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# Pediatric and Young Adult Vulvovaginal Graft-versus-Host Disease

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A B S T R A C T

Vulvovaginal graft-versus-host disease (GVHD) is an underdiagnosed and poorly recognized complication of hematopoietic stem cell transplantation (HSCT). Previous studies have reported findings restricted to predominantly adult populations. We report a case series of pediatric and young adult vulvovaginal GVHD, which was identified in 19 patients (median age, 11.8 years; range, 2.4 to 21.9 years) out of a total 302 female patients who underwent transplantation over an 8-year period at a pediatric HSCT center. The majority of patients had concomitant nongenital GVHD; only 1 patient had isolated vulvovaginal GVHD. The median time from bone marrow transplantation to diagnosis of vulvovaginal GVHD was 30 months (range, 2.3 to 97.5 months). A high percentage of the patients in our series were without vulvar or vaginal symptoms (n = 8; 42%), even though 17 patients (89%) presented with grade 3 disease based on current adult grading scales. Vulvar examination findings most frequently included interlabial and clitoral hood adhesions (89%), loss of architecture of the labia minora or clitoral hood (42%), and skin erosions or fissures (37%). Only 5 patients underwent a speculum exam, none of whom had vaginal GVHD. Examination findings of primary ovarian insufficiency (POI) can overlap with those of GVHD, and 6 patients (32%) in our cohort were diagnosed with POI. Only 1 patient was on systemic hormone replacement therapy at the time of vulvovaginal GVHD diagnosis. The majority of patients (n = 16) were treated with topical steroid therapy, with a median time to response of 43 days. Five patients (26%) had a complete response to therapy, and 10 patients (53%) had a partial response. This case series provides valuable insight into pediatric and young adult vulvovaginal GVHD and highlights the need for increased screening for vulvar disease in this population.



## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used to treat both malignant and nonmalignant conditions. Allogeneic HSCT is associated with a 30% to 70% incidence of graft-versus-host disease (GVHD), causing significant morbidity and mortality in these patients [1]. Vulvovaginal GVHD was first described in adult women and is thought to be a subtype of chronic GVHD based largely on the histological appearance of the affected tissue [2,3]. The reported incidence of vulvovaginal GVHD ranges widely, from 3% to 49%, but the true incidence is unknown, and it is thought to be severely underestimated [4,5].

Symptoms of vulvovaginal GVHD in adult women may include vulvar dryness or itching, vulvar pain, dysuria, dyspareunia or pain with tampon insertion, and postcoital bleeding [2,4]. Examination findings in adult women are described as vulvar skin erythema and pain to palpation, vulvar skin fissures or erosions, vulvar or vaginal adhesions, loss of vulvar architecture, and sclerotic changes of the vaginal mucosa; in severe cases, vaginal adhesions and sclerosis can lead to complete obstruction and hematocolpos [2,4]. Most adult women (reported rates of 30% to 100%) with vulvovaginal GVHD also have extragenital GVHD, mainly in the skin, mouth, or liver [2].

There are multiple disease scoring scales in use. In 2003, Spinelli et al. [6] published a scale using specific vulvovaginal exam findings; this scale was later modified by Stratton et al. [7] to provide greater elaboration of possible examination findings (Table 1). The 2005 National Institutes of Health (NIH) guidelines used a 0 to 3 grading scale of absent, mild, moderate, and severe disease. The 2015 NIH guidelines have been updated to incorporate specific vulvovaginal findings similar to the Stratton scale; the NIH scale also requires the presence of symptoms for all but severe disease [8].

To date, the only published descriptions of pediatric vulvovaginal GVHD are the few cases that have been included in studies of adult women. Here we describe the clinical characteristics

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**Table 1**
Stratton Scale

| Grade | Findings |
|---|---|
| 1 (Minimal) | Generalized erythema and edema of vulvar structures;<br>patchy erythema of mucosa and glandular structures of vulvar vestibule;<br>erythema around openings of vestibular (Bartholin's and Skene's) glands |
| 2 (Moderate) | Grade 1 findings, plus<br>erosions of mucosal surfaces of the vulva and fissures in vulvar folds (eg, interlabial sulci, fourchette) |
| 3 (Severe) | Grade 2 findings, plus<br>agglutination of clitoral hood,<br>introital stenosis,<br>vaginal synechiae,<br>hematocolpos or complete vaginal closure,<br>fasciitis or spasticity of levator sling |

Adapted from Stratton, et al. [7].

and management of a cohort of pediatric and young adult patients with vulvovaginal GVHD at our HSCT center.

## METHODS

This study is a case series of the clinical database of allogeneic HSCT recipients treated at Cincinnati Children's Hospital Medical Center (CCHMC) between January 1, 2008, and December 30, 2018. The study was approved by the CCHMC Institutional Review Board. All patients with transplantation follow-up at CCHMC and a diagnosis of vulvovaginal GVHD were identified, medical charts were reviewed, and data were extracted, including patient demographics, transplantation and clinical data, therapy, and overall outcomes and related complications. In this time period at our institution, it was not standard practice for all patients to undergo post-transplantation gynecologic evaluation; therefore, only patients who presented with vulvar or vaginal symptoms or whose vulvovaginal GVHD was incidentally found during evaluation for other conditions were evaluated for vulvovaginal GVHD. Nineteen patients were identified with vulvovaginal GVHD and comprised the study cohort. All patients in the cohort had undergone a single HSCT, and no patient had undergone any additional transplantations. All patients were referred by oncology to pediatric gynecology for diagnosis and comanagement of vulvovaginal GVHD.

### *Diagnosis and Grading of Vulvovaginal GVHD*

The diagnosis of vulvovaginal GVHD was made clinically based on examination findings (eg, vulvar erythema, tenderness to palpation, fissures, erosions, and/or adhesions, vaginal stenosis and/or adhesions) with or without accompanying symptoms (eg, vulvovaginal dryness, itching, or pain, dysuria, pain with tampon insertion, dyspareunia, postcoital bleeding). A chart review was performed to obtain details regarding vulvovaginal GVHD, including all vulvar and vaginal symptoms reported, treatment given, and vulvar and vaginal examination findings before and after treatment. Grading of vulvovaginal GVHD was assigned retrospectively using the Stratton scale (Table 1). Only 5 of our young patients underwent a speculum exam, and vaginal findings are described for those patients. For the remainder of our patients, only vulvar disease is described.

### *Primary Ovarian Insufficiency*

As vulvovaginal atrophy related to primary ovarian insufficiency (POI) can mimic symptoms of vulvovaginal GVHD, and because POI is also a common complication of HSCT, data were also collected regarding menarchal status, diagnosis of POI, and hormone replacement therapy (HRT) regimen. During this study period, there was no standard screening protocol for post-HSCT POI, and patients with hot flashes, menstrual irregularities, growth/pubertal delays, or abnormal laboratory test results were referred to gynecology and/or endocrinology for evaluation of POI.

### *Vulvovaginal GVHD Treatment*

Treatment regimens were prescribed based on individual provider preference, because there was no standardized treatment protocol for vulvovaginal GVHD in place at our institution during this time period. Topical steroids were the mainstay of treatment, and the choice of steroid was frequently influenced by the patient's concomitant topical treatment for nongenital GVHD, if applicable. The duration of treatment was based mainly on response to therapy; additional factors, such as the use of a maintenance regimen for highly refractory cases or the decision to continue genital steroid treatment for a patient who had responded to treatment but was about to discontinue systemic GVHD treatment, were highly individualized. Suspicion of POI also influenced the treatment approach for vulvovaginal GVHD, with the treatment regimen often involving the use of both topical estrogen and a topical steroid, with concomitant systemic HRT as indicated.

### *Vulvovaginal GVHD Response Criteria*

Complete response was defined as resolution of symptoms and resolution of any reversible examination findings. Partial response was defined as improvement or resolution of symptoms, and improvement but not resolution of reversible examination findings. Complete and partial response are distinct from Stratton scale grade; for example, a patient with improvement, but not resolution, of vulvar adhesions would continue to be a grade 3 on the Stratton scale but would be considered a partial response in this case series.

## RESULTS

### *Demographics*

The 802 consecutive allogeneic HSCT recipients treated at our institution since 2008 included 302 females. Among those, we identified 18 (5.9%) who developed vulvovaginal GVHD. An additional patient with vulvovaginal GVHD undergoing post-HSCT follow-up at CCHMC after HSCT at another institution was also included. Tables 2 and 3 present the demographic and transplantation characteristics of the cohort. The median age at the time of HSCT of the 19 patients included in the

**Table 2**
Demographics

| Characteristic | Value |
|---|---|
| Age, yr, median (IQR) | 11.8 (8.6-13.3) |
| Race (self-identified), n | |
| White, non-Hispanic, non-Arabic | 12 |
| White, Arabic | 5 |
| African American | 1 |
| Native American | 1 |
| Indication for HSCT, n (%) | |
| Malignancy | 9 (47) |
| Acute lymphoblastic leukemia | 5 |
| Acute myelogenous leukemia | 3 |
| Chronic myelogenous leukemia | 1 |
| Nonmalignant condition | 10 (53) |
| Severe combined immune deficiency | 1 |
| Dyskeratosis congenita | 2 |
| Fanconi anemia | 4 |
| Beta-thalassemia major | 2 |
| Stem cell source, n (%) | |
| Bone marrow | 15 (79) |
| Unrelated, full match | 11 |
| Related, full match | 4 |
| Peripheral blood stem cells | 3 (16) |
| Unrelated, full match | 2 |
| Related, full match | 1 |
| Umbilical cord blood | 1 (5) |
| Unrelated, full match | 1 |
| Transplantation conditioning regimen, n (%) | |
| Fully ablative | 14 (74) |
| With total body irradiation | 7 (37) |
| Reduced intensity | 5 (26) |
| Indication for genital examination, n (%) | |
| Vulvar or vaginal symptoms | 9 (47) |
| Fertility/POI evaluation/follow-up | 5 (26) |
| Incidental finding in operating room | 2 (11) |
| Menstrual management | 1 (5) |
| Nongenital GVHD | 1 (5) |

**Table 3**
HSCT Characteristics

| Patient | Diagnosis | Age at HSCT | Stem Cell Source | Related/ Unrelated Donor; Match | Conditioning Regimen | GVHD Prophylaxis | Acute GVHD Severity*/ Site | Chronic GVHD Severity*/Site | Nongenital GVHD Treatment at Diagnosis of Vulvovaginal GVHD | Nongenital GVHD Treatment During Vulvovaginal Disease Course | Nongenital GVHD Treatment at Final Follow-Up | Alive at Data Collection |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | AML | 2.4 | BM | URD; 8/8 | ATG/BU/CY | CSA/MTX | 1/skin | Extensive/skin, eyes | Pred | Pred | None | Y |
| 2 | SCID | 3.8 | BM | URD; 8/8 | Cam/Flu/Mel | CSA/Pred | None | Extensive/ MS | None | None | None | Y |
| 3 | CML | 8.7 | BM | URD; 10/10 | ATG/CY/TBI | CSA/Pred | None | Extensive/gut, liver, oral | Pred | Pred | None | Y |
| 4 | DC | 9.3 | BM | URD; 8/8 | Cam/Flu/Mel | CSA/MMF | 2/skin | Limited/ oral, skin | Rituximab, MP, MMF | Rituximab, MP, MMF, Pred, Tac | Pred, Tac, MMF | N (Pneumonia) |
| 5 | FA | 10.2 | UC | URD; 6/8 | ATG/CY/Flu/ TBI | CSA/Pred | None | Limited/skin, oral, MS | Tac | Tac, Pred, Dex po, MMF, Sirol | Pred, Dex po, MMF, Sirol | Y |
| 6 | DC | 11.9 | BM | URD; 10/10 | Cam/Flu/Mel | CSA/Pred | 2/skin | Extensive/ skin, oral | Hydrocortisone, Pred | Hydrocortisone, Pred | Hydrocortisone | Y |
| 7 | BT | 12.2 | BM | URD; 9/10 | BU/Flu/Thio | Aba/Pred | None | Extensive/ skin, lung | Infliximab, Ruxolitinib, Tac, Pred, MP, Phototherapy | Infliximab, Ruxolitinib, Tac, Pred, MP, Phototherapy | Tac | Y |
| 8 | ALL | 12.8 | PBSC | URD; 10/10 | CY/TBI | CSA/MTX | 3/skin | Limited/ oral | Bud po | Bud po, Ibru, MP, Pred | Ibru, MP, Pred | Y |
| 9 | BT | 13.2 | BM | Related; 10/ 10 | BU/Flu/Thio | CSA/Mar/Pred | None | Extensive/ oral, lung | MMF, Pred, Bud po | MMF, Pred, Bud po, Tac, Dex, Rituximab, Ibru, Phototherapy, Infliximab | Ibru, Infliximab, Pred, Dex | Y |
| 10 | AML | 13.3 | BM | URD; 10/10 | Flu/Mel | CSA/MTX | 2/skin | Extensive/ GI, skin | Infliximab, Pred, CSA, Bud po | Infliximab, Campath, Pred, CSA, Bud po | CSA, Pred, Bud po | N (primary disease) |
| 11 | ALL | 13.8 | BM | URD; 8/8 | CY/TBI | Aba/CSA/ Pred | 3/skin | Limited/ skin | Ruxolitinib, Bud po | Ruxolitinib, Bud po, Ibru, Pred | Ibru, Pred | Y |
| 12 | FA | 14.6 | BM | URD; 8/8 | ATG/BU/CY/ Flu | CSA/Pred | 2/skin | Limited/ oral | None | None | None | Y |
| 13 | ALL | 21.9 | BM | Related; 10/ 10 | CY/TBI | CSA/MTX | None | Extensive/ skin, oral | Pred, Ruxolitinib, Infliximab, Bud po | Pred, Ruxolitinib, Infliximab, Bud po | Ruxolitinib | Y |
| 14 | ALL | 12.9 | BM | Related; 8/8 | ATG/CY/TBI | MTX/Siro/TAC | None | Limited/ skin | None | None | None | Y |
| 15 | FA | 10.6 | PBSC | URD; 8/8 | ATG/BU/CY/ Flu | CSA/TCD | None | None | None | None | None | Y |
| 16 | FA | 6.5 | BM | Related; 10/ 10 | ATG/CY/Flu | ATG/CSA/MP | 3/gut | Extensive/ lung | None | None | None | N (Lung GVHD) |
| 17 | PNH | 21.3 | BM | URD; 10/10 | CAM/Flu | CSA/MP | 2/gut | None | Pred, MP, CSA | Pred, MP, CSA, Tac | None | Y |

(*continued*)

**Table 3** (*Continued*)

| Patient | Diagnosis | Age at HSCT | Stem Cell Source | Related/ Unrelated Donor; Match | Conditioning Regimen | GVHD Prophylaxis | Acute GVHD Severity*/ Site | Chronic GVHD Severity*/Site | Nongenital GVHD Treatment at Diagnosis of Vulvovaginal GVHD | Nongenital GVHD Treatment During Vulvovaginal Disease Course | Nongenital GVHD Treatment at Final Follow-Up | Alive at Data Collection |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | AML | 10.2 | BM | URD; 11/12 | BU/CY/ATG | CSA/MTX | 1/skin | Limited/ oral | Bud po | Bud po | Bud po | Y |
| 19† | ALL | 5.0 | PBSC | Related; full match | TBI-based | Unknown | None | Extensive/ skin, joints, eyes, lungs, oral | MMF, Pred | MMF, Pred, Ibru, Bud po | Pred, Ibru, Bud po | Y |

URD indicates unrelated donor; AML, acute myelogenous leukemia; SCID, severe combined immunodeficiency; CML, chronic myelogenous leukemia; DC, dyskeratosis congenita; FA, Fanconi anemia; BT, beta thalassemia; ALL, acute lymphoblastic leukemia; PNH, paroxysmal nocturnal hemoglobinuria; BM, bone marrow; UC, umbilical cord; PBSC, peripheral blood stem cells; ATG, antithymocyte globulin; BU, busulfan; CY, cyclophosphamide; Cam, Campath; Flu, fludarabine; Mel, melphalan; TBI, total body irradiation; Thio, thiotepa; CSA, cyclosporine; MTX: Methotrexate; Pred, prednisone; MMF, mycophenolate mofetil; Bud po, budesonide oral swish and spit; Dex, dexamethasone; Ibru, ibrutinib; Aba, abatacept; Mar, maraviroc; Sirol, sirolimus; Tac, tacrolimus; TCD, T cell depletion; MP, methylprednisolone.

* Severity grading per NIH consensus criteria. Chronic GVHD severity is at the time of diagnosis of vulvovaginal GVHD.

† Patient underwent HSCT at an institution outside of the country and limited records of the HSCT were available.

analysis was 11.8 years (range, 2.4 to 21.9 years). The majority (n = 17; 89%) were age <15 years at the time of transplantation. The majority of patients had a matched unrelated donor. Ten patients (53%) underwent HSCT for a nonmalignant condition.

Nine patients (47%) underwent a gynecologic examination with a subsequent diagnosis of vulvovaginal GVHD due to vulvar or vaginal symptoms. Six patients (32%) were undergoing evaluation by gynecology for POI, fertility risk assessment, or menstrual management and were incidentally found to have vulvovaginal GVHD on exam. Two patients were referred due to a new diagnosis of nongenital GVHD. Two patients were diagnosed incidentally in the operating room, including 1 during ovarian tissue cryopreservation with gynecology and 1 during a gastroenterology procedure for which gynecology was consulted intraoperatively due to findings of vulvar skin erosions during bladder catheter placement. The majority of patients (58%) were premenarchal at the time of their transplantation.

### *Diagnosis and Clinical Presentation of Vulvovaginal GVHD*

The median age at the time of diagnosis of vulvovaginal GVHD was 13.8 years (range, 3.2 to 23.0 years). The median day of diagnosis post-transplantation was 452 days. Two patients were diagnosed within 100 days after transplantation, 1 at 71 days and the other at 77 days. The longest interval from HSCT to diagnosis of vulvovaginal GVHD diagnosis was 2966 days (ie, 8.1 years).

The most frequently reported symptoms were vulvar pain, pruritus, and dysuria; 1 patient experienced severe dysuria that led to overflow incontinence due to voluntary urinary retention. Eight patients (42%) were completely asymptomatic at the time of diagnosis.

The most common examination findings were vulvar adhesions (89%), found from the labia minora to labia majora (interlabial), from the clitoral hood to the labia, and within the clitoral hood. Loss of architecture in the labia minora and clitoris was reported in 8 patients (42%). One patient had such severe changes in anatomy over time that she eventually lost any appreciable tissue of the glans clitoris and reported an inability to achieve orgasm. Seven patients had skin erosions, ranging from a single small ulcerative lesion at the posterior vaginal vestibule to diffuse erosive disease involving the labia minora and majora, clitoral hood, and vaginal vestibule. Symptoms and examination findings are summarized in Table 4, and detailed information on each case is provided in Table 5.

Of the 5 patients who underwent speculum examination, 4 were age ≥18 years at the time of the exam, and the remaining patient was age 14 years and was examined during surgery for lysis of vulvar adhesions. Of these 5 patients, 3 underwent speculum examination due to endorsement of vaginal symptoms (1 with difficulty inserting tampons, 1 with dyspareunia, and 1 with vaginal dryness). The fourth patient was the aforementioned 14-year-old who reported abnormal vaginal discharge before surgical evaluation, and the fifth patient had Fanconi anemia and started undergoing Pap smears at age 18 in accordance with current guidelines for this patient population. All patients who underwent vaginal examination had findings consistent with vaginal atrophy, but none had findings specific for vaginal GVHD.

Using the Stratton grading, only 1 patient had grade 1 disease (vulvar erythema) and 1 patient had grade 2 disease (skin excoriations) at the time of the diagnosis, with the remainder having grade 3 disease. All patients with grade 3 disease were assigned this grade owing to the presence of adhesions; 1 of

**Table 4**
Symptoms and Examination Findings at Time of Diagnosis of Vulvovaginal GVHD

| Symptoms, n (%) | | Examination Findings, n (%) | |
|---|---|---|---|
| Asymptomatic | 8 (42) | Vulvar adhesions/ agglutination | 17 (89) |
| Vulvar pain | 7 (37) | Loss of vulvar architecture | 8 (42) |
| Dysuria | 7 (37) | Vulvar skin erosions/ fissures | 7 (37) |
| Vulvar itching | 5 (26) | Vestibular pain to palpation | 2 (11) |
| Vaginal discharge | 3 (16) | Atrophic vaginal mucosa | 3 (16) |
| Urinary incontinence | 1 (5) | Abnormal vaginal discharge | 1 (5) |
| Urinary urgency/ frequency | 1 (5) | Vulvar skin hyperpigmentation | 1 (5) |
| Unknown | 1 (5) | Vulvar skin dryness/ scaling | 1 (5) |

these patients was also grade 3 due to the presence of introital stenosis. Only 2 patients with partial response had a decrease in disease grade; this was because most patients with grade 3 disease with partial response did not achieve complete resolution of vulvar adhesions.

### *Treatment*

The majority of patients received topical steroid therapy, the frequency, duration, and potency of which varied widely. Bland emollients and topical estrogen regimens were also used in some cases. By the time of the last gynecologic follow-up, 16 patients (84%) had used topical steroids, 8 patients (42%) had used topical estrogen, 1 patient (5%) had used topical tacrolimus, and 1 patient (5%) required surgical lysis of vulvar adhesions obstructing the urethral meatus.

Five of our patients achieved a complete response, all of whom received steroid therapy. Ten patients achieved a partial response, all of whom received topical steroid therapy except 1 patient who used topical estrogen alone. Among then 10 patients with a partial response, various factors affecting follow-up and response were noted. Two patients were reportedly noncompliant with treatment, 1 patient transferred care to a local gynecologist and was lost to further follow-up, and 2 patients died after achieving a partial response. Two patients chose to discontinue treatment after achieving resolution of symptoms and near, but not complete, resolution of examination findings. Over the course of the entire follow-up period, 5 patients with partial response required escalation of treatment, either by increasing the frequency or potency of initial topical therapy or by adding a secondary therapy, such as topical estrogen or topical tacrolimus.

Two patients experienced relapse after achieving a partial response. One of these patients was followed by gynecology for 9 years; systemic oral steroids for GVHD were tapered and then discontinued close to the time when relapse occurred. She showed moderate improvement with vulvar topical treatment, with remaining symptoms considered more attributable to hypoestrogenism. The second patient reported persistent nonadherence to treatment.

One patient with no response died after her second gynecology visit. One patient with unknown response transferred care to a more local provider after her initial visit with gynecology. One patient with unknown response was diagnosed in the operating room during bladder catheter placement and declined further gynecology visits.

### *Nongenital GVHD*

Only 1 patient had isolated vulvovaginal GVHD; the remaining 18 patients had either acute or chronic GVHD in other areas of the body. One of those patients had only acute GVHD of the gut, meaning that vulvar GVHD was the sole manifestation of chronic GVHD in this patient. The majority had mucosal GVHD of either the eye (n = 10) or the gastrointestinal tract (n = 2) or GVHD of the skin (n = 0), which is consistent with the adult literature. At the time of diagnosis of vulvovaginal GVHD, the majority of patients (n = 11) were receiving systemic treatment for nongenital GVHD. Agents included steroids alone for 3 patients, steroids with an immune modulator for 7 patients, and an immune modulator alone for 2 patients. Systemic treatment was used only to treat nongenital GVHD. The patients with nongenital skin GVHD sometimes used topical steroids; in this situation, the skin steroid used, if safe for the vulva, was typically applied to the vulva as well. Six patients did not require any systemic treatment for nongenital GVHD; these patients all had grade 3 vulvar GVHD and exhibited a variety of treatment responses (2 with unknown response, 2 with partial response, and 2 with complete response). The 6 patients who had a complete response to vulvar GVHD treatment received various nongenital systemic treatments for GVHD, including steroids, cyclosporine, and immunologic agents. Two patients did not receive systemic treatment for GVHD.

### *POI*

Of the 8 patients who were menarchal before HSCT, 6 had known or suspected POI at the time of diagnosis of vulvovaginal GVHD. Three of these 6 patients were highly suspicious for POI, but no formal diagnosis was made, because they were less than 1 year out from transplantation and lingering chemotherapy effects may affect serum gonadotropin levels [9]. Two of the 6 patients were diagnosed with POI at the time of diagnosis of vulvovaginal GVHD; 1 was started simultaneously on systemic HRT along with treatment for vulvar GVHD, and the other deferred HRT until further height attainment was achieved. One patient was previously diagnosed with POI and established on systemic HRT at the time of vulvovaginal GVHD diagnosis.

Most of the patients (n = 11) were premenarchal at the time of transplantation. At diagnosis of vulvovaginal GVHD, 8 of these patients remained premenarchal; 3 of these patients were diagnosed with POI and would not be expected to ever achieve spontaneous menarche. Three patients who had been menarchal at the time of HSCT had POI at the time of diagnosis of vulvovaginal GVHD and were completely amenorrheic (patients 9, 11, and 13). Throughout the course of gynecologic follow-up, a total of 9 patients (47%) had either confirmed or suspected POI (5 who had been postmenarchal and 4 who had been premenarchal at the time of transplantation). Five patients are currently within normal limits of pubertal development, including 2 patients who are premenarchal and remain prepubertal within normal limits for age and 3 who are postmenarchal who continue to have spontaneous menses (only 1 of whom was premenarchal at the time of transplantation).

## DISCUSSION

To our knowledge, this is the first case series describing vulvovaginal GVHD in a pediatric and young adult population. Although our study population is small and may limit our ability to identify differences among populations, valuable patterns did become apparent, including a high rate of asymptomatic patients,

**Table 5**
Characteristics at the Time of Diagnosis of Vulvovaginal GVHD

| Patient | Age, yr | Menstrual Status | POI | Days Post-HSCT of Nongenital cGVHD Diagnosis | Days Post-HSCT of Vulvovaginal GVHD Diagnosis | Symptoms Present | Stratton Scale Grade | Response | Time to Response | All Treatments Received |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.2 | No | No | 287 | 287 | Yes; vulvar pruritus, dysuria | 3 | PR with relapse | 642 | Beclamethasone 0.05%, tacrolimus topical, estradiol cream, betamethasone |
| 2 | 12.1 | Yes | No | 1279 | 2966 | No | 3 | U* | NA | Betamethasone cream |
| 3 | 9.9 | No | No | 317 | 452 | Yes; vulvar pain/pruritus, dysuria | 3 | PR | 43 | Betamethasone dipropionate ointment 0.1% |
| 4 | 9.5 | No | No | 34 | 71 | Yes; vulvar pain, dysuria | 2 | PR | 37 | Triamcinolone 0.1% ointment, hydrocortisone 1% ointment, estradiol cream |
| 5 | 15.2 | Yes | No | 1740 | 1811 | Yes; abnormal vaginal discharge | 3 | PR with relapse | 843 | Triamcinolone 0.1% ointment, clobetasol 0.05% ointment, estradiol cream |
| 6 | 13.8 | Yes | No | 598 | 690 | Yes; vulvar pain/pruritis, abnormal vaginal discharge, dysuria, urge urinary incontinence | 3 | PR | 379 | Clobetasol 0.05% cream, triamcinolone 0.1% ointment, estradiol cream, surgical lysis of adhesions |
| 7 | 13.8 | No | Yes | 291 | 600 | Yes; vulvar pain/pruritus, abnormal vaginal discharge, dysuria | 3 | CR | 23 | Clotrimazole, betamethasone 0.5% ointment |
| 8 | 13.4 | Yes | Suspected | 222 | 226 | No | 3 | CR | 127 | Estradiol cream |
| 9 | 14.1 | No | Yes | 276 | 313 | Yes; vulvar pain, dysuria | 3 | CR | 28 | Triamcinolone 0.1% ointment, betamethasone 0.1% ointment |
| 10 | 13.7 | No | No | 130 | 132 | Yes; vulvovaginal pain | 1 | NR | NA | Betamethasone 0.1% ointment, betamethasone 0.05% ointment |
| 11 | 15.4 | No | Suspected | 280 | 593 | No | 3 | NA† | NA | None |
| 12 | 16.5 | Yes | No | 193 | 677 | No | 3 | PR | 613 | Betamethasone 0.05% ointment, estradiol cream |
| 13 | 23.0 | No | Suspected | 318 | 381 | No | 3 | CR | 352 | Triamcinolone 0.1% ointment, estradiol cream |
| 14 | 19.8 | No | Yes | 293 | 2453 | No | 3 | PR | 42 | Clobetasol 0.05% ointment, estradiol cream |
| 15 | 17.0 | Yes | No | No cGVHD | 2286 | No | 3 | CR | 345 | Clobetasol 0.05% ointment |
| 16 | 7.2 | No | No | 395 | 290 | Yes; vulvar pain/pruritus, dysuria | 3 | PR | 14 | Clobetasol 0.05% ointment |
| 17 | 21.6 | Yes | No | No cGVHD | 77 | Yes; urinary frequency/hesitancy/ urgency | 3 | CR | 5 | Betamethasone 0.05% ointment |
| 18 | 11.3 | U | U | 360 | 376 | U | 3 | U | NA | None (declined) |
| 19 | 8.2 | No | No | 730§ | 1159 | No | 3 | PR | 12 | Triamcinolone 0.1% ointment |

NR indicates no response; PR, partial response; CR, complete response; NA, not applicable; U, unknown (patient diagnosed intraoperatively during nongynecologic procedure, declined follow-up with gynecology).

* Patient lives out of state, transferred care to local gynecologist.

† Patient with nonacute findings, no treatment indicated.

§ Date is an approximation; patient received HSCT at institution outside of the country and limited records from HSCT available

**Table 6**
Pediatric Vulvar GVHD Grading Scale

| Grade | Signs |
|---|---|
| 1 | Erythema of vulvar structures, with or without symptoms |
| 2 | Mild adhesive disease (thin adhesions);<br>presence of scattered skin erosions/fissures |
| 3 | Moderate adhesive disease (thick/diffuse adhesions, distorting architecture);<br>scattered skin erosions or fissures |
| 4 | Severe adhesive disease (partial or complete occlusion of urethra and/or vaginal opening); diffuse skin erosions or fissures;<br>loss of architecture of vulvar structures |

advanced (mainly grade 3) disease at the time of diagnosis, and several vulvar examination findings that were distinctive, although not pathognomonic, for GVHD.

Forty-two percent of our patients were asymptomatic at the time of diagnosis. This may be due to a misunderstanding and underreporting of genital symptoms in pediatric patients, as well as provider bias limiting questioning of genital symptoms/concerns in this population. Furthermore, adolescent and young adult patients are less likely to undergo discussion of sexual health and sexual dysfunction concerns with their providers, leading to underreporting [10]. Overall, the large number of asymptomatic patients may indicate that pediatric patients are at greater risk than adult women for delayed or missed diagnosis. The adult literature reports few, if any, women asymptomatic at the time of diagnosis; however, many adult case series are composed of patients who were referred based on the presence of gynecologic symptoms, resulting in potential selection bias. The true incidence of vulvovaginal GVHD is unknown in both pediatric and adult populations but is thought to be severely underestimated. In this series, convenience sampling was used, which likely underestimated the true incidence. In an adult series of 32 women, the authors noted that between 2000 and 2008, only 6 patients in their institution were diagnosed with vulvovaginal GVHD; however, in 2009 to 2010, when the institution began systematically seeing all women for gynecologic examinations at around 100 days post-transplantation, 26 patients were identified.[5]Because of these data, as well as the findings in our present series, our institution now supports routine screening for vulvovaginal GVHD for all female patients.

Examination findings for vulvovaginal GVHD may overlap with those for POI but did not appear to overlap with other vulvar dermatoses. Labial adhesions can be a common finding in healthy prepubertal adolescents but are usually seen as fusion of the labia minora in the midline, thought to be caused by vulvar inflammation in a low-estrogen environment; these midline labial minora adhesions were not found in any of our patients [11]. Adhesions were present in 89% of our patients but were consistently noted to be interlabial (between the labia minora and labia majora) or involving the labia to the clitoral hood. Furthermore, because 42% of the patients had a loss of architecture of the labia minora or clitoral hood, we postulate that these adhesions are likely an earlier finding in a progressive pathway. The adult literature reports a lower rate of vulvar adhesions, ranging from 10% to 18%. Many adults have been found to have vaginal adhesive disease (55% in 1 series), whereas vaginal adhesions were not present in any of our 5 patients who underwent speculum examination. Vulvar skin findings, such as excoriations and fissures, can overlap with vulvar dermatoses, but other findings more specific to those diseases (eg, hypopigmentation of lichen sclerosis) were not found in patients with vulvar GVHD.

In particular, POI is the most frequently cited confounding diagnosis for vulvovaginal GVHD. In the adult literature, patients are often treated empirically with topical or systemic estrogen to rule out any component of POI-related vulvovaginal findings before initiation of treatment for genital GVHD [3]. However, this might not be a feasible option in the pediatric population, in which confounding factors such as pubertal development, bone health, and final adult height must be considered when determining initiation of hormone replacement. Vulvar symptoms of POI may include atrophy, fissures, erythema, and pain; however, these are more frequently limited to the vulvar vestibule, with atrophy the most common finding within the labial or clitoral structures. Loss of architecture of vulvar structures, which in our patients was confined to loss of the labia minora and clitoris, is not a common feature of POI, although it can occur. In addition, a diagnosis of POI is not applicable to our younger prepubertal patients.

Our pediatric and young adult population had a high proportion of patients who had advanced to grade 3 disease by the time of diagnosis, similar to that in adults. This could represent failure of timely diagnosis, due to either initially asymptomatic disease or based on other factors that may contribute to delayed diagnosis, as discussed above. It may also be that the current grading system is inappropriate for our patients, because adhesions were present in almost all patients, representing a grade 3 finding that was ultimately reversible for most of our patients.

To address this, we propose a revised pediatric vulvar GVHD grading scale (Table 6). The revised 4-point scale includes vulvar examination findings only, because most pediatric patients will not tolerate vaginal examinations without sedation, and subsequent treatment of vaginal findings would be limited, as discussed below. In instances where vaginal examinations are feasible (ie, tolerant patient or those undergoing anesthesia), tested and validated scales are available. Our revised scale also may be used for asymptomatic patients. We removed vestibular gland-specific tenderness, because it is not clear that this is a distinctive finding in vulvar GVHD, and it is often very difficult to assess for point-specific areas of vulvar pain in young patients. Agglutination and/or adhesions, previously grade 3 findings, are separated into the severity of adhesive disease, which both allows patients with minimal adhesive disease to be classified with a lower grade, but also allows for differential grading of changes in severity. This may aid the classification of disease progression or response to treatment.

This study has several limitations. The small sample size precluded our ability to make statistical comparisons between our population and adult populations, or to compare groups within our pediatric population (eg, premenarchal or postmenarchal patients). In addition, owing to the study's retrospective nature, patients were followed at varying intervals and for varying durations postdiagnosis, and symptom evaluation and treatment regimens were not standardized. This obscures any conclusions regarding management and response to treatment. None of our patients had previous abnormal Pap smear or gynecologic examination findings, none had concomitant vulvar or vaginal infections, and none reported a history of vulvovaginal disease; however, these data were not consistently collected or reported in the charts, so it is possible that some patients had risk factors predisposing them to vulvovaginal disease that were not identified. In addition, patients with POI without a diagnosis of vulvar GVHD may be a useful

comparison group, but it was not consistent practice to screen for POI in all female patients post-HSCT in our institution during this study period, and those who were diagnosed with POI but who reported no vulvovaginal symptoms rarely had a vulvar examination. Although vulvovaginal GVHD does have distinct findings compared with POI, as discussed above, this represents a limitation of our study, and future studies should address vulvar symptoms and examination findings in patients with POI who do not have vulvovaginal GVHD. Finally, the incidence of vulvovaginal GVHD was very likely underestimated in our cohort, because routine screening was not done during this period.

In our population, vulvar GVHD was described in detail, but vaginal GVHD disease status remains largely unknown. Only 5 patients in our cohort underwent a speculum examination, all with findings of atrophic vaginal tissue but without any findings specific to vaginal GVHD. For most of our young patients, vaginal examination could be feasibly accomplished only either by blind passage of a Q-tip into the vagina or by vaginoscopy under sedation. From our perspective, the medical and emotional risks of a vaginal exam in a young patient are outweighed by the lack of a clear indication for the exam and paucity of treatment options if disease is found. Our young patients, unless sexually active or having difficulty with tampon insertion, were not reporting vaginal symptoms. Although asymptomatic vaginal disease in a young patient could have significant future implications, the natural history of vulvovaginal GVHD in young patients is largely unknown. Immediate management would also be limited, mainly to lysis of adhesions under sedation. Pediatric patients, if not sexually active and not using tampons, would be unlikely to participate in vaginal dilations or intravaginal treatment applications as described in the adult literature for treatment of vaginal disease. Future research may indicate a need for more aggressive treatment of vaginal disease even in young, asymptomatic patients, but at this time we do not routinely perform vaginal exams on pediatric patients with vulvar GVHD.

The diagnosis of vulvovaginal GVHD is clinical in both the pediatric and adult populations. Biopsies in adult studies reveal histology that is typical for chronic GVHD, but biopsy analysis is not required for the diagnosis of GVHD. Vulvar biopsies in pediatric patients can be emotionally traumatic and often require sedation, so routine biopsies were not done. Notably, 2 of our patients were diagnosed with vulvar GVHD very early in their post-HSCT time course (patients 4 and 17, diagnosed at 71 days and 77 days post-HSCT, respectively). These patients had no previous history of vulvovaginal pathology or POI; both were diagnosed with preceding nongenital acute GVHD and had no or limited nongenital chronic GVHD. In addition, acute GVHD is a known risk factor for all forms of chronic GVHD, and thus it is striking that 10 of the 19 patients (53%) in this series had either no acute GVHD or grade I acute GVHD. These observations suggest that perhaps our understanding of vulvovaginal GVHD as a form of chronic GVHD is incomplete.

At our institution, further studies are planned to clarify appropriate screening, diagnosis, and management protocols. For now, we have incorporated the preliminary findings of this case series into practice management changes that are aimed to reduce the risk of underdiagnosis. For female patients post-HSCT who present to the transplantation clinic for follow-up visits, screening checklists now include questions regarding vulvovaginal complaints (eg, dysuria, vulvar or vaginal pain and/or itching, abnormal vaginal discharge) with positive responses triggering a vulvar exam (with or without a vaginal examination). Post-HSCT "day 100" visits now include vulvar exams, even for asymptomatic patients. Gynecology referrals are made for any patient with exam findings concerning for vulvovaginal GVHD or who have a new diagnosis of nongenital GVHD.

This cohort provides valuable insight into pediatric vulvovaginal GVHD—namely, that young patients are often asymptomatic, that distinctive exam findings may help differentiate vulvovaginal GVHD from other pediatric vulvar dermatoses or POI, and that exam findings in many patients were reversible with steroid treatment. In addition, we found that the currently available adult grading scales for vulvovaginal GVHD are difficult to apply to our pediatric population and developed a revised pediatric vulvar GVHD grading scale. Larger, prospective studies are needed to evaluate treatment regimens and establish clinical care guidelines for pediatric vulvovaginal GVHD.

## DECLARATION OF COMPETING INTEREST

There are no conflicts of interest to report.

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