Published in final edited form as:

J Low Genit Tract Dis. 2017 April ; 21(2): 157–160. doi:10.1097/LGT.0000000000000288.

Early Diagnosis of Labial Fusion in Women after Allogeneic Hematopoietic Cell Transplant Enables Outpatient Treatment

Claire Scrivani, BS¹, Melissa A. Merideth, MD^{2,3}, Tajana Klepac Pulanic, MD⁴, Steven Pavletic, MD⁵, Richard W. Childs, MD¹, Matthew M. Hsieh, MD^{1,6}, and Pamela Stratton, MD⁷

¹Hematology Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD ²Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD ³Intramural Office of Rare Diseases, Office of the Director, National Institutes of Health, Bethesda, MD ⁴Community Health Center Zagreb East, Department of Gynecology, Svarcova 20, Zagreb, Croatia 10000 ⁵Graft-versus-Host and Autoimmunity Unit, Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland ⁶Molecular and Clinical Hematology Branch, National Institute of Diabetes and Digestive and Kidney Diseases National Institutes of Health, Bethesda, MD ⁷Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

Abstract

Objective—To describe the presentation and successful treatment of labial fusion in women after allogeneic hematopoietic cell transplantation (HCT).

Methods—During routine post-transplant gynecologic evaluation, labial fusion was identified in five female patients. Clinical data were collected regarding underlying disease, transplant regimen, genital symptoms, systemic sites of chronic graft-versus-host disease (cGvHD) and treatment, and follow-up.

Results—At presentation, women had a median age of 40 years (range: 35–50) and were 23 months to eight years post-HCT. Four of five patients with labial fusion had evidence of active cGvHD; three had severe sclerotic cGvHD, one had bronchiolitis obliterans. One had rheumatoid arthritis and had recently stopped taking etanercept, but had no sites of cGvHD. One patient presented with only a pinpoint opening for passage of urine. Her complete labial fusion was lysed under general anesthesia. Three of four others presented with dyspareunia. Their labia were fused between the clitoris and urethra narrowing the vaginal opening without obstructing the urethra. These labial adhesions were successfully lysed during an office procedure. Once the labial mucosa healed, patients applied topical clobetasol and estrogen to prevent reagglutination. On follow-up, one month to one year later, all women were significantly improved.

Corresponding Author: Pamela Stratton, MD, Bldg. 31; Room B2B32, National Institutes of Health, Bethesda, MD 20892-1109, ps79c@nih.gov, Phone number: 301-435-4449, Fax: 301 480-2973.

IRB approved clinical trials and Clinical trials.gov identifiers: 03-H-0170 (NCT00061568), 10-CH-0083 (NCT01092195), 11-H-0068 (NCT01287078) and 12-C-0197 (NCT01688466)

The authors have no conflict of interest

Conclusions—These patients highlight the importance of asking women who have undergone allogeneic HCT, especially those with severe cGvHD, about dyspareunia and dysuria. Those with genital symptoms warrant referral to a gynecologist. These cases illustrate that labial fusion, if diagnosed early enough, may be treated successfully with an office procedure and medical therapy.

Keywords

labial fusion; chronic graft-versus-host-disease; dyspareunia; lichen sclerosis

Vulvovaginal chronic graft-versus-host-disease (cGvHD) is an important, yet under-recognized site of cGvHD that affects over a quarter of women who survive after allogeneic hematopoietic stem cell transplantation.¹ Labial fusion, a rare form of vulvovaginal cGvHD, may also be seen in other settings like lichen planus and lichen sclerosis.² Labial fusion may compromise quality of life due to difficulties with urination and dyspareunia. We describe the successful treatment of five cases of labial fusion occurring after matched allogeneic peripheral blood hematopoietic cell transplantation (HCT).

METHODS

Women with labial fusion were prospectively identified while participating in an NIH Intramural clinical trial that included assessment of genital cGvHD. Clinical data were collected regarding underlying disease, transplant regimen, time of labial fusion diagnosis post-HCT, genital symptoms, systemic sites of cGvHD and treatment, and follow-up. All patients had labial fusion that was lysed under general anesthesia (Case 1) or an outpatient setting following the steps in Table 1 (all other cases). Topical skin adhesive (Dermabond™) was applied to the denuded labial surfaces to maintain labial separation during healing (Figure 2C). Consent for publication was obtained from all patients. Each author was an employee in the NIH Intramural Research Program.

RESULTS

At presentation with labial fusion 23 months to eight years post-HCT, women ranged in age from 35 to 50 years. Clinical details are presented in Table 2. Four of five patients had active cGvHD; three had severe sclerotic cGvHD, one had bronchiolitis obliterans. One patient with rheumatoid arthritis had no sites of cGvHD and had recently stopped taking etanercept. On follow-up, all women were significantly improved and, in the two who were sexually active, dyspareunia resolved.

Case 1

Within one year after HCT, Case 1 developed severe cGvHD including esophageal strictures, oral stenosis and trismus. Concurrent vulvovaginal cGvHD was treated with topical clobetasol and estrogen, then topical tacrolimus. Five years post-transplant, she developed labial fusion and vaginal scarring. At surgery, labial fusion was treated, but lysis of vaginal adhesions was not undertaken.

By eight years post-transplant, Case 1 had managed her extensive systemic cGvHD with tacrolimus and sirolimus, over 75 extracorporeal photophoresis treatments, 31 esophageal

dilatations, and steroids. Esophageal cGvHD restricted her oral intake and a PEG tube provided her nutrition.

Case 1 presented with worsening difficulty with micturition, vulvar fullness and inability to have intercourse; she had only a pinpoint opening for passage of urine (Figure 1A). Her complete labial fusion and vaginal adhesions were lysed under general anesthesia (Figure 1B) and conjugated estrogen cream was placed in the vagina. One month later, some labial reagglutination and vaginal scarring had occurred (Figure 1C).

Case 2

After HCT, Case 2 developed ocular and vulvar cGvHD while immunosuppression was tapered. She was later diagnosed with bronchiolitis obliterans. With care from both a gynecologist and dermatologist, she was given oral contraceptive pills that were stopped after seven months for elevated liver function tests, a topical antifungal medication, estradiol vaginal tablets, topical clobetasol and compounded estrogen.

At 28 months after transplant, Case 2 presented with vaginal dryness and dyspareunia. Labial fusion was not observed on initial examination but was noted with spreading the labia (Figure 2A, 2B) and was easily lysed (Table 1 and Figure 2C). On examination two months later, her labial fusion and dyspareunia resolved.

Case 3

One year after HCT, Case 3 developed sclerotic chronic GvHD which became progressive over her body. About two years post-transplant, she presented with vulvar fullness, dyspareunia, and vulvar scarring. Labial fusion was lysed in the outpatient clinic. On examination one year later, her labial fusion and dyspareunia was resolved.

Case 4

After HCT, Case 4 developed liver cGvHD and was treated with extracorporeal photopheresis. She later developed focal sclerodermic changes which became extensive and ocular cGVHD which was treated with Boston scleral lens. Five years post-HCT, she developed severe vulvovaginal GvHD with vagina scarring for which she used dilators with topical clobetasol and estrogen. On presentation, her labia minora were resorbed causing some vulvar distortion and the labia minora were fused below the clitoris to the urethral opening. Labial fusion was lysed in the outpatient clinic. On examination over several months, the labial fusion remained resolved.

Case 5

In contrast to cases 1–4, Case 5 did not have any history of non-gynecologic sites of cGvHD and was maintained on low-dose immunosuppression. Four years after HCT, Case 5 presented with labial fusion above the urethra to the base of the clitoris and arcuate vaginal scarring. She had rheumatoid arthritis and had recently stopped taking etanercept. She was currently not sexually active and was unaware of her gynecological findings. Case 5 refused to undergo biopsy to distinguish vulvovaginal GvHD from lichen sclerosis or lichen planus,

but did consent to have these adhesions lysed in the outpatient clinic. On follow up, the labial adhesions were improved.

DISCUSSION

Labial fusion is recognized as a rare form of vulvovaginal cGvHD³ with the potential to interfere with voiding, preventing sexual intimacy, and impair overall quality of life. One patient presented with complete labial fusion which significantly affected micturition and required expeditious surgical intervention. The other patients had labial fusion that might be overlooked on physical exam because it occurred in the area above the urethra. Nonetheless, this labial fusion significantly narrowed the introitus but did not compromise urination and resulted in dyspareunia among those who were sexually active. In these other patients, diagnosis and an office procedure combined with local medical therapy resolved dyspareunia and improved their clinical findings.

These cases of labial fusion all occurred in women post-HCT and four of five cases occurred in the setting of other severe cGvHD, mostly sclerotic cGvHD. We had previously reported an association between severe genital cGvHD, usually vaginal scarring, and sclerotic cGvHD.⁴ However, other conditions besides cGvHD may be associated with labial fusion, as evidenced by Case 5. This patient was without prior history, current signs or symptoms of cGvHD prior to noting labial fusion on routine examination, a finding that had not been present on examination one year earlier. She had rheumatoid arthritis and had recently stopped using etanercept. In patients with autoimmune diseases as in her case, the diagnosis of lichen sclerosis (LS) or lichen planus (LP) is possible.⁵ LS, LP and cGvHD can cause vacuolization and separation of the basal layer of mucosal cells in the vulva that can lead to labial fusion, making it difficult to distinguish among these diagnoses either histologically or clinically.⁶ While biopsy might have aided in this diagnosis, treatment by lysing adhesions and using topical steroids and estrogen would be similar. Therefore, a patient's history and physical examination are important in considering the association of labial fusion with other diseases, like cGvHD or other autoimmune diseases.

In addition to having severe sclerotic cGvHD and rheumatoid arthritis, these patients had other factors that are associated with labial fusion. All but Case 5 were hypogonadal post-transplant. Development of labial fusion may be more common in hypoestrogenic females as seen in prepubescent girls¹. Pelvic irradiation, commonly associated with scarring, was used in only one woman and thus does not appear to be an important factor in these cases.

Over a quarter of women who survive after allogeneic HCT develop vulvovaginal GvHD^{1,7}. Vulvovaginal GvHD is more common in women receiving peripheral blood HCT compared to bone marrow transplantation and typically has an insidious presentation occurring weeks to as long as eight years post-transplant.^{4,8,9} The symptoms of vulvo-vaginal burning, irritation, dyspareunia and signs of patchy erythematous inflammation and later ulceration are early clinical features of vulvar cGvHD. If left untreated, these symptoms may evolve to vulvar adhesions.^{4,9} In this cohort, labial adhesions developed despite prior systemic and sometimes local treatment with estrogen or immunosuppressive therapy. When detected

early, an office procedure followed by topical medical therapy led to significant improvement in all patients.

Coordination of care among transplant- physicians, gynecologists, and primary care providers is critical to recognizing and quickly treating any genital signs and symptoms. These patient histories highlight the importance of asking women who have undergone allogeneic HCT, especially those with severe cGvHD, about dyspareunia and pain with urination. Those with genital symptoms warrant referral to a gynecologist skilled in evaluation and treatment of women post-HCT. Labial fusion may be suspected by clinical symptoms but is easily recognized on pelvic examination. These cases illustrate that labial fusion following allogeneic HCT, if diagnosed early enough, may be treated successfully with an office procedure and medical therapy.

Acknowledgments

Sources of financial support: Intramural Research Program of the National Institutes of Health Clinical Center, National Heart Lung and Blood Institute, National Human Genome Research Institute, National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Abbreviations and Acronyms

cGvHD	chronic graft-versus-host disease
HCT	hematopoietic cell transplantation
IRB-approved	institutional review board-approved
LP	lichen planus
LS	lichen sclerosis
PEG tube	percutaneous endoscopic gastrostomy tube

References

1. Spinelli S, Chiodi S, Costantini S, et al. Female genital tract graft-versus-host disease following allogeneic bone marrow transplantation. *Haematologica*. Oct; 2003 88(10):1163–1168. [PubMed: 14555313]
2. Bradford J, Fischer G. Surgical division of labial adhesions in vulvar lichen sclerosus and lichen planus. *J Low Genit Tract Dis*. Jan; 2013 17(1):48–50.
3. Norian JM, Stratton P. Labial fusion: a rare complication of chronic graft-versus-host disease. *Obstet Gynecol*. Aug; 2008 112(2 Pt 2):437–439. [PubMed: 18669755]
4. Stratton P, Turner ML, Childs R, et al. Vulvovaginal chronic graft-versus-host disease with allogeneic hematopoietic stem cell transplantation. *Obstet Gynecol*. Nov; 2007 110(5):1041–1049. [PubMed: 17978118]
5. Fistarol SK, Itin PH. Diagnosis and treatment of lichen sclerosus: an update. *Am J Clin Dermatol*. Feb; 2013 14(1):27–47. [PubMed: 23329078]
6. Khudhur AS, Di Zenzo G, Carrozzo M. Oral lichenoid tissue reactions: diagnosis and classification. *Expert Rev Mol Diagn*. Mar; 2014 14(2):169–184. [PubMed: 24524807]
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 Transpl*. Oct; 2006 38(8):567–572.

8. Flowers ME, Parker PM, Johnston LJ, et al. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood*. Jul 15; 2002 100(2):415–419. [PubMed: 12091330]
9. Spiryda LB, Laufer MR, Soiffer RJ, Antin JA. Graft-versus-host disease of the vulva and/or vagina: diagnosis and treatment. *Biol Blood Marrow Transplant*. Dec; 2003 9(12):760–765. [PubMed: 14677115]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Figure 2.

Table 1

Office procedure for lysis of labial adhesions

1	Cleanse the affected area with betadine
2	Apply 3–4% lidocaine cream to the area of labial fusion.
3	Instill 1% lidocaine (total of 2 to 3 cc) into the subcutaneous tissue of the fused labia
4	Incise raphe/scar with iris scissors
5	Gently spread apart the area of fused labia to restore the normal anatomy between the clitoris and urethra
6	Stop areas of bleeding with silver nitrate sticks
7	Apply topical skin adhesive (Dermabond™) to the denuded labial surfaces
8	Hold the area open until the skin adhesive dries to maintain labial separation during healing

After the labia heal, a pea-sized amount of topical clobetasol ointment and a half-inch of topical conjugated estrogen cream were applied to the affected area by the patient daily for several weeks to prevent reagglutination. When the mucosa was no longer inflamed and appeared normal, usually about four to six weeks, the patient tapered and then stopped treatment.

TABLE 2

Transplant Characteristics and GvHD Diagnosis and Treatment

Patient No.	Indication for transplant	HCT cell type; Donor type; HL/A match; Donor gender	Conditioning regimen, initial GvHD prophylaxis	Acute GvHD	Time post-HCT	GvHD prophylaxis at labial fusion diagnosis	Other sites of GvHD	Symptoms	Follow Up
1	Hodgkin lymphoma then Myelo-dysplastic syndrome	Peripheral blood; Related; 6/6 Match; Brother	Unknown	Skin, mouth	8 yrs	Sirolimus and steroids	Sclerotic skin eyes, mouth, esophageal strictures; vaginal scarring	Difficulty with micturition, inability to have intercourse	1 mo; mild labial reagglutin-ation; some vaginal scarring
2	Acute Myelogenous Leukemia	Peripheral blood; Related; 10/10 Match; Sister	Busulfan, Cytoxan conditioning	None	2 yr 4 mo	None	Bronchiolitis obliterans	dyspareunia	2 mo; Labial fusion and dyspareunia are resolved
3	Ewing sarcoma then Acute MyelogenousLeukemia	Peripheral blood; Unrelated; 10/10 Match; Male	Cytoxan, TBI conditioning; tacrolimus	Skin responsive steroids	1 yr 11 mo	Tacrolimus cellcept, prednisone	Sclerotic skin	dyspareunia	1 yr; Labial fusion and dyspareunia are resolved
4	Myelofibrosis	Peripheral blood; Related; 10/10 Match; Sister	Fludarabine, busulfan conditioning; Tacrolimus, methotrexate	Mouth, skin	5 yr 9 mo	Tacrolimus prednisone, pomalidomide	Sclerotic skin, eyes, mouth, joint and vaginal scarring	dyspareunia	3, 4, 7, 11mo Labial fusion is resolved; vaginal scarring
5	Sickle cell anemia ¹	Peripheral blood; Related; 10/10 Match; Sister	300 rads TBI, campath conditioning; sirolimus alemtuzumab	None	4 yrs	Sirolimus	None, vaginal scarring	None	2 weeks and 8 mo; improvement in labial reagglutin-ation; mild vaginal scarring

¹ Patient also had severe Rheumatoid arthritis; TBI is Total body irradiation