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Case Report

Vulvar and vaginal graft versus host disease in a patient with chronic phase chronic myeloid leukemia after allogeneic stem cell transplantation

Orhan Ayyıldız[1], Abdullah Karakuş[1], Esra Pirinçci[1], Reyhan Gündüz[2]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Dicle University, Diyarbakır, Turkiye
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Dicle University, Diyarbakır, Turkiye

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ABSTRACT

Graft versus host disease (GvHD) is one of the serious complications of allogeneic stem cell transplantation in the treatment of hematological malignancies. Skin, liver, and eyes are frequently affected areas. In addition to frequently affected areas, genital involvement can also be seen. Allogeneic stem cell transplantation is one of the curative treatments for hematological malignancies seen at the young age group. And its use for therapeutic purposes in young patients is increasing daily. Vulvovaginal GvHD is a disease type that concerns female patients of reproductive age. In this case, we wanted to reportin the literature a case that underwent allogeneic stem cell transplantation after chronic myeloid leukemia diagnosis and tyrosine kinase inhibitory resistance and then developed vulvovaginal GvHD. In vaginal involvement, in addition to many genitourinary complaints, many negativities in sexual life and deterioration in quality of life are experienced. The patient is currently continuing her symptomatic local topical treatment and systemic immunsupressive treatment for GvHD with response at following up. Our aim in presenting this case is to emphasize that GvHD should be considered in the differential diagnosis of female patients with allotransplanted hematological disease and vulvovaginal sign and symptoms.

Keywords: Chronic vulvovaginal graft versus host disease, chronic myeloid leukemia, allogeneic stem cell transplantation

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INTRODUCTION

Graft versus host disease (GvHD) is a serious complication with acute and chronic stages, categorized according to the various symptoms that develop after allogeneic stem cell transplantation (allo SCT). The pathogenesis of GvHD is a complex T cell-mediated immune response; In this mechanism, grafted donor cells react against histocompatibility antigens in the recipient. GvHD may affect various organs, including skin, liver, and intestines. GvHD also occurs in the female genitals, especially the vulva and vagina, where it is known as vulvo-vaginal GvHD (VVGvHD).

A few studies have specifically addressed VVGvHD and its effects on patients' sexual health and quality of life. We observed that female patients did not focus on health problems involving their genital area when they considered a serious and life-threatening procedure such as bone marrow transplantation (BMT) and these symptoms may be overlooked by physicians

Female genital GvHD affects the vulva and vagina in approximately 25-50% of allogeneic SCT survivors, 68% in the vulva and 26% in the vulva and vagina. Onset is on average 7-10 months after allogeneic SCT. However, after a few years, vaginal GvHD may develop. The main symptoms of VVGvHD are dryness, burning, itching, pain to touch, pain during sexual intercourse, and, in a condition known as vestibular dysuria, burning when urine touches the entrance to the vagina. Vaginal atrophy must be excluded because after transplantation, estrogen deficiency occurs as most patients enter menopause. Physical findings consistent with VVGvHD include purulent discharge, mucosal erosion, vaginal stenosis, and loss of elasticity, which is graded from mild to severe.

CASE

42-year-old-female patient was diagnosed as chronic phase chronic myeloid leukemia in 2015. She was treated with imatinib 400 mg/day. After 6 months molecular response was not obtained and treatment changed to dasatinib 100 mg/day, however after 3 months of dasatinib treatment molecular and hematologic progression occurred and treatment was changed to nilotinib, and bone marrow transplantation was planned. Imatinib resistance mutations could not be investigated in the patient. After 4 months the patient transplanted successfully with HLA-matched sibling stem cell donor. Tyrosine kinase inhibitory was used till 1 year after transplantation, and Bcr/abl was negative after transplantation and until now.

During 2 months of transplantation, acute GvHD occurred and healed without any serious complication, but after 10

Corresponding Author: Orhan Ayyıldız, orhanay21@hotmail.com

months symptoms and signs of chronic GvHD developed. Dry skin, itching, and dark hyperpigmentation occurred in generalized of the body, especially in the upper extremities and ocular GvHD was the main symptoms of the patient. She used cyclosporin and steroids for prevention and treatment of GvHD, also she uses ursodeoxycholic acid for liver protection.

Chronic GvHD sustained more than 2 years especially ocular findings (drying, itching, and scarring of conjunctiva and eyelid). After 5 years of transplantation, she told her symptoms of genitalia such as vulvodinia, pain during sexual intercourse, and decreased sexual function to our nurse. She has problems with her husband for this reason. In gynecological examination, there were findings consistent with vulvodynia, but there was no genital atrophy. We prescribed 2% amitriptyline plus 2% baclofen cream two times a day for the treatment of vulvodynia.

When she came for control 1 month later of local treatment, she stated that sign and symptoms were better in terms of sexual function but could not urinate completely. Bacteriuria, pyuria, and hematuria were observed in urinalysis. Pelvic ultrasonography was normal. We treat her for a urinary tract infection. Since the patient's genital atrophy was not evident, we did not prescribe vaginal estrogen during both examinations. The symptoms and signs of the patient were healed near completely when we call to patient for evaluated last situation of disease.

DISCUSSION

Hematopoietic stem cell transplantation (HSCT) is a treatment method for malignant and benign hematological diseases as well as in the treatment of some non-hematological disorders such as autoimmune diseases.[1] Graft-versus-host disease (GVHD) is an immunity-related disease which affects 30-70% of patients after hematopoietic stem cell transplantation (allo HSCT) and is a significant contributor of morbidity and non-relapse mortality (NRM).[2] Chronic GVHD is a mucosal disease of the mouth, eyes, genitals, intestines, and lungs. It includes inflammation and fibrosis of membranes. There are some evidence that indicates clinical symptoms and pathogenesis of GVHD are similar to various autoimmune disorders such as Scleroderma, Sjögren's syndrome, and lichen planus.[3,4] Female genital GVHD was first described by Corson et al.[5] by observing Sclerosing vaginitis and structure problems in 5 women in 1982. Nowadays, it is an underdiagnosed condition and affects the quality of life which occurs in one-quarter of long-term surviving women after allogeneic stem cell transplantation.[6] The rates of genital GVHD vary widely, with rates ranging from 24.9-69%.[7] The wide variation in the incidence of genital GVHD is due to a variety of abnormalities, including the time at which incidence is calculated, the systematic and time-dependent gynecological evaluations, and the useddiagnostic criteria (findings of examination with or without symptoms, etc.).[8] The main risk factor for the development of chronic genital GVHD is using of peripheral blood as a source of stem cells; It represents a risk of three times higher than that obtained from bone marrow stem cells.[9-11] The presence of GvHD in other organs is also considered one of the other risk factor.[12] While one study found that 79% of patients with VVGvHD were previously treated for GvHD in a different organ, another study reported that almost all patients with VVGvHD had active chronic GvHD in the skin, mouth, and eyes.[13,14] Our patient was receiving immunsupresive treatment for skin and liver involvement caused by chronic GVHD. It is supported by various studies that it develops after an average of 10.2 months after transplantation.[6] In our patient, VVGvHD was diagnosed approximately 5 years after allogeneic transplantation. The clinic may be asymptomatic; the main signs and symptoms are vulvar tenderness to palpation of openings of the mucosa, erosion of the mucosa, cracks, leukokeratosis, labial or clitoral fusion, fibrous vaginal ring, vaginal shortening, vaginal adhesions, and complete vaginal stenosis. Other symptoms include dryness, burning, itching, pain to touch, dysuria, dyspareunia, and resulting sexual dysfunction takes place.[5] She has vulvodynia, pain during sexual intercourse, and decreased sexual function. Although symptoms are similar to primary ovarian insufficiency which occurs after allogeneic stem cell transplantation, synechia and adhesive bands are not encountered in primary ovarian failure. In addition, studies have shown that hormone replacement therapy is used for the prophylaxis of this condition does not affect the development rate of vulvovaginal GVHD.[11] The National Institutes of Health (NIH) Consensus Development Project proposed guidelines for screening, diagnosing, and preventing genital GVHD in HSCT survivors.[15]

CONCLUSION

Incidence and severity of genital GVHD in women should be included in GVHD intervention studies. Treatment goals for Female genital GVHD include symptom relief, disease control, and prevention of further damage. In its treatment, various patient-specific treatment modalities are advocated such as topical estrogens, topical steroids, topical immunosuppressive agents (such as cyclosporine, tacrolimus), vaginal dilators, and surgical lysis. Diagnosis and treatment of post-transplant genital GVHD require a systematic approach and collaboration between bone marrow transplant physicians, coordinators and gynecologists.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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