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Genital Chronic Graft-versus-Host Disease in Females: A Cross-Sectional Study

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A B S T R A C T

Using the National Institutes of Health (NIH) consensus criteria for chronic graft-versus-host disease (cGVHD), we assessed the prevalence, symptoms, and clinical signs of female genital cGVHD in a cross-sectional population-based study. Forty-two women were evaluated at a median of 80 months (range, 13 to 148 months) after undergoing hematopoietic stem cell transplantation (HSCT). Medical history, ongoing medications, and genital signs and symptoms were recorded. Gynecologic examination for the diagnosis and clinical scoring of genital cGVHD was combined with clinical scoring of extragenital cGVHD for the estimation of each patient's global cGVHD score. Biopsy specimens from the genital mucosa were obtained from 38 patients. Genital cGVHD was diagnosed in 22 of 42 patients (52%). Its presence was associated with systemic corticoid steroid treatment of extragenital cGVHD ($P = .001$), older age ($P = .07$), and HSCT from a sibling donor ($P = .002$). Five patients had isolated genital cGVHD. Dryness, pain, smarting pain ($P < .05$ for all), and dyspareunia ($P = .001$) were observed more frequently in the women with genital cGVHD. Twelve patients had advanced genital cGVHD (clinical score 3), which was the main factor explaining the high rate (15 of 42) of severe global cGVHD. The rate of genital cGVHD was similar ($P = .37$) in patients with a follow-up of ≥80 months (10 of 22) and those with a follow-up of <80 months (12 of 20). We found no convincing relationship between clinical diagnosis and histopathological assessment of mucosal biopsy specimens. In our group of women with a long follow-up after HSCT, genital cGVHD was common and in many cases incorrectly diagnosed. Genital cGVHD causes genital symptoms and affects sexual life, and may present without any other cGVHD, warranting early and continuous gynecologic surveillance in all women after HSCT.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is the major cause of late morbidity and nonrelapse mortality after allogeneic hematopoietic stem cell transplantation (HSCT) [1]. The pathophysiology of cGVHD is largely unknown, but typical symptoms include inflammation and fibrosis in oral, ocular, and genital mucosal membranes. Chronic GVHD is associated with diminished quality of life [2], and immunosuppressive therapy, mainly corticosteroids, increases the risk of opportunistic infections. Compared with bone marrow, the use of peripheral blood stem cells for HSCT is associated with an increased incidence and severity of cGVHD [3,4], and the incidence of symptomatic cGVHD requiring medication is 40% to 70% [5].

The National Institutes of Health (NIH) Consensus Development Program proposed criteria for the diagnosis and severity of signs and symptoms of organ-specific cGVHD, including an algorithm for calculation of global severity (mild, moderate, or severe) [6]. This classification scheme has been applied in several previous studies [2,7,8].

It is well recognized that cGVHD can affect the genitals, and that female genital cGVHD is associated with sexual dysfunction and genital symptoms, including dryness, ulcerations, and vaginal stenosis [9-13]. The estimated incidence of female genital cGVHD varies owing to different diagnostic criteria and/or selection criteria for inclusion of patients into the different studies. As recently noted by Hirsch et al. [13], there are reasons to assume that genital cGVHD is an underdiagnosed and overlooked aspect of cGVHD.

To assess the prevalence, symptomatology, and clinical features of genital cGVHD, we performed a cross-sectional study in a consecutive population-based cohort of women in the western region of Sweden with a median follow-up of 80 months after HSCT. To elucidate a relationship between clinical findings and histopathological diagnosis, biopsy

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specimens from clinically cGVHD-affected and -nonaffected areas were obtained from the vagina and/or vulva in the majority of patients.

PATIENTS AND METHODS

Patients

A total of 86 women underwent HSCT between 1996 and November 2005 in the western region of Sweden, which has approximately 1.5 million inhabitants. Fifty surviving female patients in complete remission were identified. Of these 50 women, 3 were not invited to participate owing to mental disability, 2 declined to participate, and 3 could not be treated with local estrogen and thus were excluded. In all, 42 women gave written informed consent at enrollment. The study was approved by the Regional Ethical Review Board of Gothenburg.

Before study enrollment, most of the patients had been in regular or sporadic contact with a gynecologist. Ten patients had been diagnosed with cGVHD before study entry. Six patients had undergone surgery for vaginal stenosis before study entry; 3 of these patients did not receive adequate treatment for cGVHD and subsequently relapsed. All 42 patients were in menopause (11 natural and 31 premature after HSCT).

Methods

All patients underwent HSCT and were followed as outpatients at the Section of Hematology, Sahlgrenska University Hospital, Göteborg, Sweden. Table 1 summarizes background factors and HSCT procedures. All patients with an unrelated donor received antithymocyte globulin as part of the conditioning regimen. For this study, patients were also seen at the Department of Gynecology, NU Hospital Group, Trollhättan, Sweden by 1 or 2 gynecologists (E.S.K. and/or A.-K.B.). Before the first visit, each patient completed a comprehensive questionnaire on general medical history, ongoing medication, and symptoms suggestive of any genital malfunction. The questionnaire was adapted from a document produced by the Vulva Group of the Swedish Society of Obstetrics and Gynecology for females with vulvovaginal problems. All patients were seen at least twice.

To ensure that estrogen deficiency was not be mistaken for genital cGVHD, all women with atrophic genital mucosa (n = 26) at their first visit were prescribed local estrogen treatment for at least 6 weeks before the second visit. In these women, final diagnosis and scoring of clinical signs and symptoms were done at the second visit. Supplemental local estrogen therapy given at the first visit to women with signs of hormone deficiency did not affect diagnostic and distinctive signs of genital cGVHD.

Gynecologic examination with detailed structured documentation of vulvovaginal signs was performed in all women. Photographic documentation of the vulva was obtained at most visits, and information on ongoing local or systemic immunosuppressive treatment was recorded.

Clinical Diagnosis of Genital cGVHD

For the diagnosis of genital cGVHD, the NIH consensus criteria were applied based solely on genital signs. Vaginal synechia or scarring, partial or total stenosis, and marked lichen planus–like features, such as reticular white lines in the genital mucosa, were considered diagnostic of cGVHD. Distinctive signs of genital cGVHD (eg, erosions, fissures, ulcers) together with concurrent extragenital organ involvement were sufficient for a diagnosis of cGVHD.

Symptoms

With the aim of getting a broad view of the patients' discomfort, the questionnaire inquired about 12 symptoms associated with genital dysfunction, including itching, smarting pain, swelling, pain (with and without touching), blisters, fissures/wounds, dryness, discharge, vaginal and/or vulvar constriction, and dyspareunia. The patients rated the frequency of each symptom as 0, never; 1, seldom; 2, sometimes; 3, often; or 4, always.

Clinical Scoring of Genital cGVHD

For evaluation of the functional status of cGVHD affected genital organs, patients' clinical signs and reported symptoms on coitus and/or at gynecologic examination were combined and scored according to NIH criteria [6]. According to these criteria, 0 represents no symptoms; 1, symptoms, mild signs on physical examination, no effect on coitus, and minimal discomfort on gynecologic examination; 2, symptoms, moderate signs on examination, and mild dyspareunia or discomfort on gynecologic examination; 3, symptoms, advanced signs, and severe pain with coitus or inability to insert a vaginal speculum. If signs and symptoms diverged, symptoms were used for scoring, and consequently asymptomatic patients were scored as 0 irrespective of signs.

Global Scoring of cGVHD

Global scoring of cGVHD according to the NIH criteria is based on the number of organs involved and the clinical scoring of each affected organ, with the aim of characterizing the clinical impact of cGVHD on the individual's total functional status. For this study, data on the occurrence and severity of extragenital cGVHD were retrieved retrospectively from medical records. The global severity of each patient's cGVHD was categorized by combining genital and extragenital clinical scores.

Acquisition of Genital Biopsy Specimens for Histopathological Examination

To obtain genital mucosal biopsy specimens, a 4-mm punch biopsy was used in the vulva, and forceps biopsy specimens were performed in the vagina. A total of 56 biopsy specimens (19 vaginal and 37 vulvar) were obtained from 38 patients from areas macroscopically suspicious for cGVHD (n = 25) or from mucosa with no clinical cGVHD (n = 31). To avoid systematically skewed results owing to multiple biopsy specimens, only the first biopsy from each patient was used for the analysis of the relationship between clinical signs and histopathological features.

Histopathological Scoring of cGVHD

Mucosal biopsy specimens from the vulva and vagina were fixed in neutral buffered formalin and embedded in paraffin wax. Serial sections were stained with hematoxylin and eosin and examined by 2 pathologists. The histopathological criteria of Shulman et al. [14] were used to diagnose cGVHD. A global assessment of histopathological findings for each biopsy specimen was performed to arrive at a final diagnosis that was standardized

Table 1
Clinical Characteristics of Patients with and without Genital cGVHD in a Cross-Sectional Study of 42 Women after HSCT

Characteristic	All Patients (n = 42)	Genital cGVHD (n = 22)	No Genital cGVHD (n = 20)	*P* Value*
Patients and diagnosis				
Age at HSCT, yr, median (range)	39 (19-68)	47 (26-68)	37 (19-60)	.07
Acute leukemias, n	21	12	9	.80
Other, n†	21	10	11	
Transplantation				
Time after HSCT, mo, median (range)	80 (13-148)	57 (13-148)	87 (27-119)	.36
Time between HSCT and GynDx <80/≥80 mo, n	20/22	12/10	8/12	.37
Previous acute GVHD, yes/no, n	26/16	12/10	13/7	.54
Donor, sibling/unrelated, n	19/23	15/7	4/16	.002
Donor sex, female/male, n	17/25	11/11	6/14	.22
Stem cell source, BM/PBSC, n	12/30	4/18	8/12	.18
Conditioning, reduced/full intensity, n	13/29	6/16	7/13	.74
Total body irradiation, yes/no, n	19/23	9/13	10/10	.76
Systemic cGVHD				
Systemic corticosteroid treatment, yes/no, n	15/27	13/9	2/18	.001
Extragenital cGVHD, yes/no, n	26/16	17/5	9/11	.055

GynDx indicates date of diagnostic visit; BM, bone marrow; PBSC peripheral blood stem cells.
* Differences between patients with genital cGVHD and those without genital cGVHD.
† Chronic myelogenous leukemia, n = 17; myeloma, n = 1; myelodysplastic syndrome, n = 3.