Vulvovaginal Graft-Versus-Host Disease

Rachel I. Kornik, MD[a,*], Alison S. Rustagi, PhD[b]

KEYWORDS

• Graft-versus-host disease • Vulvovaginal • Genital
• Hematopoietic stem cell transplant

KEY POINTS

- Genital chronic graft-versus-host disease (cGVHD) is an underrecognized complication of hematopoietic stem cell transplantation (HCT) that has a significant impact on quality of life.
- Early diagnosis is essential to optimize treatment outcomes and avoid severe sequelae, such as anatomic disfigurement, sexual dysfunction, and pain.
- Patients should be educated on signs and symptoms of cGVHD and examined approximately 3 months after transplant to improve early detection.
- Treatment focuses on local immunosuppressive therapy with topical steroids, topical tacrolimus, and dilators to maintain vaginal patency. Addressing estrogen deficiency may be an important adjunct.
- Female recipients of allogeneic HCT are at higher risk of condylomas and cervical dysplasia and neoplasia. Performing cervical cytology screening may be prudent before and after HCT.

INTRODUCTION

There are approximately 8000 allogeneic hematopoietic stem cell transplants (HCT) performed in the United States each year, to treat a variety of malignant and nonmalignant conditions. This number has steadily increased over the past 3 decades and is likely to continue to increase,[1] requiring clinicians to become familiar with the issues facing this complex patient population.

PATHOPHYSIOLOGY

Chronic graft-versus-host disease (cGVHD) occurs when immunocompetent donor T cells recognize host tissue as foreign. This is a double-edged sword, because

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[a] Department of Dermatology, University of Wisconsin, 1 South Park Street, 7th Floor, Madison, WI 53715, USA; [b] UCSF School of Medicine, 505 Parnassus Avenue, San Francisco, CA 94143, USA
* Corresponding author.
E-mail address: rkornik@dermatology.wisc.edu

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patients with cGVHD may have a reduced relapse rate, owing to graft-versus-tumor effect, but severe cGVHD has a profound effect on quality of life and mortality risk.[2,3] The pathophysiology of cGVHD is a complicated multi-step process. There is still much to be elucidated as current research points out. The sequence is likely triggered by the conditioning regimen which damages host tissue, particularly the gastrointestinal system, allowing the translocation of bacteria. The result is the release of cytokines and T-cell activation. The activated T-cells contribute to a pro-inflammatory cascade leading to dysregulation of both cell-mediated and humoral immunity. T-cell mediated toxicity and inflammation result in end-organ damage and fibrosis that is variable among patients.[4,5]

EPIDEMIOLOGY

GVHD is classified as acute or chronic based on clinical features rather than the temporal relationship to transplant.[6] Because there is very limited literature on acute GVHD affecting the genitals, this section focuses on cGVHD.

Chronic GVHD is the most common complication facing HCT patients with 60% to 70% affected at some point during their transplant course.[7,8] This number is increasing in frequency owing to a variety of factors: the increase in use of HCT, older recipient age, improvements in supportive care leading to increased survival, and more common use of peripheral blood stem cell grafts.[9,10] Chronic GVHD is the leading cause of nonrelapse mortality 2 years after transplantation. It also contributes to functional impairment, decreased mental health, and pain, resulting in a significant reduction in quality of life.[3,11]

The skin and mucous membranes are the most common sites of involvement followed by the liver and the eyes. Other less frequent sites include the gastrointestinal tract, lung, esophagus, female genital tract, male genitalia, and joints.[5,7]

The reported incidence of genital cGVHD varies according to study with a range of 19% to 52% of HCT recipients affected. Symptoms may be overlooked by patients and physicians alike, and are often misdiagnosed.[12,13] It has severe consequences for a woman's quality of life, including sexual health and interpersonal relationships, yet is rarely discussed before transplantation. Among 138 women who underwent allo-HCT at an institution in France that provided routine gynecologic follow-up at approximately 100 days after transplantation, 19% were diagnosed with genital cGVHD with a median follow-up time of 40 months (range, 13–117).[14] In a cohort of women (n = 61) undergoing active surveillance for genital cGVHD from 1999 to 2004, the cumulative incidence of genital cGVHD was 35% (95% CI, 25%–50%) and 49% (95% CI, 36%–63%) at 1 and 2 years, respectively, and was significantly higher among recipients of peripheral versus marrow blood progenitors (hazard ratio, 3.07; 95% CI, 1.22–7.73).[15] A retrospective study of 213 women from 1980 to 1999 found a cumulative genital cGVHD incidence of 25%.[16] In a cross-sectional study of 42 women evaluated at a median of 80 months posttransplantation (range, 13–148), 52% were diagnosed with genital cGVHD.[13] Reported median time of onset from transplant to genital cGVHD varies from 7[16] to 10[15,17] to 13 months,[14] but has been diagnosed up to 8 years after transplantation.[12,18] GVHD may manifest as GVHD prophylactic medications are tapered after transplantation, which varies from patient to patient.

Although risk factors for the development of chronic cGVHD are well-described and include a history of acute GVHD, older age of recipient, and a high degree of HLA mismatch,[9,10,19] risk factors for genital cGVHD are less well-characterized. Peripheral blood stem cell grafts correlate with increased risk of global cGVHD compared with