the NIH consensus criteria, 40 patients (42%) presented with oral manifestations compatible with cGVHD. Moreover, most of them presented these manifestations during the late post-HSCT period (n = 29; 73%).

According to the medical record data collected, 25% of the individuals with oral manifestations of cGVHD had previously presented with acute GVHD, and 68% had a history of cGVHD that affected several organs besides the mouth. In addition, patient age, post-HSCT period, and history of manifestations of cGVHD in other organs were found to have statistically significant associations with the presence of oral alterations compatible with cGVHD, according to the NIH consensus ($P < .001$, $P = .007$, and $P = .010$, respectively).

All patients with oral manifestations of cGVHD were classified according to the diagnostic signs exhibited, including hyperkeratotic plaques and lichenoid lesions. White plaques were observed in 95% (n = 38) of the patients with oral lesions of cGVHD. Lichenoid manifestations, atrophy, erythema, and ulcers were also identified. However, the