CASE REPORT

Novel management of vaginal chronic graft-versus-host disease causing haematometra and haematocolpos

Alice Buchan,^{1,2} Melissa A Merideth,^{3,4} Richard W Childs,⁵ Pamela Stratton^{6,7}

¹Institute of Genetic Medicine, Newcastle University, Newcastle Upon Tyne, UK

²Gynaecology, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK

³Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA

⁴Intramural Office of Rare Diseases, Office of the Director, National Institutes of Health, Bethesda, Maryland, USA

⁵Hematology Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

⁶Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA

⁷National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

Correspondence to
Dr Pamela Stratton,
strattonp@mail.nih.gov

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SUMMARY

Genital chronic graft-versus-host disease (GVHD) in women posthaematopoietic cell transplantation may cause vaginal mucosal sclerosis. Human papillomavirus (HPV) reactivation, also common post-transplantation, limits local immunosuppressive, but not oestrogen treatment. A 36-year-old nulliparous woman developed coincidental genital chronic GVHD and HPV 22 months after transplant for aplastic anaemia. Topical immunosuppression for GVHD led to an eruption of warts successfully treated with laser surgery and cone biopsy. She maintained normal ovarian function and used extended cycle combined hormonal contraception. A vaginal oestrogen ring used continuously limited most scarring for 8 years. Progressive apical vaginal scarring obstructed menstrual flow leading to haematocolpos and haematometra. Normal anatomy was restored with a cruciate incision in the cervicovaginal scar performed during menses. When HPV disease limits use of topical immunosuppression in women with vaginal GVHD, the local scar-reducing effect of a vaginal oestrogen ring is limited, and surgery may be needed and can be successful in treating haematocolpos. This study was registered in ClinicalTrials.gov with trial registration number of NCT00003838.

BACKGROUND

Allogeneic haematopoietic cell transplantation (HCT) is used in the management of haematological malignancies and bone marrow conditions such as aplastic anaemia. Chronic graft-versus-host disease (GVHD) is one of the major long-term complications of HCT and may affect anywhere in the body, with a predilection for the skin, eyes and gastrointestinal mucosa.

Genital chronic GVHD is common in women who have undergone HCT. It manifests in a number of ways,¹ including as scarring or narrowing of the vaginal canal or as tender inflamed areas in the vagina or vulva. Topical immunosuppression (usually corticosteroids) is the treatment of choice for genital GVHD as systemic immunosuppression does not slow genital GVHD progression. Topical immunosuppression may be complemented by topical oestrogen which serves to thicken epithelium and may contribute to limiting mucosal scarring.² As the number of long-term post-transplant survivors increase, an increasing number of women are living with genital GVHD.

Many women develop ovarian insufficiency and are menopausal post-transplant due to toxicity from their conditioning or previous chemotherapy, yet women receiving non-myeloablative, reduced-intensity conditioning for bone marrow failure may have normal ovarian function and regular menses. Haematocolpos or haematometra may occur when GVHD-related scarring completely occludes the cervicovaginal opening and may occur in women having menstrual bleeding regardless of whether it results from normal cycles or withdrawal from contraception or hormone therapy.

Viral reactivation is a common problem after transplant as these patients are immunosuppressed, immune reconstitution is not immediate in the first few months after transplant or longer in the context of chronic GVHD treatment, and humoral immunity wanes over time. In the genital area, the use of topical immunosuppression may be limited by pre-existing or reactivated genital human papillomavirus (HPV).³ As in healthy women, HPV may lead to premalignant and malignant changes in the vulva, vagina and cervix. Cervical cancer is a reported secondary malignancy in survivors of allogeneic HCT.^{4,5}

We present a case of the successful surgical treatment of haematocolpos and haematometra occurring in a woman post-transplant a few years after HPV disease and Epstein-Barr virus reactivation in the genital tract.

CASE PRESENTATION

A 36-year-old nulliparous woman was diagnosed with aplastic anaemia at age 8 and underwent a matched, related (her brother), non-myeloablative, reduced-intensity transplantation at National Institutes of Health (NIH) at age 28, as part of a clinical trial (registration NCT00003838). Post-transplant, she experienced no acute GVHD but did have chronic oral and ocular GVHD from 1 year post-transplant. She resumed normal ovarian function and had menstrual cycles post-transplant.

Her post-transplant course over the next few years was complicated by vaginal chronic GVHD leading to adhesions. As this was the primary manifestation of chronic GVHD, systemic immunosuppression had been discontinued. Treatment with topical corticosteroids, oestrogen cream and dilators led to florid HPV disease (many verrucous lesions, with vaginal intraepithelial neoplasia 1 on

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biopsy) along the track where the creams and dilators had been used. Topical immunosuppression was stopped, and the HPV disease affecting the vagina and cervix was ablated using laser,³ and subsequently a cone biopsy was performed for cervical intraepithelial neoplasia. The pathology report from this cone biopsy demonstrated Epstein-Barr virus reactivation in addition to cervical intraepithelial neoplasia 1. After the cone biopsy, the cervical os opening narrowed but remained patent.

Due to poor healing of the areas of vaginal mucosa that had been treated with laser, and the inability to use steroids to prevent further GVHD, an ultralow-dose oestrogen ring (2 mg oestradiol vaginal ring, releasing 7.5 µg/day, replaced every 90 days) was used.³ She additionally continued an extended cycle combined contraceptive pill for contraception (0.3 mg norgestrel/0.03 mg ethinylestradiol). Every 3 months, she stopped using the oestrogen ring for a few days during withdrawal bleeding.

Seven years post-transplant, she presented for routine follow-up, and was found to have adherence of the cervix to the right vaginal wall representing severe vaginal GVHD.¹ At this time, she had minimal HPV disease; colposcopy done concurrently was normal, with no high-risk HPV on hybrid capture II testing.

One year later, she did not have the normal withdrawal bleeding after she completed the extended cycle oral contraceptive and removed her ring. Awaiting her menses, she discontinued both methods. Two months later, she presented to the emergency department with abdominopelvic pain. At this visit, a transvaginal ultrasound showed a 7 cm cervical mass. One day later, she experienced prolonged and heavy vaginal bleeding, lasting 8 days. She used 15 pads on the first day of bleeding. This bleeding was associated with relief of her pelvic pain.

INVESTIGATIONS

She was seen at NIH 1 week later, at which time there was significant scarring in the right side of the vagina, but the cervical os was visibly patent, and there was no obvious cervical mass. The vaginal capacity was normal. However, a transvaginal ultrasound (figure 1) and MRI demonstrated a dilated cervix and uterus, presumably filled with blood (figure 2). Given the history, haematocolpos and haematometra due to scarring in the vagina appeared to cause the amenorrhoea and pelvic pain, and relief of pain and heavy bleeding occurred when haematocolpos had suddenly burst making a hole in the scar.

One month later, she was examined under anaesthesia with the goal of performing colposcopy, hysteroscopy, endometrial biopsy and ablation of HPV lesions. However, no opening in the

Figure 1 Transvaginal ultrasound image demonstrating cervical mass (arrow). LMP, last menstrual period; SAG UT, Sagittal Uterus.

Figure 2 Sagittal T2-weighted MRI image demonstrating cervical mass (arrow).

cervicovaginal scar was identified, and aspiration of the area did not identify blood, and the procedure was abandoned.

TREATMENT

She reinitiated her extended cycle contraceptive regimen and 3 months later had vaginal bleeding at the conclusion of her pill package. On examination under anaesthesia, the cervicovaginal area was completely scarred as a thick anteroposterior wall without an opening. We only identified the cavity by operating during menses so some blood was present on the vaginal wall. A 16-gauge needle attached to a 20 cc syringe was used to aspirate the haematocolpos in the area of vaginal bleeding. Viscous blood was obtained and confirmed that we were in the area of accumulated menstrual blood rather than the bladder or bowel. She underwent an incision and drainage of the 5–6 cm haematocolpos by using a cruciate incision in the vaginal scar (figure 3A).

The interior of the upper vagina and uterine cavity were inspected by hysteroscopy, and no lesions were noted. As shown in figure 3B, after hysteroscopy, the incisions were marsupialised by suturing the four points of the incision back onto the vaginal mucosa.

OUTCOME AND FOLLOW-UP

One month postoperatively, the os was visible and open on examination, and the patient was menstruating. MRI demonstrated resolution of the haematocolpos (figure 4).

DISCUSSION

In this case, we presented a patient with severe, progressive vaginal chronic GVHD that occurred despite having normal vaginal breadth and depth. Although she had signs of genital GVHD for some years prior to her presentation with haematocolpos and haematometra, attempts to treat it using any topical

Figure 3 (A) Drawing of the cruciate incision made in the cervicovaginal wall. (B) Drawing of the 4-point marsupialisation of the everted edges of the cruciate incision.

corticosteroids were thwarted by a dramatic recurrence of genital HPV disease manifesting as widespread lesions and multifocal intraepithelial neoplasia. Laser surgery of these lesions led to thinned mucosa but did not affect the cervical opening or vaginal calibre.³ Subsequent cone biopsy led to narrowing but not occlusion of the cervical os. Even though a low-dose oestrogen ring aided in healing postsurgical, denuded areas of vaginal mucosa and in lessening scarring adjacent to the ring, this approach was insufficient to prevent progression of GVHD which led first to adherence of the cervix to the right vaginal wall and then occlusion of the upper vaginal canal. While many women are postmenopausal after HCT owing to the chemo/radiotherapy in the conditioning regimen, our patient still had regular cycles, and thus presented with abdominopelvic pain and haematocolpos following 3 months of amenorrhoea.

In both congenital and acquired causes of haematocolpos and haematometra, the principle of management is to mechanically

relieve the obstruction by lysis of adhesions and allow passage of menstrual blood. Previous case reports of women presenting with haematocolpos or haematometra after haematopoietic cell transplant presumed the vaginal scarring to be due to genital GVHD.⁶ Some women had not undergone regular gynaecology follow-up and were not using any topical therapies intended to treat or prevent GVHD. Many women who are posthaematopoietic cell transplant will not be menstruating due to the effects of their conditioning or previous treatment for malignancy. Although patients who are not menstruating may not present acutely, vaginal obstruction secondary to chronic GVHD may have a significant impact on their quality of life and psychosexual function.

Chronic GVHD is one of the major complications of haematopoietic cell transplant.¹ The most common sites of chronic GVHD are the skin and other mucosal surfaces, such as the oral cavity, gastrointestinal and genital tracts, and the eye. Genital tract GVHD may manifest as vaginal scarring leading to narrowing and shortening of the canal, often with arcuate ridges or synechiae or present as red, inflamed, tender erosions/ulcers of mucosa in the vulva. Mucocutaneous GVHD is most commonly treated with topical steroids. Oestrogen also has a role in the management of genital GVHD, as it supports growth and repair of the mucosal surfaces. It also may help in postmenopausal women (unlike our patient) where there is a component of atrophic vaginitis.

The relationship between chronic GVHD and viral reactivation is unclear. Whether the GVHD itself, or the additional immunosuppression it necessitates, is causative of viral reactivation or viral reactivation itself leads to GVHD is not known. Our patient had both HPV and Epstein-Barr virus detected in the genital tract. Women who are immunosuppressed are less able to clear HPV and thus are at higher risk for the dysplastic and neoplastic changes it can cause. In one study of cervical dysplasia in 38 posthaematopoietic cell transplant women at NIH, 43% of women had squamous intraepithelial lesions, most of whom had biopsy-proven HPV disease, with more than half having high-grade lesions.⁵ Another cohort of 89 female long-term post-transplant survivors found that 68.5% had cervical cytological abnormalities.⁶ In this patient group, chronic vulvovaginal GVHD was the single largest independent risk factor for cervical dysplasia.

Chronic GVHD and viral reactivation are commonly seen together in patients post-HCT, and there is a delicate balance required when treating one to avoid a flare of the other. Viral reactivation may predispose to a more proinflammatory microenvironment in which alloimmune activation becomes more likely. Presentation of host antigen in the context of damage-associated molecular patterns and pathogen-associated molecular patterns may increase the likelihood of proinflammatory immune activation rather than anergy or an anti-inflammatory response.⁷ Matzinger's danger model suggests that the context of antigen presentation influences the immune response, and that non-self antigen alone is not enough to trigger a response,⁷ an observation seen both experimentally and in practice. Thus, when host self-antigen is presented in this context to the allogeneic (donor) immune system, immune activation and local GVHD may be more likely.

In other mucosal environments, such as the lungs, an association between viral reactivation and chronic GVHD has been seen. In this context, alloantigen is necessary but not sufficient for the onset of GVHD, and viral infection in combination with alloantigen may trigger GVHD.⁸ Further experiments in mice have demonstrated that bacterial danger signals can also

Figure 4 Sagittal T2-weighted MRI image demonstrating normal anatomy following marsupialisation of the vaginal scar.

Patient's perspective

Before this happened, I knew that I had genital graft-versus-host disease. I had contacted you, my NIH gynecologist, to ask you (her) why I wasn't getting my period when I expected to. Then, one day I had severe pain that really scared me. I went to the local emergency room and they thought that I had cancer of the cervix. The next day, I bled a lot. Then, I came to the NIH Clinical Center and had more imaging tests. You (the gynecologist) showed the images to me so I could see the large blood clot and you explained everything, including what you were going to do at surgery. The surgery was not a big deal. Since then, the dryness that had been happening for years has gone away and everything is fine. I am thankful that you showed me the images, so I could see the big blood clot and you made sure I understood everything before I had the surgery.

Learning points

- ▶ Coexisting genital human papillomavirus disease may limit the use of topical immunosuppression to treat genital chronic graft-versus-host disease.
- ▶ In this situation, an oestrogen ring alone aided healing of denuded vaginal mucosa but may have limited effects on vaginal chronic graft-versus-host disease, especially above or below the ring.
- ▶ Haematocolpos and haematometra, while previously noted in women post-transplant without regular gynaecology surveillance, may also occur in women with regular follow-up, underscoring the importance of gynaecological care after transplant.
- ▶ In this case, a cruciate incision in the cervicovaginal scar performed during menses drained the haematocolpos and haematometra, and normal anatomy was restored within 1 month.

potentiate GVHD.⁹ These results suggest that the combination of alloantigen and an inflammatory stimulus may be necessary and sufficient for GVHD to occur.

In this case, our patient presented to her first post-transplant gynaecology appointment with both GVHD and HPV reactivation.

Genital chronic GVHD and HPV disease are common in women posthaematopoietic cell transplant necessitating regular gynaecological surveillance.² Treatments for chronic genital GVHD may increase the risk of HPV or other viral

reactivation. In an already higher-risk population, chronic vulvovaginal GVHD appears to be an independent risk factor for HPV-associated dysplasia. The treatment of HPV disease in women post-HCT may limit options for the management of their genital GVHD. Oestrogen may support the vaginal mucosa but in this case was insufficient to prevent progression of GVHD and ultimately led to haematocolpos and haematometra, despite periodic gynaecological follow-up. Surgical incision and drainage with marsupialisation was successful in treating the obstruction and recreating the cervix.

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