Late follow-up of genital and ophthalmologic chronic graft-vs-host disease in females after allogeneic stem cell transplantation

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Abstract

Introduction: Genital chronic graft-vs-host disease (cGVHD) is a common late effect after allogeneic stem cell transplantation. In a previous cross-sectional study, prevalence, signs and symptoms of genital and extra-genital cGVHD were accounted for in a cohort of 42 women. Classifications of cGVHD were performed as per the National Institutes of Health (NIH) 2005 criteria. In this follow-up study on surviving women, the aim was to assess genital and extra-genital cGVHD status after long period of time. Our hypothesis was that signs and symptoms of cGVHD alleviate over time.

Material and methods: All surviving women (n = 38) were re-examined by an ophthalmologist, a gynecologist and a hematologist. Signs and symptoms were classified according to the NIH 2014 criteria. Clinical scorings of affected organs were combined for estimating global score of cGVHD. To make possible comparisons between the two studies, data from the original study were re-classified as per the NIH 2014 criteria, and the four dead women were excluded. The same questionnaires were completed. Cervical smear, human papilloma virus test and vulvar photo-documentation were performed.

Results: Median time after original study was 8.4 (5.8–12) years and after transplant 14.5 (10–19.3) years. The prevalence of genital cGVHD was similar in the original (50%) and follow-up (58%) studies (p = 0.646) as well as extra-genital cGVHD. Systemic corticosteroid treatment of cGVHD was ongoing in 34% and 29%, respectively (p = 0.805). Ocular cGVHD was found in 24 of 37 examined women (65%) in the follow-up study. Genital cGVHD had disappeared in three women and developed in two women 5–12 and 9–17 years, respectively, after transplantation. The severity of global cGVHD changed over time in 14 women, but was the same on group level (p = 0.345). Atrophic mucous membranes as in estrogen deficiency were seen in 66%. Three women had human papilloma virus genotypes associated with the risk of developing cervical cancer.

Abbreviations: alloSCT, allogeneic stem cell transplantation; cGVHD, chronic graft-vs-host disease; GvHD, graft-vs-host disease; HPV, human papilloma virus; NIH, National Institutes of Health.
Conclusions: Chronic GvHD did not alleviate over time. Allotransplanted women require early and continuous life-long contact with a gynecologist and an ophthalmologist for the detection of cGvHD. Specific attention should be given to the need for local estrogen and the risk of genital epithelial malignancies.

KEYWORDS
allogeneic stem cell transplantation, chronic graft-vs-host disease, dyspareunia, eyes, female genitals, human papilloma virus, late follow-up, treatment

1 | INTRODUCTION

The indications for allogeneic stem cell transplantation (alloSCT) have widened, from acute and chronic leukemias in young patients, to an array of malignant, and sometimes non-malignant, hematological diseases in patients up to the age of 70 years. The curative potential of alloSCT is due to the combination of chemo/radiotherapy and the immunologic graft-vs-leukemia effect, exerted by the donor’s immunocompetent cells. Graft-vs-host disease (GvHD) is an attack of donor immunocompetent cells on the patient’s healthy tissues. Chronic GvHD (cGvHD) is the major cause of late morbidity (complications occurring beyond 3 months after alloSCT) and contributes to non-relapse mortality after alloSCT.1-3 The features of cGvHD typically include inflammation and fibrosis of mucous membranes, eg in the mouth, eyes, genitals, gut and lungs. Female genital cGvHD was previously underrated and insufficiently treated.

The first description of female genital cGvHD was by Stephen Corson et al.4 Between 2003 and 2012, five different studies were published, retrospective (n = 4) and observational (n = 1), on genital cGvHD, estrogen and local immunosuppressive treatment.5-9 Prevalence was 52% in a cross-sectional study in 2014,10 cumulative incidence 56% at 1 year and 66% at 3 years in a prospective study.11 A retrospective study on long-term consequences of genital cGvHD was published 2020.12 Early clinical guidelines mentioned endocrine genital dysfunction after alloSCT and an elevated risk for cervical malignancy.13

From 2006, focus was on the female genital cGvHD, and post-transplant gynecologic examination was recommended in symptomatic women1,2,14 or all women.2,15,16 A review on genital cGvHD was published 2017.17

The objective of this follow-up study of all surviving women from an earlier cross-sectional study was to assess current cGvHD status, and compare this with findings in the original study.10 Our hypothesis was that signs and symptoms of genital, ocular and other cGvHD had alleviated over time.

2 | MATERIAL AND METHODS

2.1 | Patients

Forty-two women, median age 39 (19–68) years, allotransplanted August 1996 to January 2006, participated in the original population-based cross-sectional study at a median of 6.7 (1.1–12.3) years after transplant.10 Since that study, four women—three of whom had severe global cGvHD—have died of cGvHD, pancreatic cancer, leukemic relapse and amyotrophic lateral sclerosis. In the present study, all surviving women underwent clinical examination and grading of genital (ESK), ocular (KS) and other (MB/YB) cGvHD.

Key message
Chronic graft-vs-host disease (cGvHD) had not mitigated over time. Eyes, mouth and female genitals are major targets for cGvHD after long time. Life-long examinations are necessary to diagnose and treat ophthalmological and genital cGvHD, and prevent genital epithelial malignancy.

2.2 | Re-classification of data

In the original study, cGvHD symptoms and signs were identified and categorized as per the National Institutes of Health (NIH) 2005 consensus criteria.18 For the present study, all data were re-classified as per NIH 2014 criteria.19 For this, detailed descriptions of clinical genital and extra-genital signs and symptoms, and photographic evidences were used. NIH 2005 clinical scoring of genital cGvHD focused on symptoms, whereas in NIH 2014, signs determined the scores.

Notably, in the original study only women with severe ocular cGvHD were referred to an ophthalmologist. Thus, the majority of ocular scores were set by the hematologists.

2.3 | Genital cGvHD

In the original study, all women used local estrogen therapy at least 6 weeks before the diagnosis of genital cGvHD. In the follow-up study the diagnosis was made irrespective of estrogen therapy. Women with genital cGvHD in the original study were referred for continued local immunosuppressive treatment by their ordinary gynecologist.5,6,8,20 A treatment scheme was enclosed and a dilator recommended for vaginal cGvHD. Between these studies, 11 women were treated by four gynecologists with interest and knowledge in
the field, whereas 25 women were seen by gynecologists with minor experience of genital cGvHD. Two women had no gynecologic controls, only cervical smears taken by midwives.

In the follow-up study the women completed the same comprehensive questionnaire on general medical history, ongoing medication and self-reported gynecologic symptoms, as in the original study (see Table S1 in ref. 11).

Clinical examination included structured documentation of all genital signs. Cervical smear and human papilloma virus (HPV) tests were performed. The vulva was photo-documented. See Table 1 concerning the diagnosis of female genital cGvHD according to NIH 2014. A fibrous string in the vaginal wall was considered a diagnostic sign, whereas red and white spots seen together, giving the mucosa a mottled appearance, were deemed a distinctive sign. The NIH 2014 term “circumferential vaginal banding” denotes the same sign as the traditional term “partial stenosis.”

2.4 | Clinical and global scoring

Clinical scoring 0–3 of cGvHD in NIH 2014 is based on no, mild, moderate or severe symptoms and/or signs; the genitals on signs only. Global scoring of cGvHD in NIH 2005 was mainly unchanged in NIH 2014. The scoring is based on the number of organs concerned and the clinical scoring of each affected organ, with the purpose of characterizing the clinical impact of cGvHD on the individual’s total functional status.

2.5 | Statistical analyses

Fisher’s exact test was applied to dichotomous variables, with \( p < 0.05 \) considered statistically significant. Analyses were performed in IBM® SPSS® Statistics for Mac version 24.0 (IBM Corp, Armonk, NY, USA).

2.6 | Ethical approval

The study was approved by the Central Ethical Review Board of the University of Gothenburg (Reference number 164-15) on 23 April 2015. All women signed an informed consent.

3 | RESULTS

All comparisons between data from the original and the follow-up studies were based on the 38 surviving women. For women’s characteristics in both studies, and details of transplants and cGvHD, see Table 2. Summing-up, 28 of 38 (74%) and 31 of 37 (84%) women in the original and follow-up studies (no extra-genital data in one patient), respectively, had cGvHD at any location (\( p = 0.40 \)).

For menopause, systemic estrogen treatment and pregnancies in both studies, see Table S1.

3.1 | Genital cGvHD signs

In the original study, 19 of the surviving 38 women were diagnosed with genital cGvHD. Of these, three had no genital cGvHD signs in the follow-up study and no scarring after cGvHD. All three had lichen planus-like signs, reticular white lines, in the original study, and one of them also a sore vaginal string. Two women without genital signs of cGvHD in the original study, had developed genital cGvHD, labial fusions and stenosis of the cervix in one of them, 5–12 years and 9–17 years after alloSCT, respectively.

Another four women in the original study had photo-documented vulvar labial fusions and resorptions, then diagnosed as long estrogen deficiency. In the follow-up study, these fusions had expanded and were now diagnosed as genital cGvHD. In total, 22 women were diagnosed with genital cGvHD, a prevalence of 58%.

Chronic GvHD was observed in the original and follow-up studies, respectively, in vulva only \( (n = 8^a/n = 7) \), vagina only \( (n = 9/n = 3) \) and at both locations \( (n = 6/n = 12) \). The four women with changed diagnosis of the vulva in the original study were included (see Section 4). Locations were changed between the studies, but without any obvious pattern (data not shown).

Table 3 shows genital signs observed in both studies. No new total stenosis was observed. The two total stenoses in the follow-up study were the same as in the original study, and belonged to women who declined surgery. The four women with partial stenosis in the original study underwent surgery \( (n = 2) \) and/or local immunosuppressive therapy with a vaginal dilator; none had partial stenosis in the follow-up study. The two women who accepted surgical and local immunosuppressive treatment of their total stenoses...
had partial stenosis in the follow-up study. The other two women with partial stenosis in the follow-up study had aggressive genital cGvHD with recurrences when treatment was tapered. Vaginismus was found in six women in the follow-up study.

In the follow-up study, genital cGvHD was observed in 13 of 16 women (81%) after a sibling donor transplant, and in nine of 22 women (41%) after an unrelated donor transplant ($p = 0.02$).

### 3.2 | Self-reported genital symptoms

Self-reported genital symptoms in the original and follow-up studies are presented in Figure 1. Dryness and itching were more common in the follow-up study reported by women both with and without genital cGvHD. There are women without symptoms in both groups, that is, also among women with genital cGvHD. In the follow-up study, 18 women were treated with total body irradiation and 20 were not. There was no significant difference concerning self-reported symptoms between the groups treated and not treated with total body irradiation, eg pain when touched, ($p = 0.14$). In the follow-up study, 27 women had had full intensity conditioning and 11 reduced intensity conditioning. We found no statistical connection between the genital symptoms and the kind of conditioning (eg dryness $p = 0.71$). Three women were HPV-positive. One reported no symptoms, one reported occasional itching and fissures and had no coitus, the third reported frequent dryness, occasional pain when touched, discharge and dyspareunia.

Dyspareunia—“sometimes, often or always”—was reported in 44% in the original study and 56% in the follow-up study ($p = 0.59$) among women having coitus. In the original study, dyspareunia was more common in women with genital cGvHD vs no cGvHD ($p = 0.002$). In the follow-up study the difference was not significant ($p = 0.06$). The reports of individual dyspareunia in the two studies are presented in Table 4 together with comments on signs that caused pain. Sixteen women gave the same report on dyspareunia in both studies, seven reported more frequent dyspareunia, five women had stopped having coitus, five reported less frequent dyspareunia and five women changed from no coitus to dyspareunia often or always.
3.3 | Extra-genital cGvHD

Any extra-genital cGvHD was diagnosed in 58% and 68% in the original and follow-up studies, respectively \((p = 0.48)\). The prevalence of oral cGvHD was similar in the original and follow-up studies: 42% and 46%, respectively. Most common in the follow-up study was cGvHD of the eyes \((n = 24; 65\%)\). See Table 5 on cGvHD in different organs in both studies.

3.4 | Treatment

All women in the original study were recommended continued local estrogen therapy. However, 64% and 63%, respectively, in the group of women with and without genital cGvHD in the follow-up study were prescribed complementary or renewed local estrogen therapy.

Eight (21%) women were on local genital immunosuppressive treatment (clobetasol and/or tacrolimus); two of them using a vaginal dilator. Five of these had also systemic immunosuppressive treatment, but on other indications than genital cGvHD. Local immunosuppressive treatment was re-activated in another two women. The six women (two new and four undiagnosed in the original study) with newly diagnosed genital cGvHD in the vulva were treated with local estrogen and expectancy. Systemic corticosteroid treatment of cGvHD was ongoing in 34% in the original study and 29% in the follow-up study \((p = 0.81)\) (none because of genital cGvHD). Detailed information about systemic immunosuppressive treatment is presented in Table 6. Four women were on corticosteroid eye-drops, and another three were prescribed that treatment.

3.5 | Clinical and global score

Table S2 shows the clinical scoring of cGvHD in the follow-up study. Table 7 demonstrates global scores in the two studies with individual changes \((n = 14)\) of global severity of cGvHD between the original and follow-up studies. On a group level, however, severity was similar after long time \((p = 0.35)\) (data not shown).

3.6 | Pre-malignancies and malignancies

Histopathologic dysplasia of the cervix had been found and treated in four women, and of the vulva in one woman, four of whom had genital cGvHD. In the follow-up study, all cervical smears were
normal. However, three women had HPV genotypes associated with the risk of developing cervical cancer. Five women had been treated for six new malignancies: three in the oral cavity, two basal cell carcinomas and one colon cancer.

Our hypothesis that signs and symptoms of genital, ocular and other cGvHD would alleviate over time, was not confirmed. The prevalence of genital and extra-genital cGvHD, and systemic corticoids was almost identical.

The modification of NIH 2014 genital clinical scoring implies that asymptomatic features with a clinical score 0 in NIH 2005, such as vulvar and vaginal synchieae, are categorized in NIH 2014 as clinical score 3. This may contribute to individual differences of global severity between the studies. Nevertheless, global score was the same on group level in both studies.

The prevalence of genital cGvHD, 58% (n = 22) in the follow-up study was similar compared with 50% (n = 19) in the original study (p = 0.65). But, according to the current guidelines\(^1\) (listing labial fusion and resorption as diagnostic signs of genital cGvHD), the prevalence in the original study should be corrected to 61% (n = 23). In that case as well there is no difference between the studies (p = 1.0).
Severe ocular cGvHD were referred to an ophthalmologist.

**TABLE 4** Self-reported dyspareunia in individual women presented on the same line in the original and follow-up studies

| Original study/reported frequency | Follow-up study/reported frequency | Pain-causing signs and other comments |
|----------------------------------|-----------------------------------|-------------------------------------|
| 0                                | 0                                 | Vulvar atrophy and synechia (n = 1); VV atrophy and synechia (n = 1) |
| 4                                | 4                                 | Bact.vaginosis, partial stenosis (n = 1); VV atrophy and synechia, vulvar ret.white lines (n = 1); erosion, sore vag. string, vaginismus (n = 1) |
| No coitus                        | No coitus                         | No partners (n = 3); VV atrophy, edema, synech.vulvae (n = 1) |
| 0                                | No coitus                         | No partner (n = 2); vulvar fissure and synechia (n = 1) |
| 3,2                              | No coitus                         | Total vag. stenosis (n = 2), no partner (n = 1) |
| No coitus                        | 3, 4                              | Sore vaginal string, vulvar atrophy, vaginismus (n = 1); synechia vulvae, urethritis, vulvar atrophy (n = 1); lichen scl.vulvae + partial vaginal stenosis (n = 1); |
| 0,1,2                            | 2,2,3                             | Synechia vulvae, vaginismus (n = 1); lich.scl.like vulvae (n = 1); partial vag.stenosis, erosion vulvae (n = 1); VV atrophy (n = 3) |
| 4,4                              | 2,1                               | Synechie vulvae (n = 1); lich.planus-like vulva, vaginal synechia (n = 1); VV atrophy (n = 2) |

**Women with no genital cGvHD in the follow-up study**

| Original study/reported frequency | Follow-up study/reported frequency | Pain-causing signs and other comments |
|----------------------------------|-----------------------------------|-------------------------------------|
| 0                                | 0                                 | Vulvar atrophy (n = 1); VV normal (n = 3) |
| 4                                | 4                                 | VV atrophy, vaginismus (n = 1) |
| No coitus                        | No coitus                         | no partners (n = 2) |
| No coitus                        | 4                                 | VV atrophy (n = 2), vaginismus (n = 2) |
| 0                                | 1, 2, 1                           | Vulvar atrophy (n = 1); VV atrophy (n = 1); VV normal (n = 1) |
| 1,3,4                            | 0                                 | Vulvar atrophy (n = 3); no dyspareunia with lubricants (n = 3) |
| 2                                | 3                                 | VV atrophy (n = 1) |

Note: Dyspareunia was self-reported as: 0 never; 1 seldom; 2 sometimes; 3 often; 4 always and no coitus.

Abbreviations: cGvHD, chronic graft-vs-host disease; VV, vulvo-vaginal.

*Number of women.

**TABLE 5** Chronic graft-vs-host disease in different organs in the original and follow-up studies (n = 37) after allogeneic stem cell transplantation

| Organ involved (n) | Study | Originala | Follow-upa |
|--------------------|-------|-----------|------------|
| Gastrointestinal   | 0     | 2         |
| Skin               | 5     | 3         |
| Liver              | 2     | 1         |
| Lung               | 1     | 3         |
| Mouth              | 16    | 17        |
| Eye                | 12b   | 24        |
| Genital            | 18c   | 22        |
| Other              | 6d    | 11e       |

*Data missing in the follow-up study concerning extra-genital cGvHD in one woman not included in this table.

bMost diagnoses were made by the hematologists; only women with severe ocular cGvHD were referred to an ophthalmologist.

cAnother four women had labial fusion and resorption not diagnosed as cGvHD.

dJoints and fascia (n = 5); cramps (n = 1).

eJoints and fascia (n = 7), cramps (n = 1), fatigue (n = 2), urethra (n = 1).

The late debut of genital cGvHD in two women emphasizes the need for continued genital control of allotransplanted women without genital cGvHD.

The chronic feature of severe fibrotic vaginal cGvHD is illustrated by two women with vaginal partial stenosis in the follow-up study without extra-genital cGvHD. Their stenoses were surgically treated 9 and 17 years before the follow-up study, respectively, but relapsed when adequate postoperative treatment was tapered off. As already known, surgery may open a closed vagina but does not cure cGvHD.\(^5,22\)

In our follow-up study, 17 women had oral cGvHD; of these, 16 also had ocular cGvHD and 13 genital cGvHD. The need for regular ophthalmological and genital control of allotransplanted women is evident. Only three women had cGvHD in the skin in the follow-up study. In other studies, cGvHD of the skin had the same frequency as cGvHD of the eyes\(^8,9\) or an even greater frequency.\(^7\) There could be a bias in our prevalence of cGvHD in the eyes from diagnosis by an ophthalmologist compared with skin cGvHD diagnosed by hematologists.

It is difficult to know when fibrosis is a sign of ongoing cGvHD or when it is a sign of a healed process, as pointed out by Jagasia et al.\(^19\)

One woman had synechiae vulvae as the only genital sign of cGvHD.
TABLE 6 Systemic immunosuppressive medications in individual women in the follow-up study

| Women with genital cGvHD | Extra-genital cGvHD/other indication |
|-------------------------|------------------------------------|
| Prednisolone dosage/day |                                    |
| 2.5 mg e.o.d.           | Periods of cGvHD in the skin       |
| 5 mg                    | Mouth, eyes, muscles, joints       |
| 2.5–10 mg               | Mouth, eyes, muscles, joints       |
| 5.0–10 mg               | Mouth, eyes, joints, pain          |
| 10 mg                   | Mouth, eyes, skin                  |
| 15 mg                   | Mouth, eyes, tiredness             |
| Prednisolone + cyclosporin dosage/day | |
| 5 mg + 50 mg            | Mouth, eyes, GI, tiredness         |
| 10 mg e.o.d. + 50 mg    | Mouth, eyes, urethra               |
| 10 mg + 50 mg           | Mouth, eyes, lungs, muscles, joints, cramps |

| Women without genital cGvHD | Extra-genital cGvHD/other indication |
|-----------------------------|------------------------------------|
| Prednisolone dosage/day     |                                    |
| 5 mg                        | Mb Bechterew (no extra-genital cGvHD) |
| Prednisolone + cyclosporin dosage/day | |
| 2.5 mg + 50 mg              | Mouth, eyes, skin, liver, muscles, joints, cramps |

Tacrolimus + mycophenolic acid dosage/day

Missing data

Heart and kidney transplantation between the studies. (cGvHD in mouth and eyes no indication)

Abbreviations: cGvHD, chronic graft-vs-host disease; e.o.d., every other day; GI, gastrointestinal.

Genital cGvHD was not the indication for immunosuppressive treatment of any woman.

in both studies. In the follow-up study she had very few symptoms, but the synchieae had expanded.

There are many symptoms reported by the women (Figure 1). These symptoms might be caused for example both by estrogen deficiency and genital cGvHD as well as HPV. The symptoms are not diagnostic and demand a genital examination. A woman with no symptoms also needs a genital examination to exclude or diagnose genital cGvHD. At a median of 14.5 years after alloSCT, sexual problems were still common in the form of dyspareunia. Of women having coitus 41% reported pain often or always. Estrogen has an alleviating effect on symptoms of atrophy in the female genitals and contributes to better healing of genital cGvHD. However, in the follow-up study, and reasonably due to lack of compliance, 66% of the women presented with atrophic mucous membranes as seen in estrogen deficiency (Table 4). Coitus with vulvovaginal atrophy and synechiae was also reported without pain with the use of lubricants (and/or a good sexual technique [data not shown]).

TABLE 7 Global score of cGvHD according to NIH 2014 in the original and the follow-up studies after alloSCT with individual changes of global severity of cGvHD between the studies

| Original study | Changes | Follow-up study |
|---------------|---------|----------------|
| n = 37        |         | n = 37         |
| None (n = 10) | Mild (n = 3) | None (n = 6) |
| Mild (n = 7)  | None (n = 1) | Mild (n = 6) |
| Moderate (n = 5) | Mild (n = 2) | Moderate (n = 4) |
| Severe (n = 15) | Severe (n = 15) | Severe (n = 21) |

Note: Arrows show movements of individual women between the two studies.

Abbreviations: alloSCT, allogeneic stem cell transplantation; cGvHD, chronic graft-vs-host disease; NIH, National Institutes of Health.

Data missing in the follow-up study concerning extra-genital cGvHD in one woman not included in this table.

The choice of treatment of the six newly diagnosed vulvar cGvHD was dependent on the fact that one woman had HPV16 (a carcinogenic type), one woman had been treated because of vulvar dysplasia, and the four other women had very few symptoms. The use of local immunosuppressive treatment increases the risk for infections and may reactivate HPV and augment the risk of malignancy. All six patients were referred for continued gynecologic control, and immunosuppressive treatment, should constrictions or uncomfortable symptoms appear.

The new extra-genital malignancies developed between the studies are reminders of the known increased risk of squamous cell cancers in alloSCT patients. We saw no genital malignancy. All women were taking part in the Swedish screening program for cervical cancer. The HPV infections and the risk of genital epithelial malignancies underline the importance of life-long genital control.

AlloSCT from an unrelated donor was significantly associated with less genital cGvHD in both the original and follow-up studies. Reasonably, this was due to the use of anti-thymocyte globulin in the unrelated donor setting.

5 | CONCLUSION

Rate and severity of genital, ocular, oral and other cGvHD do not alleviate over time. Absence of symptoms does not exclude genital cGvHD. Detection of oral cGvHD should raise the suspicion...
of ongoing development of cGvHD at other locations. All women require life-long gynecological and ophthalmological control after alloSCT for the detection and treatment of cGvHD.  

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

K. Sundfeldt, M.B., K. Stenberg and E.S.K. were involved in initiating the study and the study outline. The clinical investigations were done by K. Stenberg (ophthalmologist), Y.B. and M.B., (both hematologists) and E.S.K. (gynecologist). M.N. did the statistical calculations. All authors took part in the data analyses, writing and revising of this article.

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REFERENCES

1. Mohty M, Apperley JF. Long-term physiological side effects after allogeneic bone marrow transplantation. Hematology. 2011;2010:229-236.
2. Shanis D, Merideth M, Pulanic TK, Savani BN, Battiwalla M, Stratton P. Female long-term survivors after allogeneic hematopoietic stem cell transplantation: evaluation and management. Semin Hematol. 2012;49:83-93.
3. Dignan FL, Scarisbrick JJ, Cornish J, et al. Organ-specific management and supportive care in chronic graft-versus-host disease. Br J Haematol. 2012;158:62-78.
4. Corson SL, Sullivan K, Batzer F, August C, Storb R, Thomas ED. Gynecologic manifestations of chronic graft-versus-host disease. Obst Gynecol. 1982;60:488.
5. Spirya LB, Lauber MR, Soffer RJ, Antin JA. Graft-versus-host disease of the vulva and/or vagina: diagnosis and treatment. Biol Blood Marrow Transplant. 2003;9:760-765.
6. Spinnelli S, Chiodi S, Costantini S, et al. Female genital tract graft-versus-host disease following allogeneic bone marrow transplantation. Haematologica. 2003;88:1163-1168.
7. Zantomio D, Grigg AP, MacGregor L, Panek-Hudson Y, Szer J, Ayton R. Female genital tract graft-versus-host disease: incidence, risk factors and recommendations for management. Bone Marrow Transplant. 2006;38:567-572.
8. Stratton P, Turner ML, Childs R, et al. Vulvovaginal chronic graft-versus-host disease with allogeneic hematopoietic stem cell transplantation. Obst Gynecol. 2007;110:1041-1049.
9. Hirsch P, Leclerc M, Rybojad M, et al. Female genital chronic graft-versus-host disease: importance of early diagnosis to avoid severe complications. Transplantation. 2012;93:1265-1269.
10. Smith Knutsson E, Bjork Y, Broman AK, et al. Genital chronic graft-versus-host disease in females: a cross-sectional study. Biol Blood Marrow Transplant. 2014;20:806-811.
11. Smith Knutsson E, Bjork Y, Broman AK, et al. A prospective study of female genital chronic graft-versus-host disease symptoms, signs, diagnosis and treatment. Acta Obstet Gynecol Scand. 2018;97:1122-1129.
12. Lev-Sagie A, Adar-Walling E, Gumer A, Grisarui S, Avni B. Management and long-term consequences of genital graft versus host disease following hematopoietic stem cell transplantation. Bone Marrow Transplant. 2020;55:2234-2243.
13. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2006;12:138-151.
14. Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Transplant. 2006;12:375-396.
15. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Hematol Oncol Stem Cell Ther. 2012;5:1-30.
16. Carpenter PA, Kikko CL, Eld S, et al. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 ancillary therapy and supportive care working group report. Biology Blood Marrow Transplant. 2015;21(7):1167-1187.
17. Hamilton BK, Goje O, Savani BN, Majhail NS, Stratton P. Clinical management of genital chronic GvHD. Bone Marrow Transplant. 2017;52:803-810.
18. Filippovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11:945-956.
19. Jagasia MH, Greinix HT, Arora M, et al. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: II. The 2014 diagnosis and staging working group report. Biology Blood Marrow Transplant. 2015;21(3):389-401.e1.
20. Wolff D, Gerbitz A, Ayuk F, et al. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. Biol Blood Marrow Transplant. 2010;16:1611-1628.
21. Neill SM, Lewis FM. Non-infective cutaneous conditions of the vulva. In: Neill SM, Lewis FM, eds. Ridley’s the vulva. 3rd ed: Wiley-Blackwell; 2009:123-127.
22. Riera C, Deroyer Y, Marechal M. Severe vaginal chronic graft-versus-host disease (GVHD): two cases with late onset and literature review. Eur J Gynaecol Oncol. 2010;31:703-704.
23. Syrjala KL, Kurland BF, Abrams JR, Sanders JE, Heiman JR. Sexual function changes during the 5 years after high-dose treatment and hematopoietic stem cell transplantation for malignancy, with case-matched controls at 5 years. Blood. 2008;111:989-996.
24. Li Z, Mewawalla P, Stratton P, et al. Sexual health in hematopoietic stem cell transplant recipients. Clin Obst Gynecol. 2015;58:476-491.
25. Lev-Sagie A. Vulvar and vaginal atrophy: physiology, clinical presentation, and treatment considerations. Clin Obst Gynecol. 2019;58:476-491.
26. Frey Tirri B, Hausermann P, Bertz H, et al. Clinical guidelines for gynecologic care after hematopoietic SCT. Report from the international consensus project on clinical practice in chronic GVHD. Bone Marrow Transplant. 2015;50:3-9.
27. Savani BN, Stratton P, Shenoy A, Kozanas E, Goodman S, Barrett AJ. Increased risk of cervical dysplasia in long-term survivors of allogeneic stem cell transplantation-implications for screening and HPV vaccination. Biol Blood Marrow Transplant. 2008;14:1072-1075.
28. Sri T, Merideth MA, Pulanic TK, Childs R, Stratton P. Human papillomavirus reactivation following treatment of genital graft-versus-host disease. Transpl Infect Dis. 2013;15:E148-E151.
29. Rizzo JD, Curtis RE, Socie G, et al. Solid cancers after allogeneic hematopoietic cell transplantation. Blood. 2009;113:1175-1183.
30. Baron F, Labopin M, Blaise D, et al. Impact of in vivo T-cell depletion on outcome of AML patients in first CR given peripheral blood stem cells and reduced-intensity conditioning allo-SCT from a HLA-identical sibling donor: a report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2014;49:389-396.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.