Surgically treated genital chronic graft-versus-host disease in women: A report of three cases

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Running Title: Surgically treated genital chronic GVHD

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Abstract

Hematopoietic stem cell transplantation is a crucial treatment for hematological malignancy. Gonadal dysfunction occurs at an early stage after this treatment, and such patients may require hormone replacement therapy. Genital chronic graft-versus-host disease is a lesser-known complication of hematopoietic stem cell transplantation that begins with vulvar discomfort and dysuria and progresses to sexual dysfunction and retention of menstrual blood due to vaginal stenosis and obstruction, thus significantly impairing the patient's quality of life. We describe three women who underwent vaginal reconstruction because of genital chronic graft-versus-host disease. We discuss the surgical techniques, including double cross plasty, that were performed in each case. Surgical interventions enabled continuation of HRT and facilitated sexual intercourse. In conclusion, gynecologists should be aware that genital chronic graft-versus-host disease can occur after hematopoietic stem cell transplantation, and that surgical treatment options are available to improve patients' symptoms and quality of life.

Key words: double cross plasty, genital chronic graft-versus-host disease, hematocolpos, hematopoietic stem cell transplantation, vaginal reconstruction

Introduction

Hematopoietic stem cell transplantation (HSCT) is a crucial treatment for hematological malignancies and enables long-term survival. In these cases, however, the recipient's immune system and reproductive capacity are usually destroyed with radiation or chemotherapy before transplantation[1]. Therefore, hormone replacement therapy (HRT) is required for women with ovarian dysfunction after HSCT [2,3]. Infections, secondary cancer, and graft-versus-host disease (GVHD) are other major complications of HSCT[1,4].

Chronic GVHD (cGVHD) is classically defined when symptoms occur 100 days or more after HSCT[5]. Clinical manifestations often appear within 12 months after HSCT, but some develop several years later[4,6]. Chronic GVHD can occur in all organs, and its pathophysiology thought to involve inflammation, cell-mediated immunity, humoral immunity, and fibrosis[4,5].

Genital cGVHD starts with vulvar discomfort and dysuria due to erosions, fissures, and ulcers, and subsequently progresses to sexual dysfunction due to vaginal stenosis and obstruction[2,4,5]. Additionally, for patients receiving HRT, retention of menstrual blood makes it difficult to continue treatment. Surgical interventions are occasionally necessary in severe cases to enable continuation of HRT and facilitate sexual intercourse[2,5]. Herein, we describe three women who underwent surgery for vaginal obstruction due to genital cGVHD.

Case Report

For all cases, the diagnosis of genital cGVHD was based on diagnostic signs (vaginal scarring or labial agglutination) and symptoms[4]. After institutional review board approval was obtained

(No. 2010-015), all the cases were retrospectively analyzed. All patients provided written consent for the surgical procedures.

Case 1

A 24-year-old Japanese, unmarried, nulligravida woman was referred to us for hematometra and hematocolpos. She had been diagnosed with acute lymphoblastic leukemia (ALL) at 15 years of age and was treated with immediate standard therapy. However, ALL relapsed at 18 years of age, and she received allogeneic HSCT. Her regular menstruation stopped after HSCT. Subsequently, she started Kaufmann therapy, and a few months later, she complained of severe lower abdominal pain without genital bleeding. Her former gynecologist diagnosed vaginal obstruction and hematocolpos (diameter: 6 cm). She received vaginal fenestration several times, but the vagina subsequently reclosed.

At the first visit, her vulvar synechia was very firm, and a small hole was created at the center of the vulva (Fig. 1A). A tender pelvic mass was felt by rectal examination. Transrectal ultrasonography showed a large pelvic hematoma. Magnetic resonance imaging (MRI) revealed hematocolpos and hematometra, with an extended uterine cervix and closure of the lower part of the vagina (Fig. 2A). Results of routine hematological and biochemical tests were normal. Relapse of ALL was not confirmed by the hematologist-oncologist.

We planned two-stage surgery. During the first surgery, we released the vulvar synechia and estimated the degree of vaginal adhesion. Under general anesthesia, the patient was placed in the lithotomy position. We found that the labia minora were fused at the midline,

with no visible vaginal introitus (Fig. 2B). A small hole was identified as the urethral os, into which a Foley catheter was inserted. Vulvar adhesiolysis was meticulously performed with a sharp-pointed knife (Fig. 2C). After the vaginal introitus became visible (Fig. 2D), a large needle was inserted into the vaginal hematoma through the introitus under ultrasound guidance. After removing about 200 mL of sticky menstrual blood, we could identify the contour of the uterine cervix with a 17-mm long vaginal adhesion (Fig. 2E). The vulvar mucosal defect was covered with artificial dermis made of atelocollagen (Terudermis^{R}, Terumo Co., Ltd., Tokyo, Japan) (Fig. 2F).

Three months later, vaginal reconstruction and laparoscopy were performed during the second surgery. The patient underwent additional vulvar adhesiolysis (Fig. 3A). Double cross plasty[7] was performed as follows: an X-shaped incision was made in the vestibular mucosa, and the vaginal adhesions were carefully resolved during rectal examination (Fig. 3B). A cross-shaped incision was made in the deepest part of the vaginal canal (Fig. 3C). After confirming the uterine cervix, triangular mucosal flaps were interdigitated and sutured (Fig. 3D).

She had an uncomplicated postoperative course and was discharged on postoperative day six. She re-started Kaufmann therapy. Twelve weeks postoperatively, a 3-cm diameter handmade Styrofoam dilator was easily inserted 8 cm into the vagina (Fig. 3E, 3F).

Case 2

A 33-year-old Japanese, married, nulligravida woman was referred to us with dyspareunia. She married at 27 years of age. She conceived twice but miscarried both pregnancies. She was diagnosed with acute myelogenous leukemia (AML) at 31 years of age

and was immediately treated with standard therapy. As she had high-risk AML, she received allogeneic HSCT 5 months later. Her menstruation stopped after HSCT, but the former gynecologist was hesitant to start HRT because of concerns about thrombosis. Vaginal intercourse became difficult for her, so she visited the former gynecologist for an examination. Her labia minora was found to be fused to the labia majora bilaterally. Although the vaginal orifice was normal, the vagina was blind-ending and 3-cm long (Fig. 1B). Transvaginal ultrasonography and MRI showed an atrophic uterus with minimal fluid retention. A predisposition to thrombosis was ruled out.

She underwent one-stage vaginal reconstruction. Double cross plasty was conducted as follows: an X-shaped incision was made in the blind end of the vaginal mucosa. The bladder and rectal lumen were carefully detached under rectal and ultrasound examinations. A cross-shaped incision was made in the deepest part of the vaginal canal, and the uterine cervix was identified. Interdigitated suturing was performed in a similar fashion. Finally, a vaginal canal measuring at least 3 cm in diameter and 8 cm long was secured.

She was discharged uneventfully on postoperative day six, and Kaufmann therapy and topical medication were initiated. She reported being able to have sexual intercourse 6 weeks postoperatively.

Case 3

A 22-year-old Japanese, unmarried, nulligravida woman was referred to us for treatment of hematocolpos. She had been diagnosed with AML at 19 years of age and was treated with standard therapy immediately. However, AML relapsed at 20 years of age, and she received allogeneic HSCT. Her menstrual cycles stopped after HSCT. When Kaufmann therapy

was started by the former gynecologist, she complained of severe lower abdominal pain without genital bleeding. Transabdominal ultrasonography showed a hematoma in the pelvis.

The labia minora were found firmly adhered at the midline, and the vaginal introitus was not visible (Fig. 1C). MRI revealed an atrophic uterus with minimal fluid retention and a 39 mm × 25 mm hematoma in the upper third of the vagina.

She underwent one-stage vaginal reconstruction. The dissection was meticulously performed with a sharp-pointed knife to resolve the fused labia minora, and the vestibular part of the vagina became visible. Double cross plasty was performed in a similar fashion.

She was discharged uneventfully on postoperative day seven and restarted Kaufmann therapy. Her vagina was at least 3 cm in diameter and 8 cm in length. She reported being able to have sexual intercourse 4 months postoperatively.

Discussion

The present case study has two important findings. First, female genital cGVHD is an important gynecological problem for women after HSCT. Second, vaginal reconstruction plays a pivotal role in treating cGVHD-mediated vaginal occlusion to enable continuation of HRT and facilitate sexual intercourse. To our knowledge, this is the first report of the use of double cross plasty[7] (also known as the Granjon procedure), an operative procedure for transverse vaginal septum, for the treatment of genital cGVHD.

Genital cGVHD is a lesser known and probably underestimated complication of allogeneic HSCT[5,6]. It occurs in 25%–49% of allogeneic HSCT survivors[3,5,6,8]. However, since patients are hesitant to report it because of embarrassment, its actual incidence is currently unknown[3,5,6,8].

Early gynecologic intervention is recommended for patients to minimize the risk of developing severe genital cGVHD[6,8]. Systemic HRT is often given to women with ovarian dysfunction after HSCT. Symptoms of early genital cGVHD overlap with those of genital tract atrophy caused by ovarian dysfunction after HSCT[5,6]. HRT may relieve the genital symptoms[2,3], but estrogen has insufficient anti-inflammatory effects to address genital cGVHD[3,8]. Several reports recommended the combination of topical highly potent glucocorticoids and estrogen for the treatment of genital cGVHD[2,3,5,6,8]. Topical immunosuppressive agents have also been applied[2,5,6]. Moreover, vaginal dilator treatment is often useful to prevent vaginal narrowing and scarring[2,3,6].

Despite these prophylactic measures, hematoma formation with severe pain or dyspareunia can develop. Vaginal reconstruction is occasionally required for patients with extensive synechiae and complete obliteration of the vaginal canal[5]; however, patients' clinical conditions tend to vary greatly. Therefore, surgical intervention should only be performed for the underlying disease with the attending physician's agreement.

The surgical procedure should be considered on an individual basis. If there is only hematocolpos with a normal or atrophic uterus, one-stage vaginal reconstruction with vulvar adhesiolysis is indicated. However, if hematocolpos coexists with hematometra, it is often difficult to distinguish between the extended uterine cervix and the vaginal wall[9]. Additionally, if the defect of the vulvovaginal mucosa is too wide after surgical separation, an artificial dermis may be useful for vaginal reconstruction[10]. Postoperatively, using topical medication with dilators or sexual intercourse can prevent vulvo-vaginal restenosis[2,5].

A limitation of this case series is that histopathologic confirmation of GVHD was not obtained in all cases.

178 In conclusion, gynecologists should be aware that genital chronic GVHD can occur
179 after HSCT, and that surgical treatment options are available to improve patients' symptoms and
180 quality of life.
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Disclosures

The authors declare no conflicts of interest.

Data sharing statement

The data are not publicly available due to privacy restrictions.

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Figure Legends

Figure 1: Vulvar findings at the first visit

(A) Case 1

(B) Case 2

(C) Case 3

Figure 2: The first surgery (Case 1)

(A) T2-weighted magnetic resonance imaging reveals hematocolpos, hematometra and closure of the vagina.

(B) The labia minora are fused at the midline, and the vaginal introitus is not visible.

(C) Vulvar adhesiolysis is meticulously performed with a sharp-pointed knife.

(D) The vaginal introitus becomes visible.

(E) The contour of the uterine cervix (Cx) with a 17-mm long vaginal adhesion (▲) can now be identified, under transrectal ultrasonography. (UB: urinary bladder).

(F) The vulvar mucosal defect is covered with artificial dermis.

Figure 3: The second surgery (Case 1)

(A) Sharp and blunt dissection is performed to resolve the vulvar synechia.

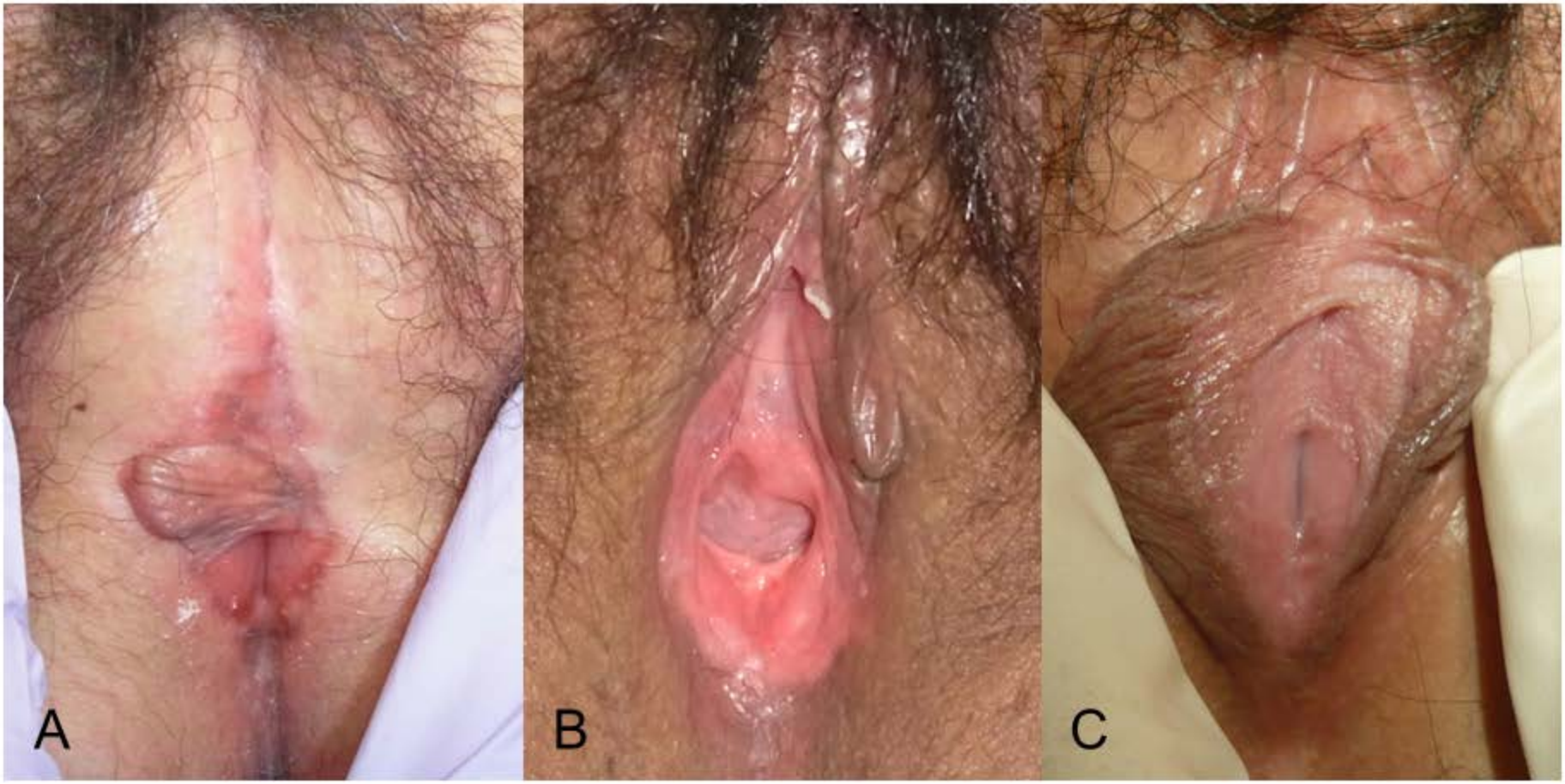
(B) An X-shaped incision is made in the vestibular mucosa, and the vaginal adhesions are carefully resolved.

(C) A cross-shaped incision is made in the vaginal mucosa located in the deepest part of the vaginal canal.

(D) The triangular mucosal flaps are interdigitated and sutured.

245 (E) The vulvar findings 12 weeks postoperatively.

246 (F) A 3-cm diameter handmade Styrofoam dilator can be easily inserted.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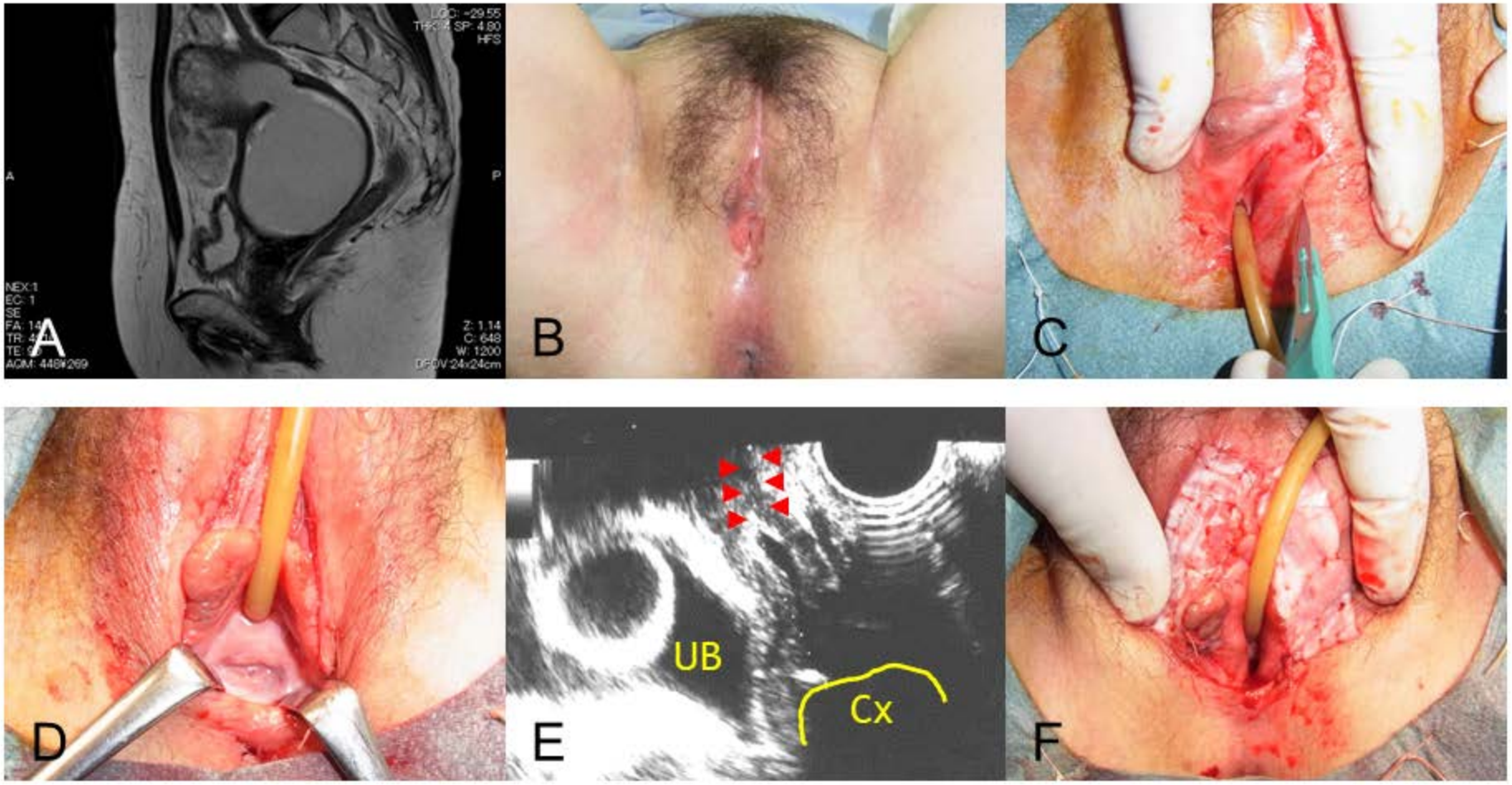
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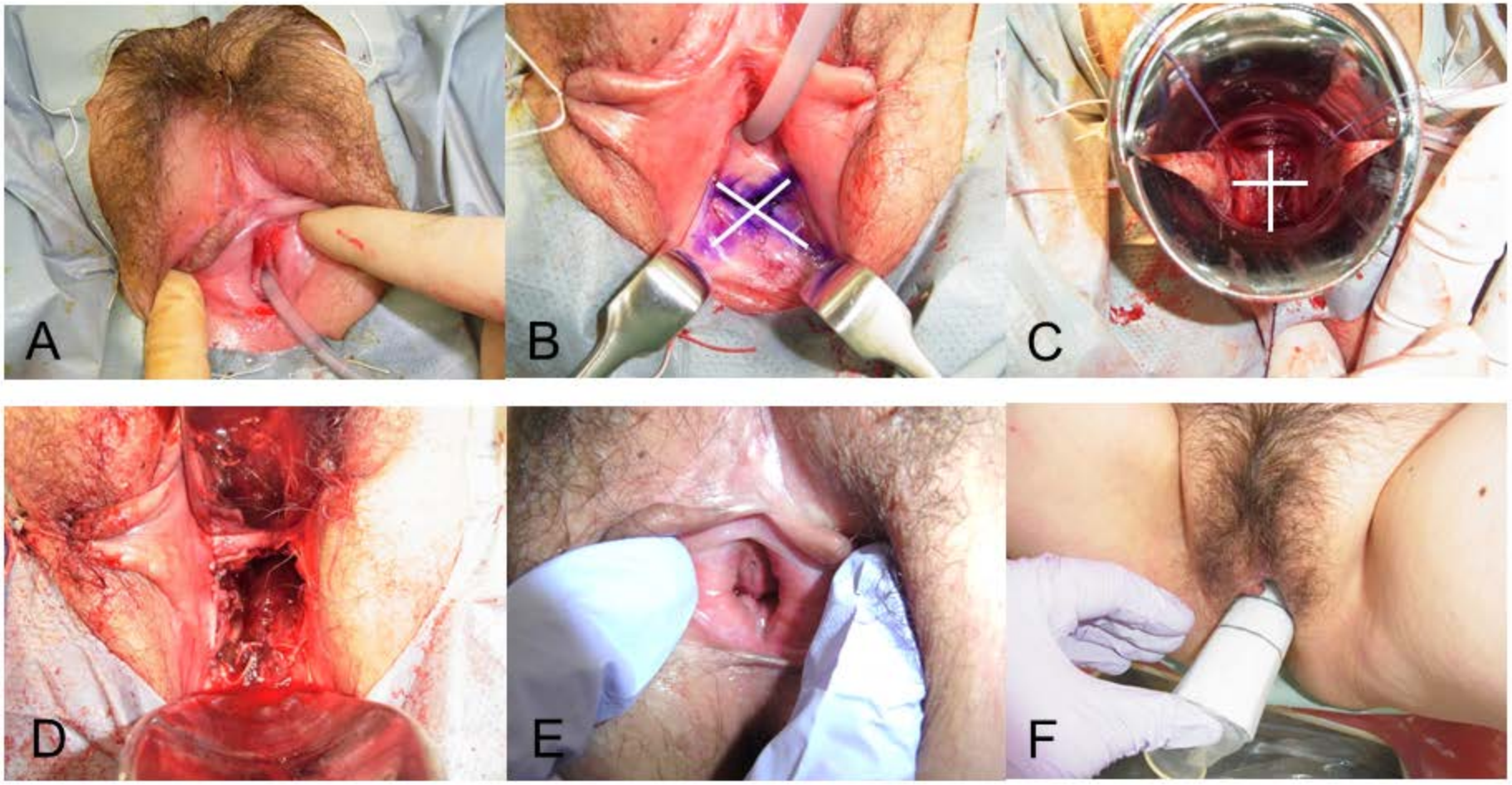
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