Cross-sectional Study

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Vaginal complications of graft-versus-host disease after hematopoietic stem cell transplantation: a cross-sectional study

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Background: Stem cell transplantation is a clinical approach used to treat certain types of cancers, such as hematologic malignancies. Graft-versus-host disease (GVHD) occurs in 30–70% of cases and often diminishes the quality of life of transplant patients. This study aimed to determine the prevalence of vaginal complications of GVHD following hematopoietic stem cell transplantation.

Methods: This study employed an analytical cross-sectional design. All patients referred to Shariati Hospital in Tehran between 2019 and 2020 who underwent hematopoietic stem cell transplantation were considered for inclusion in this study if they met the inclusion criteria. Inclusion criteria encompassed nonnot sexually active women aged 18–70 who received stem cell transplantation more than 100 days prior. Exclusion criteria comprised patients who experienced GVHD during the first 100 days posttransplantation. Additionally, individuals over 75 and patients with metastatic cancer were excluded.

Results: A total of 55 patients were recruited, with ages averaging 40 ± 9.9 years for recipients and 38.5 ± 12.8 years for donors. Notably, 63.3 and 58.2% of patients exhibited oral and ocular symptoms, respectively. Regarding genital involvement, 49.1% experienced vaginal symptoms, while 25.5% had vulvar involvement. Among the 27 patients with vaginal involvement, two (7.4%) were categorized as mild, 17 (63%) as moderate, and eight (29.6%) as severe. Univariate analysis identified reduced vaginal discharge [odds ratio (OR = 6.56)], vaginal tightness (OR = 6.23), pelvic pain (OR = 5.50), and vaginal involvement (OR = 3.81) as significant predictors of other organ symptoms. Moreover, vaginal involvement (OR = 3.68) emerged as the sole significant predictor of the cooccurrence of oral, ocular, and other organ symptoms. In the multivariate analysis, reduced vaginal discharge (OR = 8.24) and vaginal tightness (OR = 3.92) significantly predicted other organ symptoms ($P = 0.009$).

Conclusion: Reduced vaginal discharge and vaginal tightness remained significant predictors of other organ symptoms.

Keywords: graft-versus-host disease, stem cell, stem cell transplantation, vaginal complications

Introduction

Stem cell transplantation is a clinical approach used to treat certain types of cancers, such as hematologic malignancies[1]. Recently, there has been a notable increase in the number of stem cell transplantations, particularly for acute myeloid leukemia and acute lymphoblastic leukemia[2]. GVHD affects a significant percentage of cases, ranging from 30 to 70%, and often leads to a decline in the quality of life for transplant recipients[3–6]. GVHD is initiated by a complex immune response involving T-cells, where the transplanted marrow fails to recognize the host's body (receptor) and subsequently attacks its tissues[7]. This disease typically manifests as a syndrome characterized by a combination of cellular (innate and adaptive) and humoral immune responses, as well as irregular immune regulation and fibrosis. The clinical manifestations closely resemble those seen in autoimmune disorders such as scleroderma, Sjögren syndrome, and lichen planus[6,7]. GVHD predominantly targets specific organs and regions, including the skin, eyes, mouth, lungs, liver, intestines, and genitals. These manifestations typically emerge within the first year following hematopoietic stem cell transplantation (HSCT), often coinciding with the cessation of immune

HIGHLIGHTS

- Stem cell transplantation is a clinical approach to treat certain types of cancers, such as hematologic malignancies.
- Graft-versus-host disease (GVHD) occurs in 30–70% of cases and often reduces the quality of life of transplant patients.
- Reduced vaginal discharge and vaginal tightness remained significant predictors of other organ symptoms.

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Abbreviations: cGvHD, chronic GvHD; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.

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suppression[6–8]. Symptoms usually begin anywhere between 2 months and 6 years after HSCT, although approximately 10% of patients may experience symptoms after 1 year[9].

Genital GVHD is a less common complication that affects about 25% of women undergoing HSCT[10]. Primary indications and symptoms include sensitivity or tenderness in the vestibular glands or vulvar mucosa, mucosal erosion, fissures, increased white blood cell count, fusion of the labia or clitoris, fibrosis causing a vaginal ring, shortened vaginal length, adhesions within the vagina, and complete vaginal stenosis. Additional symptoms include dryness, a burning sensation, itching, pain upon touch, burning sensation during urination, dyspareunia, and subsequent sexual dysfunction[11,12]. Vaginal GVHD typically manifests as a chronic condition around 7–10 months after HSCT, emphasizing the importance of providing preventive care for women and ensuring timely diagnosis and treatment to minimize complications[13]. Pretransplant clinical assessment should include recommendations regarding vulvovaginal GVHD, its early signs, potential complications, and the importance of regular gynecological check-ups to prevent severe gynecological complications[14]. Left untreated, these complications can be irreversible and significantly impact the quality of life[15]. Most gynecologists may not recognize the complications of obstetrics and gynecology that occur after HSCT. Therefore, this study aimed to determine the prevalence of vaginal complications of GVHD after HSCT.

Methods and materials

Study design

This study was an analytical cross-sectional study. All females referred to Shariati Hospital in Tehran who underwent HSCT were considered for inclusion in this study if they met the inclusion criteria.

Sampling and data collection

The sampling method in this study was a census. All patient information was extracted from the hospital archive and examination files in the gynecological clinic and entered into a premade checklist.

Women who were not sexually active, aged between 18 and 70, and had undergone a stem cell transplant more than 100 days ago were eligible for inclusion.

Exclusion criteria

Female patients who developed GVHD during the first 100 days of stem cell transplantation were excluded, as were individuals over 75 years old and patients with metastatic cancer and female patients with previous autoimmune diseases, dryness, etc.

Clinical symptoms

Clinical symptoms, such as transplant complications, duration of GVHD after transplantation, prevalence of vaginal GVHD, and duration of the postoperative period (including vaginal dryness, burning sensation during urination, and pelvic pain), as well as vaginal inflammation, clitoris scarring, vaginal shortening, vaginal stenosis, and vaginal closure, were assessed. Additionally, the type of transplanted cells (stem cell, UCB, peripheral) was recorded based on patients' previous records. Hospitalization data were collected from outpatient blood clinics in 2019 and 2020 and underwent examination in gynecology clinics.

Statistical analysis

SPSS 26 was utilized for statistical analysis. A χ^2 test was used to examine the relationship between nominal variables, and either an analysis of variance or Kruskal–Wallis H test was employed to compare continuous variables among patients with eye, oral, or other organ symptoms. Finally, multiple binary logistic regression was performed to predict the occurrence of different symptoms.

This study was approved by the Research Ethics Board of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.704).

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The work has been reported in line with the STROCSS criteria[16].

Results

Fifty-five patients participated. Among them, seven individuals (12.7%) were excluded due to being older than the menarche age. Among the 48 participants, 37 (77.1%) had reached menarche more than 3 months ago, while 11 (22.9%) had not reached menarche yet.

Out of 55 individuals, seven (12.7%) were in the menopausal age group and were excluded from postmenstrual bleeding analysis. Among the remaining 48 individuals, three (6.3%) had postmenstrual bleeding, while 45 (93.8%) did not.

None of the individuals simultaneously had menstruated for more than 3 months and experienced postmenstrual bleeding (Table 1).

Based on the χ^2 test, there is a significant relationship between vulvar involvement and vaginal involvement ($P = 0.001$). Specifically, out of 14 individuals with vulvar involvement, 12 individuals (85.7%) also had vaginal involvement. Meanwhile, out of 41 individuals without vulvar involvement, 26 individuals (63.4%) did not have vaginal involvement.

Three individuals (5.5%) had vaginal closure, while 52 individuals (94.5%) did not have vaginal closure. Three individuals (5.5%) had vaginal adhesions, while 52 individuals (94.5%) did not. Of the three cases with adhesions, one had two-thirds of the vagina obstructed, while the other two had one-third of the upper vagina obstructed.

Three individuals (5.5%) had no symptoms of GVHD. Among the remaining individuals, 15 (27.3%) had mild symptoms, 27 (49.1%) had moderate symptoms, and 10 (18.2%) had severe symptoms.

The mean age of individuals without symptoms was 31.67 ± 2.30 it with mild symptoms was 40.67 ± 12.93 it with moderate symptoms, was 41.56 ± 9.22, and with severe symptoms was 41.40 ± 7.39.

The mean age of onset in individuals without symptoms was 36 ± 5.19 with mild symptoms was 16.36 ± 35.87, with moderate symptoms, was 40 ± 11.32, and with severe symptoms was 39 ± 13.01.

Analysis of variance test

There is no significant difference in the mean age of transplant recipients based on the severity levels of GVHD (none, mild, moderate, and severe) ($P = 0.445$).

Table 1

Frequency of symptoms among patients.

	Mean (SD)
Age	40.7 (9.9)
Number of Children	1.4 (1.1)
Sex before transplant	4.4 (2.1)
Sex after transplant	1.1 (1.7)
Donor age	38.5 (12.8)
	n (%)
Ocular symptoms	32 (58.2)
Oral symptoms	35 (63.6)
Other organs symptoms	32 (58.2)
Background disease	
Acute lymphoblastic leukemia	12 (21.8)
Acute myeloid leukemia	27 (49.1)
Lymphoma	7 (12.7)
Aplastic anemia	4 (7.3)
MM	3 (5.5)
MT	1 (1.8)
PNH	1 (1.8)
CMV antibody reactive	55 (100.0)
HPV test negative	55 (100.0)
Source of stem cell	
Peripheral	55 (100.0)
Umbilical	0 (0.0)
Stem cell	0 (0.0)
Genital involvement	
Vulvar involvement	14 (25.5)
Vaginal involvement	27 (49.1)
Signs and symptoms of genital involvement	
Reduced vaginal discharge	46 (83.6)
Hypopigmentation of the vulva	11 (20.0)
Vulva scar	8 (14.5)
Vaginal ulcers	9 (16.4)
Vaginal erythema	12 (21.8)
Vaginal tightness (stenosis)	28 (50.9)
Adhesion of the labia minora	6 (10.9)
Vaginal shortening	4 (7.3)
Vaginal fibrosis	22 (40.0)
Vaginal adhesions	3 (5.5)
Scar on the clitoris	4 (7.3)
Vaginal closure	3 (5.5)
Wart	1 (1.8)
Pap smear	54 (98.2)
Dyspareunia	43 (78.2)
Dysuria	23 (41.8)
Vaginal dryness	41 (74.5)
Vulva itching	25 (45.5)
Pelvic pain	13 (23.6)
Itching	12 (21.8)
Postmenstrual bleeding	5 (9.1)
Donner information	
Donors gender	
Male	22 (40.0)
Female	33 (60.0)

CMV, Cytomegalovirus; HPV, Human papillomavirus; MM, Multiple myeloma

Similarly, there is no significant difference in the mean age of donors based on the severity levels of GVHD (none, mild, moderate, and severe) ($P = 0.778$) (Table 2).

Based on Fisher's exact test results, there is no significant relationship between ocular symptoms, oral symptoms, involvement of other organs, or the gender of the transplant recipient, and the severity levels of GVHD ($P = 0.114, 0.166, 0.202, 0.574$).

Table 2

Characteristics of patients according to ocular, oral, and other organ symptoms.

	n (%)			
	Ocular ($n = 32$)	Oral ($n = 35$)	Other ($n = 32$)	
Vulvar involvement	8 (57.1)	10 (71.4)	10 (71.4)	
Vaginal involvement	17 (63.0)	18 (66.7)	22 (53.7)*	0.019
Source of stem cell				
Peripheral	32 (58.2)	35 (63.6)	20 (74.1)	
Reduced vaginal discharge	27 (58.7)	30 (65.2)	12 (42.9)*	0.026
Hypopigmentation of the vulva	6 (54.5)	7 (63.6)	32 (58.2)	
Vulva scar	4 (50.0)	6 (75.0)	0 (0.0)	
Vaginal ulcers	5 (55.6)	6 (66.7)	0 (0.0)	
Vaginal erythema	6 (50.0)	8 (66.7)	30 (65.2)	
Vaginal tightness (stenosis)	18 (64.3)	18 (64.3)	2 (22.2)**	0.002
Adhesion of the labia minora	5 (83.3)	6 (100.0)	7 (63.6)	
Vaginal shortening	4 (100.0)	4 (100.0)	25 (56.8)	
Vaginal fibrosis	15 (68.2)	16 (72.7)	3 (37.5)	
Vaginal adhesions	2 (66.7)	2 (66.7)	29 (61.7)	
Scar on the clitoris	4 (100.0)	4 (100.0)	5 (55.6)	
Vaginal closure	3 (100.0)	3 (100.0)	27 (58.7)	
Wart	1 (100.0)	1 (100.0)	6 (50.0)	
Pap smear	32 (59.3)	35 (64.8)	26 (60.5)	
Dyspareunia	25 (58.1)	30 (69.8)	22 (78.6)	
Dysuria	15 (65.2)	14 (60.9)	10 (37.0)	
Vaginal dryness	25 (61.0)	29 (70.7)	4 (66.7)	
Vulva itching	16 (64.0)	18 (72.0)	28 (57.1)	
Pelvic pain	9 (69.2)	8 (61.5)	3 (75.0)*	0.027
Itching	7 (58.3)	8 (66.7)	29 (56.9)	
Postmenstrual bleeding	3 (60.0)	5 (100.0)	16 (72.7)	
Donor sex				
Male	13 (59.1)	15 (68.2)	16 (48.5)	
Female	19 (57.6)	20 (60.6)	2 (66.7)	

*The level of significance $P < 0.05$.
**The level of significance $P < 0.01$.

Additionally, no significant difference was found in the prevalence of vaginal adhesions across various 6-month periods ($P = 0.455, 0.639$), nor between GVHD grades and the duration since transplantation ($P = 0.831$) (Table 3).

Discussion

Indications for stem cell transplantation range from acute and chronic leukemias in young patients to nonmalignant hematologic diseases in patients up to the age of 70 years. The therapeutic efficacy of stem cell transplantation results from the combination of chemotherapy and radiotherapy, along with the immune response from transplanted donor cells against leukemia. However, a challenge arises in the form of GVHD, where the immunocompetent donor cells attack the healthy tissues of the recipient. Chronic GVHD (cGVHD) stands as the primary cause of late complications, occurring more than 3 months after stem cell transplantation[17–19].

Characteristics of cGVHD usually involve inflammation and fibrosis affecting mucous membranes, such as those in the mouth, eyes, genitals, intestines, and lungs[20]. However, there has been insufficient research conducted on genital cGVHD in women. The initial documentation of female genital cGVHD was by Corson*et al.*[21]. Subsequently, from 2003 to 2012, five different studies, including four retrospective and one observational, were published on genital cGVHD, estrogen, and topical

Table 3

Logistic regression results.

	R^{2a}	OR [95% CI]	P
To predict occurrence of other organ symptoms[b]			
Vaginal involvement	0.131	3.810 [1.218–11.919]	0.022
Reduced vaginal discharge	0.134	6.562 [1.218–35.371]	0.029
Vaginal tightness (stenosis)	0.225	6.233 [1.889–20.566]	0.003
Pelvic pain	0.125	5.500 [1.085–27.890]	0.040
To predict cooccurrence of oral, ocular, and other organ symptoms[b]			
Vaginal involvement	0.114	3.680 [1.070–12.583]	0.038
To predict occurrence of other organ symptoms[c]			
Pelvic pain		4.161 [.592–29.263]	0.152
Vaginal involvement (controlled)		0.531 [.131–2.160]	0.377
Vaginal tightness (stenosis)	0.382	3.927 [1.011–15.251]	0.048
Reduced vaginal discharge		8.243 [1.111–61.165]	0.039
Overall model		0.001	0.009

[a]Nagelkerke R^2.
[b]Univariate analysis, multivariate analysis controlled for vaginal involvement.
[c]Multivariate analysis.

immunosuppressive therapy[22–26]. In one cross-sectional study, its prevalence was found to be 52%, while a separate prospective study reported a cumulative incidence of 56% within 1 year and 66% within 3 years[27,28]. Early clinical guidelines highlighted genital endocrine dysfunction poststem cell transplantation and an elevated risk of cervical malignancy[29]. Since 2006, there has been a specific focus on genital cGVHD, leading to recommendations for posttransplant screening in symptomatic women or all women who have undergone stem cell transplantation[19,30].

The results of our study showed that in general, three patients did not have symptoms of GVHD (5.5%). Of the remaining 15 patients (27.3%), 15 had mild symptoms, 27 patients had moderate symptoms (49.1%), and 10 patients had severe symptoms (18.2%). In one study, the prevalence of genital cGVHD was 58% (n = 22) and in another study, it was 50% (n = 19), the results of which are inconsistent with our study. The prevalence in our study was higher than in other studies[31]. According to current guidelines (e.g., listing labial fusion as a diagnostic sign of genital cGVHD), this difference in prevalence in different studies and our study can be shown. In one study, it was stated that the late onset of genital GVHD in two women indicates the need for continuous monitoring of the genitals of transplanted women[20].

In this research, three patients (5.5%) experienced complete vaginal closure, and three patients (5.5%) had vaginal adhesions. Among the cases of vaginal adhesions, one involved two-thirds of the vagina, while the remaining two affected the upper third of the vagina. In another study, out of 38 patients, two individuals (19%) exhibited the chronic characteristic of severe fibrotic vaginal GVHD leading to relative vaginal stenosis. Surgical intervention was performed to address their vaginal stenosis, but it should be noted that as indicated in previous studies, surgery can reopen a closed vagina, but it does not cure GVHD[22,31].

In our study, there was no significant relationship between oral symptoms and degrees of GVHD. In one study, 17 women had symptoms of oral GVHD. Of these, 16 had ocular GVHD and 13 had genital GVHD. The need for regular eye and genital control of transplanted women is very important.

As Jagasia*et al.*[29], it is difficult to distinguish when fibrosis is a sign of GVHD or a sign of an improved process. In two studies, the vulvar synechiae was present as the only sign of genital GVHD[20,30]. Numerous women expressed experiencing symptoms related to estrogen deficiency, genital GVHD, and HPV infection. These symptoms are not definitive for diagnosis and necessitate a genital examination. Even asymptomatic women require a genital examination to exclude or identify genital GVHD. After an average of 14.5 years following alloSCT, sexual issues persisted, primarily in the form of dyspareunia. Among women who engaged in sexual activity, 41% reported experiencing pain frequently or consistently[13,32]. Estrogen plays a soothing role in alleviating symptoms of atrophy in the female genitalia and contributes to improving genital GVHD. Some reports suggest that intercourse with vulvovaginal atrophy and synechiae can be made painless with the use of lubricants. However, it is essential to be cautious when using topical immunosuppressants for treatment, as they can heighten the risk of infections and potentially reactivate HPV, increasing the risk of malignancies. Regular monitoring of patients for any contractions or distressing symptoms is necessary. Studies have shown a higher incidence of extragenital malignancies, particularly squamous cell carcinoma, in alloSCT patients, emphasizing the importance of lifelong genital monitoring and heightened awareness of the risk of genital epithelial malignancies[13].

Conclusion

Among the patients with vaginal involvement, the severity varied, with 7.4% classified as mild, 63% as moderate, and 29.6% as severe. Univariate analysis revealed several significant predictors of other organ symptoms, including reduced vaginal discharge, vaginal tightness, pelvic pain, and vaginal involvement. Furthermore, vaginal involvement was found to be the sole significant predictor of the cooccurrence of oral, ocular, and other organ symptoms. When considering the multivariate setting, reduced vaginal discharge and vaginal tightness remained significant predictors of other organ symptoms. The odds ratio values of 8.24 and 3.92, respectively, indicated a strong association between these factors and the presence of additional symptoms.

Ethical approval

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.704), and with the Helsinki Declaration of 1975, as revised in 2013. This study was approved by the Research Ethics Board of Islamic Azad University.

Consent

Informed consent was obtained from each participant.

Sources of funding

None.

Authors contributions

M.Y.: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. T.M.: designed the data collection instruments, collected data, carried out

the initial analyses, and reviewed and revised the manuscript. S.A. M.: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. V.H.: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Conflict of interest disclosure

There are no conflicts of interest.

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Data availability statement

All relevant data and materials are provided within the manuscript.

Provenance and peer review

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