Improvement of abnormal cervical cytology possibly due to a graft-versus-tumor effect: A case report and literature review

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Introduction

Graft-versus-host disease (GVHD) is a potentially serious complication of allogenic stem cell transplantation (allo-SCT), but patients who develop GVHD also have a low incidence rate of leukemia recurrence, suggesting a graft-versus-leukemia effect due to the donor lymphocytes.[1] This effect has also been suggested in solid tumors. In the case here, cervical cytology transformed from squamous cell carcinoma to negative for intraepithelial lesion or malignancy (NILM), possibly due to a graft-versus-tumor (GVT) effect following allo-SCT. The cervical cytology has continued changing, although the dose of immunosuppressant likely also has an effect. Here we describe our experience in this case and review the literature.

Key words

Cervical cancer, Cervical cytology, graft-versus-tumor effect, allogenic stem cell transplantation

Key Clinical Message

In this case, the cervical cytology of our patient transformed from squamous cell carcinoma to negative for intraepithelial lesion or malignancy, possibly due to a graft-versus-tumor effect following allogenic stem cell transplantation.

Case History

A 32-year-old woman (para 0) was referred to our hospital because of abnormal vaginal bleeding. She had a history of sexually transmitted infection at age 14 years and had been diagnosed with acute myeloid leukemia at age 26 years, for which she had received allo-SCT. Cervical cytology showed squamous cell carcinoma (Figure 1). We performed cervical conization and the pathological diagnosis was cervical intraepithelial neoplasia (Figure 2). The cervical margin was negative. After conization, the cervical cytology persistently showed squamous cell carcinoma or high-grade squamous intraepithelial lesion (HSIL). Ideally, re-conization or hysterectomy would have been performed. However, we could not perform these procedures as the patient had pancytopenia caused by late marrow failure following allo-SCT. Hence, transfusions were frequently performed for the pancytopenia. Because there was no evidence of cervical tumor on MRI, she underwent a second allo-SCT before gynecological treatment. She then developed acute GVHD, with high fever, skin eruptions, and diarrhea. Although chronic GVHD developed after acute GVHD, the dose of immunosuppressant was gradually decreased and she was discharged 4 months after the second allo-SCT. The patient still has chronic GVHD and requires regular adjustment of the immunosuppressant dose.

Although the cervical cytology showed squamous cell carcinoma prior to the second allo-SCT, it transformed to HSIL at 4 months (Figure 3), atypical squamous cells of undetermined significance at 11 months (Figure

4), and NILM at 16 months (Figure 5) after the second allo-SCT. The cervical cytology remained NILM for 1 year, but again changed to HSIL 33 months after the second allo-SCT. Since the abnormal cervical cytology persisted, we performed abdominal total hysterectomy and bilateral salpigo-oophorectomy 4 years after the second allo-SCT. The pathological diagnosis was cervical intraepithelial neoplasia, grade 3/HSIL (Figure 6). The surgical margin was negative. Though the vaginal stump cytology showed squamous cell carcinoma after the operation (Figure 7), it improved to HSIL 5 months postoperatively (Figure 8). Three years after the hysterectomy, the cytology had transformed from HSIL to NILM without treatment (Figure 9).

Discussion

This case is unique because the cervical cytology changed in a short time. The change in cervical and vaginal stump cytology without treatment is rare, so we speculate that this change was associated with allo-SCT.

GVHD is among the most potentially serious complications of allo-SCT, but patients who develop GVHD also have a low incidence of leukemia recurrence,[1] suggesting a GVT effect due to the donor lymphocytes in association with GVHD.

Eibl et al. reported a breast cancer patient with liver and bone metastases who underwent allo-SCT and had complete resolution of the liver metastases on CT 27 days later.[2] On the same day, the patient developed acute GVHD of the skin. Considering this clinical course, Eibl et al. attributed the resolution of the metastases to a GVT effect. Child et al. performed allo-SCT in 19 patients with refractory metastatic renal-cell carcinoma, of whom 3 had complete response and 7 had partial response. [3] They noted that regression of metastases occurred at a median of 129 days after transplantation, often following withdrawal of cyclosporine and the establishment of complete donor T cell chimerism. Cyclosporine suppresses the increase of T cells and the production of cytokines. This agrees with the previous study suggesting that the graft-versus-leukemia and GVT effect is caused by donor T cells.[4]

There are many reports of the GVT effect in patients with solid tumors. To our knowledge, however, this is the first report showing a GVT effect for only abnormal cytology. Some studies have reported that the cervical cytology after allo-SCT was affected by immune status.

Shanis et al. studied 82 women who underwent allo-SCT and found the cumulative incidence rate of any genital HPV infection at 20 years after transplantation to be 40.1%.[5] Women who developed extensive and genital chronic GVHD had a cumulative HPV infection rate of 67.1%, compared with 18.4% in women without chronic GVHD. They also reported that the cumulative rate of severe dysplasia reached 19% at 20 years after transplantation, and the rate was significantly different between women with and without chronic GVHD (41.2% versus 2.5%). In contrast, there was no association between acute GVHD and the rate of HPV infection. Shanis et al. suggested that, since sexual activity after allo-SCT is generally decreased, the increased HPV infection rate was due to reactivation of HPV rather than new infection. Moreover, viral reactivation may have been influenced by chronic GVHD and/or immunosuppression. Similarly, Bipin et al. reported that genital HPV disease occurred in one-third of 38 patients.[6] All of them were long-term survivors of allo-SCT on prolonged immunosuppressive therapy. Bipin et al. suggested that prolonged systemic immunosuppressive treatment for chronic GVHD was associated with a higher risk of developing genital HPV disease.

Our patient may have already been infected with HPV before she underwent the first allo-SCT considering her history of sexually transmitted infection. The abnormal cervical cytology may represent HPV reactivation due to prolonged immunosuppression.

We suggest that our patient developed a GVT effect associated with GVHD, which resulted in transient improvement of the cervical cytology after the second allo-SCT. This GVT effect may have been suppressed later by immunosuppressive therapy, resulting in worsening of her cervical cytology. As shown in Figure 10, the cervical cytology changed from NILM to HSIL. When GVHD recurred and the immunosuppressant dose was increased, the cervical cytology improved. When the immunosuppressant dose was again decreased

because of improvement of GVHD, the cervical cytology worsened. Although we speculate that the cervical cytology was affected by a GVT effect mediated by the immunosuppressant dose, there is no direct evidence that the cervical cytology improved because of a GVT effect. However, transformation of the cervical cytology from NILM to HSIL without treatment is rare. Although the possibility of sampling error cannot be excluded, if it were to occur, then there would be no correlation between cytology, GVHD and the immunosuppressant dose.

The cervical cytology of patients after allo-SCT is likely to change depending on their immune status. Regular gynecologic follow-up is needed even after improvement of the cervical cytology to monitor for changes.

Author contribution

Yasuhito Kato: Supervision. Hiroe Miyakawa: Conceptualization. Toshiyuki Nakata: Conceptualization. Kenichi Tamate: Project administration. Tomoki Kikuchi: Resources, Writing-review & editing. Masahiko Obata: Resources.

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Figure 1. First cervical cytology: squamous cell carcinoma (×40 Pap smear).

Figure 2. Pathological specimen from conization: carcinoma in situ (×20 hematoxylin and eosin stain).

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Figure 4. Cervical cytology 11 months after the second allogenic stem cell transplantation: atypical squamous cells of undetermined significance (×40 Pap smear).

Figure 5. Cervical cytology 16 months after the second allogenic stem cell transplantation: negative for intraepithelial lesion or malignancy (×40 Pap smear).

Figure 6. Pathological specimen from hysterectomy: cervical intraepithelial neoplasia, grade 3/HSIL (×20 hematoxylin and eosin stain).

Figure 7. Cervical cytology 2 months after hysterectomy: squamous cell carcinoma (×40 Pap smear).

Figure 8. Cervical cytology 5 months later after hysterectomy: high-grade squamous intraepithelial lesion (×40 Pap stain).

Figure 9. Cervical cytology 3 years after hysterectomy: negative for intraepithelial lesion or malignancy (×40 Pap stain).

Figure 10. Course of cervical cytology and dose of immunosuppressant. ASC-H, atypical squamous cells cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; ATH+BSO, abdominal total hysterectomy and bilateral salpingo-oophorectomy; HSIL, high-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; SCC, squamous cell carcinoma.

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