

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.

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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 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, $n = 3$.

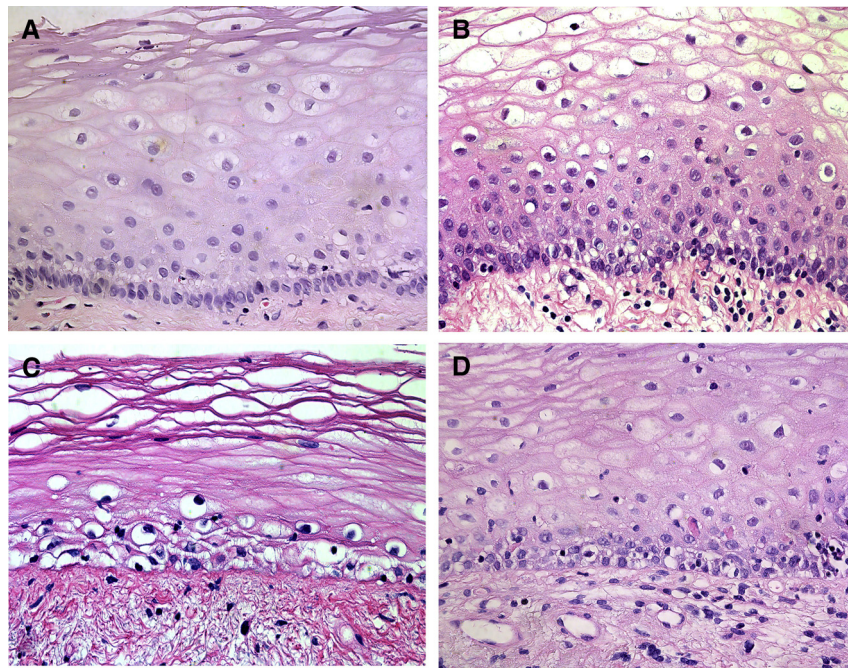


Figure 1. Biopsy specimens from the vulvar mucosa demonstrating normal mucosa (A), possible GVHD (B), consistent with GVHD (C), and GVHD (D). Lymphocytes infiltrating the squamous epithelium (B and D) and apoptotic cell bodies (D) are evident. (Hematoxylin and eosin staining.)

into 1 of 4 categories: no cGVHD, possible cGVHD, consistent with cGVHD, or cGVHD (Figure 1). Biopsy specimens judged to be normal were classified as no cGVHD. Biopsy specimens were classified as possible cGVHD if they contained an inflammatory infiltrate of mostly lymphocytes, accompanied by epithelial changes; as consistent with cGVHD if in addition to inflammation and epithelial changes they contained a band-like inflammatory infiltrate or apoptotic bodies; and as cGVHD if they contained both a band-like inflammation and apoptotic bodies.

Statistical Analysis

Associations between different variables and genital cGVHD versus no genital cGVHD was tested using Fisher's exact test for dichotomous variables and Wilcoxon's rank-sum test for continuous variables. Ordered categorical variables were analyzed using a nonparametric trend test [15].

RESULTS

Study Population

Patient characteristics of the entire cohort and of the subgroups of patients with genital cGVHD ($n = 22$) and without genital cGVHD ($n = 20$) are presented in Table 1. Ten women in the genital cGVHD group and 11 women in the no genital cGVHD were receiving estrogen hormone replacement therapy. The prevalence of cGVHD at any location was 74% ($n = 31$) in the entire cohort. Of the background factors, only HSCT from a sibling donor was associated with a higher prevalence of genital cGVHD ($P = .002$). The presence of genital cGVHD was significantly associated with systemic corticosteroid treatment of extragenital cGVHD ($P = .001$). The prevalence of genital cGVHD was higher than that of cGVHD at any other localization: 52%, compared with 43% for oral, 40% for ocular, 10% for skin, 7% for lungs, and 12% for all other. Five patients had isolated genital cGVHD.

Diagnosis of Genital cGVHD

Clinical signs consistent with the NIH criteria of genital cGVHD were found in 22 of 42 patients (52%). Diagnostic signs of cGVHD were observed in 21 patients, and 1 patient with distinctive genital signs of cGVHD and extragenital cGVHD also met the criteria for genital cGVHD (Table 2). Of

the 21 patients with diagnostic signs, 16 had vaginal strictures (in 3 cases combined with reticular white lines), and the other 5 had lichen planus–like signs with reticular white lines (Figure 2). cGVHD in the vagina or vulva was observed in 14 and 5 patients, respectively, and 3 patients had cGVHD at both locations. Two additional genital signs, vaginal strings and teleangiectatic areas, were observed only in patients with confirmed genital cGVHD (Table 2).

Symptoms of Genital cGVHD

Genital symptoms reported in the questionnaire and confirmed orally at the time of diagnostic gynecologic examinations are listed in Table 3. Mucosal dryness, pain, smarting pain, and dyspareunia were significantly more common in women with diagnosed genital cGVHD. Vaginal examination was associated with marked discomfort in 5 patients, 3 of whom had partial or total vaginal stenosis. Many women reported remitting flare-ups of genital symptoms appearing synchronously with symptomatic cGVHD at other locations.

Clinical Scoring of Genital cGVHD

Two patients had diagnostic genital cGVHD but were assigned a score of 0 because they reported no symptoms and experienced no discomfort on gynecologic examination. The other 20 patients were assigned a score of 3 ($n = 12$), 2 ($n = 2$), or 1 ($n = 6$). Three patients scoring 3 had genital signs as the sole cGVHD manifestation.

Global Scoring of cGVHD

Fifteen patients (36% of all participants) had severe global cGVHD. In 12 of these patients, this classification was based on a clinical score of 3 for genitals, whereas the remaining 3 patients had pulmonary disease in addition to a genital score of 1–2 (Table 4).

Table 2
Clinical Genital Signs in Patients with and without Genital cGVHD in a Cross-Sectional Study of 42 Women after HSCT

NIH Criteria ^a	Genital cGVHD (n = 22), n			No cGVHD (n = 20), n			P Value ^f
	Total	Vulvar	Vaginal	Total	Vulval	Vaginal	
Diagnostic signs							
Synechia vaginae	12			0			
Vaginal partial stenosis	5			0			
Vaginal total stenosis	4			0			
Reticular white lines	8	6	2	0			
Distinctive signs							
Synechia vulvae	4			2			.67
Fissures/ wounds	2	2	0	2	2	0	1.00
Hyperkeratotic plaque	1	1	0	0			1.00
Additional signs							
Vaginal string ^g	5			0			.049
Telangiectatic areas ^h	4	1	3	0			.11
Red and white spots ⁱ	6	5	1	1	1	0	.096
Thin mucousa	17	16	10	11	11	1	.19
Edematous	3	2	1	0			.23
Reddened	2	2	0	1	1	1	1.00
Red spots (no white)	6	4	4	5	3	3	1.00
White spots (no red)	2	2	0	1	1	0	1.00
Dry mucosa	3	3	1	4	4	0	.69

One patient could have more than 1 sign in the vulva and/or the vagina.

^a Filipovich et al.⁹

[†] Refers to “total” differences between patients with genital cGVHD and no genital cGVHD, respectively.

[‡] A 2- to 4-mm fibrotic string felt at gynecologic examination as part of the vaginal wall, not visible for the examining eye, circular, or semicircular, horizontal, or more or less vertical and most often sore.

[§] The term “telangiectatic areas” is used to describe many small red vessels grouped together.

[¶] The red and white spots are seen together in the vulva and/or vagina, giving a mottled appearance.

Histopathological Assessment

In 8 of 14 patients with diagnostic clinical cGVHD, histopathological findings were consistent with or confirmatory for cGVHD (Table 5). Twenty-four biopsy specimens were obtained from areas without clinical genital cGVHD, and in this group, 7 specimens obtained from the vulvar mucosa demonstrated histopathological signs consistent with cGVHD. Four of these 7 women had diagnostic vaginal cGVHD with stenosis and/or synechia.

DISCUSSION

Based on the NIH criteria, 22 of the 42 women (52%) were diagnosed with genital cGVHD, 9 of whom had partial or total vaginal stenosis. Twelve women had a clinical score of 3, indicating advanced signs and symptoms. Consequently, genital cGVHD had a strong impact on global cGVHD categorization; in addition to the 12 women with advanced

genital cGVHD, only 3 patients with pulmonary cGVHD were classified as having severe global cGVHD. As expected, genital cGVHD was associated with marked symptoms affecting sexual life, including dryness, pain, smarting pain, and dyspareunia.

Despite the long duration of follow-up, a majority of patients (74%) had signs of some form of cGVHD, and indeed 36% of patients were still receiving systemic corticosteroid treatment. There was a close association between extragenital and genital cGVHD. Seventeen women had both genital and extragenital cGVHD, 5 had isolated genital cGVHD, and 9 had only extragenital cGVHD. Two-thirds of the patients with extragenital cGVHD had genital cGVHD as well. Notably, of the 22 patients with genital cGVHD, 13 (59%) were receiving systemic corticosteroid therapy, with extragenital cGVHD as the indication in all cases. Three patients scored 3 for genital cGVHD without any extragenital cGVHD. These data indicate that genital cGVHD should be actively asked and looked for, not only in patients with other manifestations of cGVHD.

The prevalence of genital cGVHD after a long follow-up has not been accounted for in other studies. However, Zantomio et al. [11] estimated a 49% cumulative incidence of genital cGVHD at 32 months after HSCT. In an Italian study, the median time of onset of genital cGVHD was 7 months after HSCT, and 25% of patients developed acute or chronic genital cGVHD up to 107 months after HSCT [9]. In another retrospective study, Hirsch et al. [13] evaluated 138 women who underwent HSCT between 2008 and 2010. All patients were followed by a gynecologist from 3 months post-HSCT, and 26 (19%) were eventually diagnosed with cGVHD based on clinical signs or histopathological analysis. The criteria for diagnosing genital cGVHD used in that study were not described in detail. The higher prevalence of genital cGVHD in our study compared with most previous studies may be related to differences in diagnostic criteria; it is possible that



Figure 2. Vulvar cGVHD with reticular white lines.

Table 3
Genital Symptoms in Patients with and without Genital cGVHD in a Cross-Sectional Study of 42 Women after HSCT

Reported Symptoms	Patients with Genital cGVHD (n = 22)					Patients with No Genital cGVHD (n = 20)					P Value for Trend*
	0	1	2	3	4	0	1	2	3	4	
Dryness	7	1	4	5	5	14	1	2	2	1	.010
Pain†	11	1	0	3	5	15	0	2	1	0	.033
Smarting pain	12	0	4	2	2	16	1	1	0	0	.028
Fissures/wounds	14	0	4	2	0	16	1	0	0	1	.16
Itching	13	2	5	1	0	15	0	3	0	0	.16
Dyspareunia‡	2	1	2	2	6	11	1	1	0	1	.001

A patient could have multiple symptoms. Symptoms were self-reported as 0, never; 1, seldom; 2, sometimes; 3, often; or 4, always.

* Refers to differences between patients with genital cGVHD and no genital cGVHD, respectively.

† With or without touching.

‡ Among 13 patients with genital cGVHD and 14 patients with no genital cGVHD having or attempting coitus.

the NIH criteria are broader than the definitions used in other studies.

In our patient cohort, the prevalence of genital cGVHD was similar in patients with follow-up time under and over the median of 80 months. The NIH criteria do not distinguish between an ongoing inflammatory process and a fixed deficit, however, and thus it is likely that in some women in our study, the finding of diagnostic signs of genital cGVHD represents an end-stage fibrotic sequel rather than a progressive disease. This assumption is indirectly supported by the lower prevalence of corticosteroid therapy (for extra-genital cGVHD) in patients with longer than median follow-up (4 of 21 patients versus 10 of 21 patients with shorter than median follow-up). Consequently, it seems unlikely that our finding of a high prevalence of severe global cGVHD, based mainly on clinical scoring of genital cGVHD, is associated with a significantly reduced survival. Arai et al. [8] reported a marked impact on survival in patients with severe global cGVHD, but that study had a comparatively short follow-up (18.5 months), and cGVHD severity was based on high clinical scores in the eyes, mouth, and lungs.

We did encounter some difficulties in using the NIH criteria for genital scoring, especially with the distinction between scores 1 and 2, that is, mild signs and minimal discomfort versus moderate signs and mild dyspareunia or discomfort on gynecologic examination. Experienced discomfort can vary depending on multiple factors, and indeed 2 patients (with no sexual activity) scored 0 (ie, no discomfort) on gynecologic examination despite having diagnostic signs of vaginal cGVHD. However, this finding is consistent with the notion that the clinical organ-related

scoring of cGVHD should reflect the functional status of the affected organ.

Two additional signs, vaginal strings and telangiectatic areas, were observed exclusively in women with concurrent diagnostic signs of genital cGVHD (Table 2). The finding of vaginal strings in genital cGVHD also has been reported by Spiryda et al. [10] and Stratton et al. [12], and telangiectatic areas have previously been associated with genital lichen planus [16]. In addition, red and white spots occurring together, giving the mucous membrane a mottled appearance, were seen in patients with genital cGVHD, and similar mucosal features were described by Hirsch et al. [13]. It seems plausible that a vaginal string heralds a fibrotic cGVHD process, and if confirmed in future studies, all 3 of the foregoing signs might be considered diagnostic of genital cGVHD.

Our data on the relationship between clinical and histopathological features of the genital mucosa must be interpreted with caution for several reasons. First, biopsy specimens were obtained at the diagnostic visit were obtained in only a minority of patients (18 of 42). Second, the remaining 38 biopsy specimens were obtained sporadically at follow-up visits in patients with or without typical clinical genital features. In patients with clinical diagnostic cGVHD at the location of the biopsy (n = 14), the histopathological grades were evenly distributed from 0 to 3, suggesting that biopsy may be of limited value if the clinical diagnosis is settled. In mucosa without clinical genital cGVHD, biopsy specimens were more often confirmative, with 17 of 24 biopsy specimens graded 0-1; however, 4 of 7 patients with positive (grade 2-3) biopsy specimens obtained from clinically normal vulvar mucosa exhibited clinical diagnostic features of vaginal cGVHD.

Our data suggest that biopsy may be indicated in patients with genital symptoms but without diagnostic genital signs. The presence of systemic cGVHD may widen the indication for histopathological assessment.

Table 4
Global Scoring of cGVHD in a Cross-Sectional Study of 42 Women after HSCT

Clinical Diagnosis	Global Score				Total
	None	Mild	Moderate	Severe	
Genital cGVHD, n	0	2	5	15	22
No genital cGVHD, n	11	6	3	0	20
Total	11	8	8	15	42

Scoring is based on the NIH criteria: none, no cGVHD; mild, cGVHD involving 1 or 2 organs with a clinical score of 1; moderate, cGVHD at least 1 organ with a clinical score of 2 in any affected organ or site, or ≥3 organs or sites with a clinical score of 1; severe, cGVHD with a clinical score of 3 in any organ or a lung score of 2.

Clinical scoring: 0, no symptoms; 1, symptomatic with mild signs on examination and no effect on coitus and minimal discomfort with gynecologic examination; 2, symptomatic with moderate signs on examination and mild dyspareunia or discomfort with gynecologic examination; 3, symptomatic with advanced signs and severe pain with coitus or inability to insert a vaginal speculum.

Table 5
Clinical Diagnosis and Histopathological Grading of First Biopsy Specimen Obtained from the Genital Mucosa in 38 Women after HSCT*

Clinical Diagnosis	Histopathological Grade [†]				Total
	0	1	2	3	
cGVHD, n	3	3	5	3	14
Not cGVHD, n	6	11	7	0	24
Total	9	14	12	3	38

* From a total of 56 biopsy specimens from 38 patients; only the first biopsy specimen obtained from each patient is shown.

† Histopathological grading of cGVHD: 0, normal; 1, possible; 2, probable/consistent with; 3, confirmed. See text for details.

In conclusion, our assessment of the prevalence, clinical signs, and symptoms of genital cGVHD in a cross-sectional study using the NIH consensus criteria has revealed that the patients' genital symptoms had not been correctly diagnosed by the patients' own gynecologists and had been treated only with hormone replacement therapy and in some cases surgery, with poor outcomes. Our findings indicate a high prevalence (52%) of genital cGVHD, similar to that of ocular and oral cGVHD. The clinical signs and symptoms seen in our cohort suggest that in a nonrelapsed cohort with a long follow-up, the presence of genital cGVHD or its sequelae is common and associated with serious consequences for sexual life. Importantly, severe genital cGVHD may arise in the absence of any other diagnosed cGVHD, and even without any genital symptoms if the woman is not having sexual intercourse. Our findings emphasize that regardless of genital symptoms, systematic and early surveillance by a gynecologist with a special interest in genital cGVHD is important.

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