

Modified Vecchietti's vaginoplasty with Remeex® system in patient with chronic graft-versus-host disease

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ABSTRACT

We present a case report of a chronic graft-versus-host disease manifestation in 33-year-old patient with an unusual complication of vaginal stenosis with complete obstruction after allogeneic bone marrow transplantation for myelocytic leukemia. The patient complained on a progressive dyspareunia and sexual intercourse inability. She has received hormone replacement therapy due to the ovarian failure after the chemotherapy treatment. The hormonal treatment was used in continuous combined manner and hematocolpos wasn't seen during an abdominal ultrasound examination. The reconstructive surgery was performed by the modified Vecchietti's neovagina technique with a Remeex® system after histological confirmation of main diagnosis. The immediate postoperative course was uneventful with gradual normalization of sexual function.

Keywords: Graft-Versus-Host Disease; Bone Marrow Transplantation; Vaginal Stenosis

1. INTRODUCTION

Chronic Graft-versus-host disease (cGVHD) is one of the major complications after performing an allogeneic bone marrow transplant (BMT), *i.e.* HLA (Human Leukocyte Antigen) matched cells from a healthy donor. It is reported to occur in 25% - 60% of the patients who survive for more than 4 months [1]. It is caused by an immune reaction of the graft cells against the antigen receptor mediated T-cell immunocompromised, while producing the desired antineoplastic effect, eliminating residual tumor cells, and is responsible for serious side effects by affecting healthy tissues of the recipient.

Graft-versus-host disease (GVHD) is a disorder affecting several organs such as liver, skin, lacrimal and salivary glands as well as the mucous membranes. Female genital tract cGVHD is an under-recognized com-

plication, reported to occur in a quarter of long-term female survivors [2]. Vaginal involvement cause symptoms such as dryness, dyspareunia and abrasions but exceptionally may occur synechia and stenosis.

We report a patient who presents the rare complication of complete vaginal stenosis secondary to cGVHD after BMT with symptoms like progressive dyspareunia but not hematocolpos. This patient needed reconstructive vaginal surgery and we performed a Vecchietti's neovagina technique modified by using a Remeex® system. It is the first reported case in which this surgery is used for cGVHD vaginal affection.

2. CASE REPORT

We report a 33-year-old female without relevant family history, menarche when she was 10 years old. She had a normal pregnancy and normal vaginal delivery in 2001. She was diagnosed with acute myeloid leukemia (AML) with granulocytic maturation (AML-M2) in October 2002 at her local hospital where she was treated with chemotherapy according to the following schemes: a) induction therapy with idarubicin and arabinofuranosyl Cytidine (ARA-C), b) second induction therapy: ARA-C, Mitoxantrone and etoposide phosphate (VP16), achieving complete hematologic and cytogenetic remission, c) consolidation therapy with ARA-C and Mitoxantrone. She tolerated chemotherapy well and had no several complications. In April 2003 was performed allogeneic bone marrow transplantation from HLA-identical brother. Since then, the patient is in complete remission.

The pre-transplantation therapy had caused secondary amenorrhea. FSH and LH levels confirmed the premature ovarian failure (POF). Combined oral hormone replacement therapy (HRT) was used in a continuous manner because of patient desire (the patient did not want to have menstrual cycles). HRT was started with estradiol hemihydrate 1 mg and drospirenone 2 mg (Angelic®). The patient presented dyspareunia which worsened gradually despite the immunosuppressive therapy

used for the other symptoms of cGVHD. She decreased the frequency of sex relations and, then, the penetration became impossible. She consulted her gynaecologist about these symptoms in July 2005 and the examination revealed complete vaginal occlusion, so she was referred to our center. Abdominal ultrasound, due to the inability to perform vaginal ultrasound, showed a uterus with linear atrophic endometrium and no adnexal pathology; we did not objective hematocolpus.

Vaginoplasty was proposed. Reperfusion by dissection was not achieved and we performed Vecchiotti's modified technique by using a Remeex® system: invagination of the vaginal mucosa by placing a methacrylate ball 2 cm of diameter in the introital; this ball is joined by 2-wire tractors to a reflection pulley on the hypogastric skin. To place the Remeex® device system is necessary to visualize the peritoneal cavity by laparoscopy. During each postoperative day, tractors shorten wires 1 cm/day. At discharge, the patient used dilators and gradually increased the thickness. The immediate postoperative course was uneventful. By now, she has normal sexual function.

3. DISCUSSION

Graft-versus-host disease is one of the major complications of hematopoietic cell transplants and organs containing lymphoid cells [3,4]. This entity will combine a series of immunological events between the grafted tissue and the receiver, fired by their antigenic differences, resulting in various clinical inflammatory and/or fibrosing events from mild to severe, which may even compromise the patient's life. In current medical practice, GVHD is an increasingly common entity due to the implementation of transplantation as a therapeutic tool for various diseases. The group of patients receiving BMT, especially allogeneic, is the most affected by GVHD [5].

GVHD has two forms of presentation: acute and chronic, and each one is clinical, immunological and histological different from the other. The acute form appears during the first 100 days post-transplant, especially between days +7 and +21, with an average frequency of 35% [6-8]. It produces a selective epithelial inflammation, which mainly affects skin, gastrointestinal tract and liver, but eyes and bronchial tubes can also be affected.

Chronic graft-versus-host disease occurs after 100 days post-transplant, but in some cases early manifestations can be observed in the first 40 days. It may be either a sclerodermatous or lichenoid nature, or it may be a mixture of both types [9]. Many of the clinical features associated with cGVHD resemble those seen in various connective tissue disorders such as systemic sclerosis. The skin is affected in almost all cases, with intense fibrosis and elastosis. The most common liver disorder is cholestasis, although in severe cases has been associated with cirrhosis and portal hypertension. The ocular lesions

are mucosal involvement, such as xerophthalmia or dry eye syndrome (DES). Almost 90% of the patients suffer oral mucosa involvement and is manifested by a feeling of dryness, soreness, erythema, lichenoid lesions and mucosal atrophy of the glandular mucosa and duct ectasia. A cGVHD consequence affecting the esophagus may be structuring and dysphagia. Other damages are less frequent: gastrointestinal involvement is rare in contrast to acute GVHD. It can affect the respiratory tract too and the patient can develop bronchiolitis obliterans that it is often resistant to bronchodilator therapy; and neuromuscular involvement can include myasthenia gravis and polymyositis [10,11].

Low frequency of gynecological affection is reported and can include vaginitis and retraction of the vaginal walls with synechias. Vulvovaginitis has been associated with cGVHD in 3% of bone-marrow recipients [8,12]. Clinical symptoms appear around 10 months post-transplant and the most common symptoms are dryness, irritation, dyspareunia and postcoital bleeding. The injuries include abrasions, ulcerations of the mucosa, and adhesion which causes obliteration [13]. For many years, these symptoms were attributed to total body irradiation or secondary hypoestrogenism to the POF due to chemotherapy for BMT, but this was discarded because the process does not improve with topical or systemic estrogen therapy. In 1982, Corson *et al.* [14] described the gynecologic manifestations of cGVHD in five allogeneic BMT patients and they were the first to describe the vaginal involvement was due to immunological abnormalities based on cGVHD histology. Unlike the findings due to atrophic hypoestrogenism, patients with vaginal involvement cGVHD have a marked inflammatory component level of the mucosa and submucosa, which indeed corresponds with the inflammatory symptoms that these patients have [12,15]. In this context, the vaginal stenosis perhaps is exacerbated by the total body irradiation, and the hormonal disorders present after BMT which leads to atrophy of the vagina and glandular structures.

Within this process, we can distinguish mild-moderate involvements, including abrasions and any adhesions that may benefit with simple water-based lubricants and may progress to topical ultra-high-potency glucocorticoids; also treatment with topical immunosuppressant such as cyclosporine, in preventing the development of advanced lesions. Topical estrogen therapy is indicated for concomitant low-estrogen states. In these patients, the use of vaginal dilators may be effective to avoid surgery combined with topical therapy. The severe disease with extensive adhesions or obliteration of the vagina requires surgery in the first instance and adding topical cyclosporine for the adjuvant treatment [14,16,17].

The ideal time for surgical treatment of these patients would be when the inflammatory component was mini-

mal or nonexistent because the inflammation of the mucosa compromises the surgery outcome, but due to the pathophysiology of the process is difficult to avoid this problem. Also, the hypoestrogenism makes difficult the surgery outcome. Severe adhesions may require surgical lysis and sometimes vaginal reconstruction [18-20].

Our patient presents complete vaginal stenosis and we decide a neovagina technique for the reconstructive surgery. We performed a reconstructive vaginoplasty using Vecchiotti's modified technique with Rimmex® system and vaginal dilators in the postoperative time, gradually increasing the thickness [21,22]. This is the first case report of vaginal stenosis in cGVHD where this technique is described. Some similar cases were reported by DeLord *et al.* [16] and Yanai *et al.* [6] solvented by surgical drainage with good response, but despite the cases described by these authors, our patient did not presented hematocolpus, which made difficult the diagnosis and the surgery. In patients with impaired vaginal cGVHD is advisable to avoid surgical techniques using skin grafts due to the high rate of graft rejection caused by the immunological process.

Genital tract GVHD is often associated with cGVHD in other organs. Hence a high index of suspicion for genital tract GVHD is particularly warranted in women with extensive cGVHD. Zantonio *et al.* [23] in 2006 describes a higher incidence of genital tract cGVHD than that reported previously: 36% at first year post-transplant and 49% at second year [2,16].

Because it is an under-recognized complication of cGVHD impacting on quality of life, and the majority of published case reports are skewed to the advanced stenosing lesions requiring surgical therapy, this author describes a prospective surveillance programme for female genital cGVHD to better characterize incidence, risk factors and clinical features and the impact of a structured intervention policy: first, systemic and topical hormone therapy, to eliminate atrophic component; second, topical glucocorticosteroid therapy; third, topical cyclosporine therapy; and fourth, vaginal dilators to prevent surgery.

Our opinion is that a regular gynaecological follow-up may mitigate the development of such situations or allow early diagnosis for appropriate therapy. As genital tract cGVHD impacts on quality of life, early recognition and treatment are an important part of post-transplant management.

4. CONCLUSION

The possibility of vaginal and genital cGVHD should be considered in all females undergoing BMT in order to detect symptoms of ovarian failure and avoid genital lesions, and regular examination may aid in making an earlier diagnosis. Mild lesions can be successfully treated with steroids and topical cyclosporine therapy, with a

program of vaginal dilators. In case of vaginal adhesions or complete vaginal stenosis, as this case reports, surgical intervention are recommended.

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