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CASE REPORT

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

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Abstract

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

KEYWORDS

allogeneic stem cell transplantation, cervical cancer, cervical cytology, graft-versus-tumor effect

1 | INTRODUCTION

Graft-versus-host disease (GVHD) is one of the most serious complications of allogeneic stem cell transplantation (allo-SCT). However, patients who develop GVHD have a low rate of recurrent leukemia, which suggests the presence of a graft-versus-leukemia effect caused by the donor lymphocytes. Further research has suggested that this effect might also be found in solid tumors, and the phenomenon was termed the graft-versus-tumor (GVT) effect. In the case described here, the cervical cytology (CC) of the patient seems to have improved due to the GVT effect. She received allo-SCT twice following the diagnosis of acute myeloid leukemia. After her second allo-SCT, her CC seemed to change from squamous cell carcinoma to negative for intraepithelial lesion or malignancy. This change was likely linked to the degree of GVHD because when GVHD recurred and the immunosuppressant dose was increased, her CC improved. When the immunosuppressant dose was again decreased because of improvement of GVHD, her CC worsened. We report our experience together with a review of the literature.

Graft-versus-host disease (GVHD) is a potentially serious complication of allogeneic stem cell transplantation (allo-SCT), but patients who develop GVHD also have a low 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 (SCC) 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.

2 | 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 SCC (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 SCC 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 SCC 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

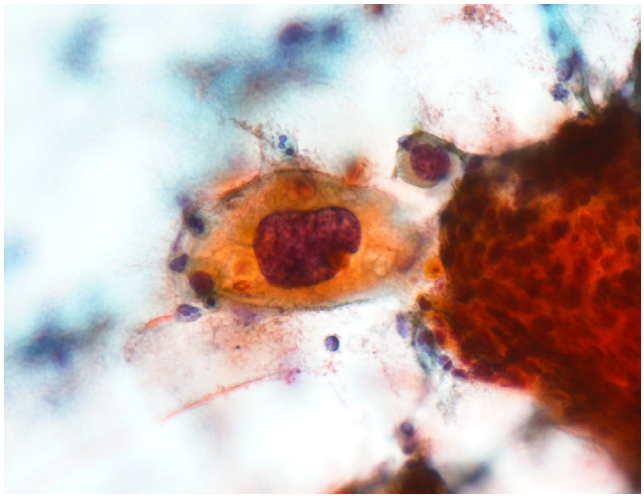

FIGURE 1 First cervical cytology: squamous cell carcinoma, atypical keratinizing cell with high N/C ratio, coarse chromatin, and irregular contours (×40 Pap smear)

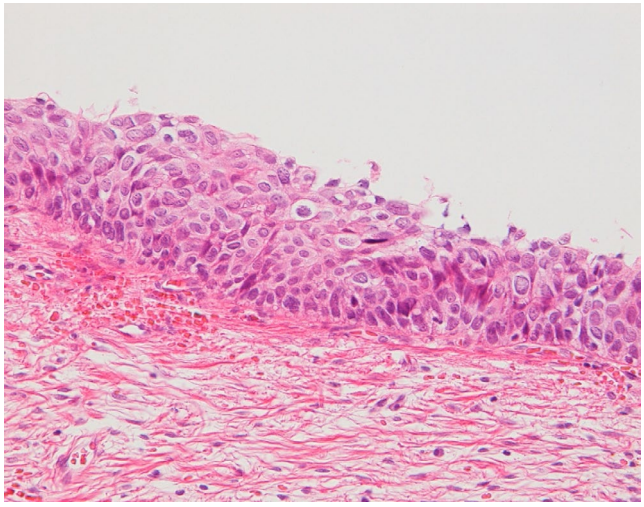

FIGURE 2 Pathological specimen from conization: High-grade squamous intraepithelial lesion showing full-thickness abnormalities with increased N/C ratio (×20 hematoxylin and eosin stain)

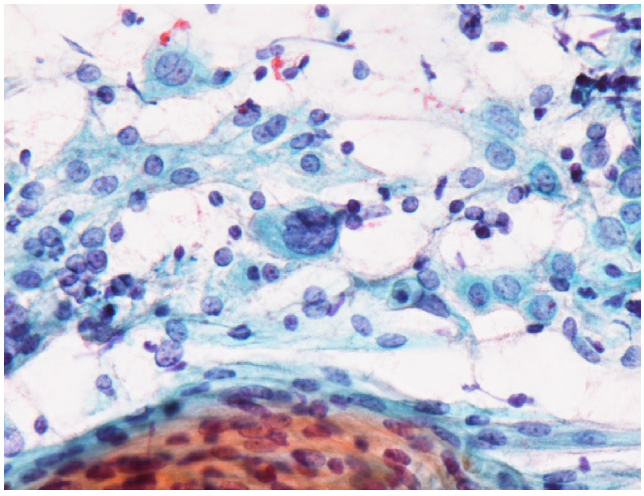

FIGURE 3 Cervical cytology 4 months after the second allogenic stem cell transplantation: high-grade squamous intraepithelial lesion showing atypical cells with high N/C ratio, coarse chromatin, and irregular contours (×40 Pap smear)

(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. Because 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 SCC after the operation (Figure 7), it improved to HSIL 5 months postoperatively (Figure 8).

It has been more than 7 years since her second allo-SCT and the leukemia has not recurred, although she is

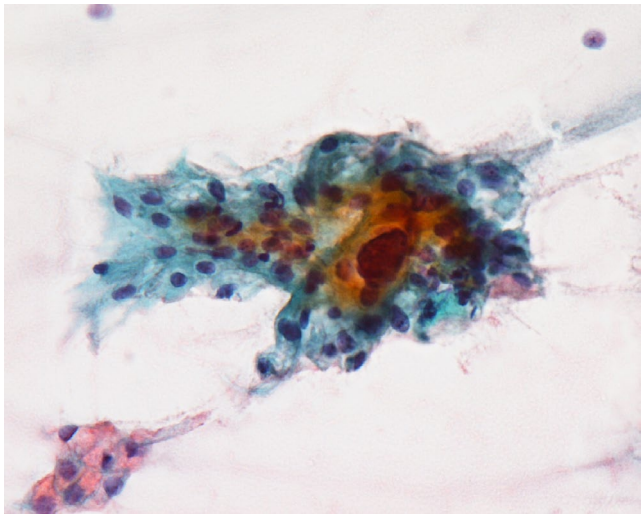

FIGURE 4 Cervical cytology 11 months after the second allogenic stem cell transplantation: atypical squamous cells of undetermined significance, with swollen nuclei but no apparent increased N/C ratio (×40 Pap smear)

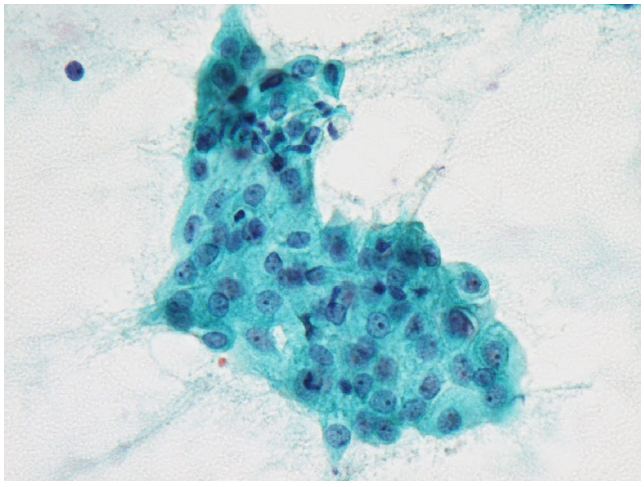

FIGURE 5 Cervical cytology 16 months after the second allogenic stem cell transplantation: negative for intraepithelial lesion or malignancy (×40 Pap smear)

still taking small doses of immunosuppressant. It has also been more than 3 years since the hysterectomy, and the cytology has transformed from HSIL to NILM without treatment (Figure 9).

3 | 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.

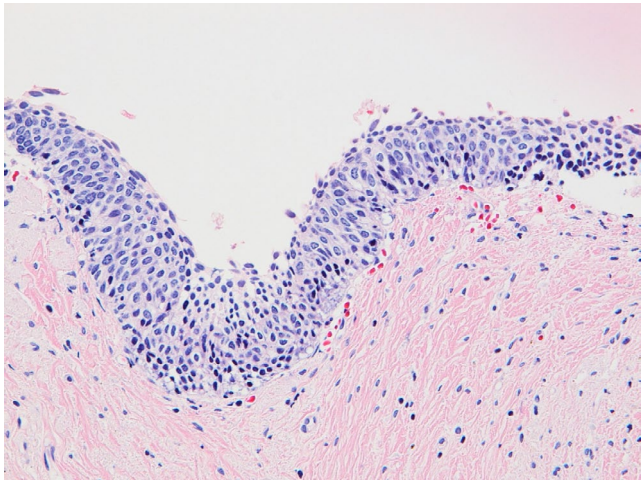

FIGURE 6 Pathological specimen from hysterectomy: cervical intraepithelial neoplasia, grade 3/HSIL showing full-thickness abnormalities with increased N/C ratio (×20 hematoxylin and eosin stain)

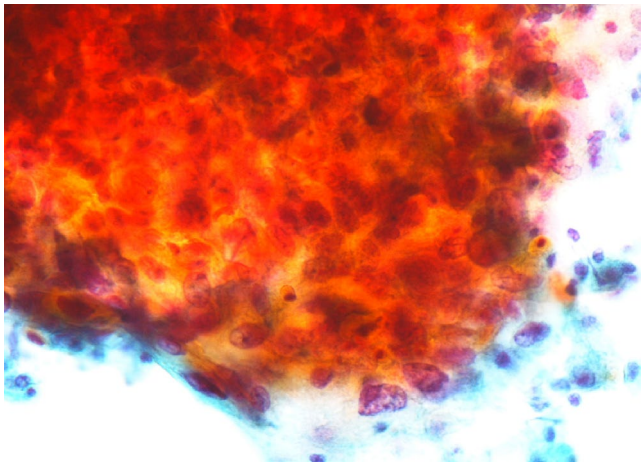

FIGURE 7 Cervical cytology 2 months after hysterectomy: squamous cell carcinoma showing aggregated atypical keratinizing cells with high N/C ratio, coarse chromatin, and irregular contours (×40 Pap smear)

Graft-versus-host disease is among the most potentially severe 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. Although the comprehensive mechanism underlying the GVT effect remains unknown, both donor T lymphocytes and natural killer cells are involved. It is believed that donor T lymphocytes recognizing several classes of antigens on the surface of tumor cells are the central mediators of the GVT effect in allo-SCT recipients. The natural killer cells target the recipient's proteins, which are overexpressed by the tumor.[2]

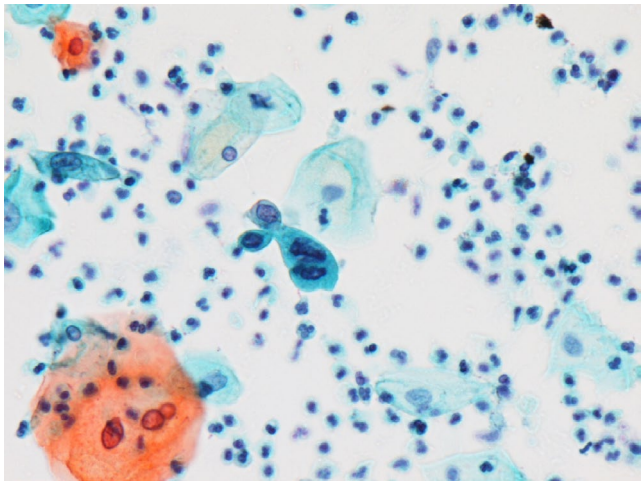

FIGURE 8 Cervical cytology 5 months later after hysterectomy: high-grade squamous intraepithelial lesion showing binucleated atypical cell with high N/C ratio, coarse chromatin, and irregular contours (×40 Pap stain)

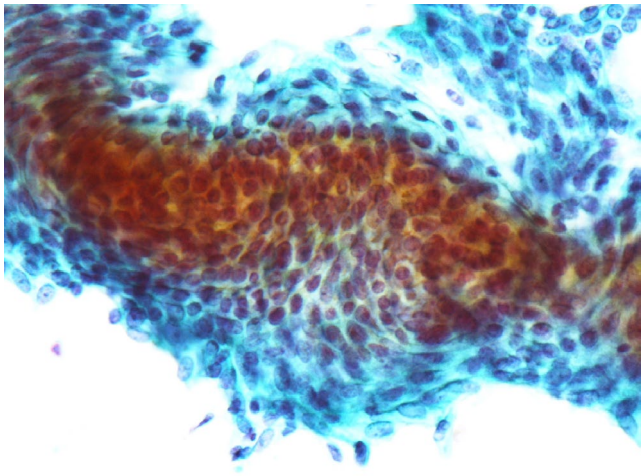

FIGURE 9 Cervical cytology 3 years after hysterectomy: negative for intraepithelial lesion or malignancy with no atypia (×40 Pap stain)

Eibl et al.[3] 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. 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. Childs et al.[4] performed allo-SCT in 19 patients with refractory metastatic renal-cell carcinoma, of whom three had complete response and seven had partial response. 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.[5]

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.[6] studied 82 women who underwent allo-SCT and found the cumulative incidence rate of any genital human papillomavirus (HPV) infection at 20 years after transplantation to be 40.1%. 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, because sexual activity after allo-SCT is generally decreased, the increased HPV infection rate was due to reactivation of

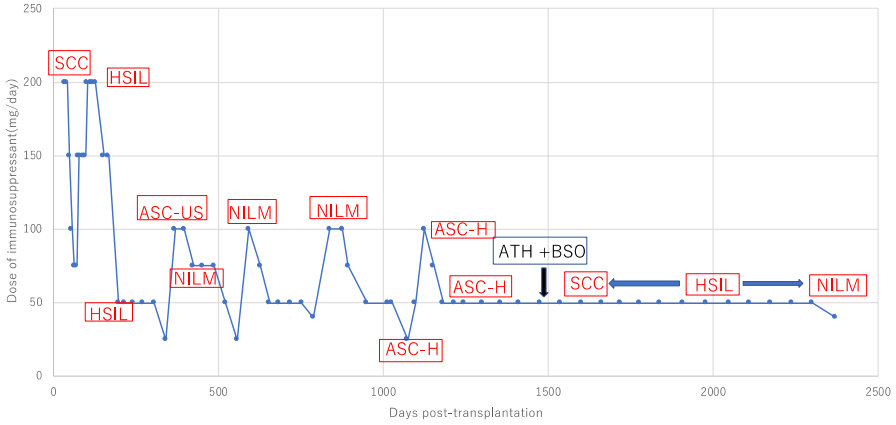

FIGURE 10 Course of cervical cytology and dose of immunosuppressant. ASC-H, atypical squamous cells cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; ATH+BSO, abdominal total hysterectomy and bilateral salpingo-oophorectomy; HSIL, high-grade squamous intraepithelial lesion;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

HPV rather than new infection. Moreover, viral reactivation may have been influenced by chronic GVHD and/or immunosuppression. Similarly, Savani et al.[7] reported that genital HPV disease occurred in one-third of 38 patients. All of them were long-term survivors of allo-SCT on prolonged immunosuppressive therapy. Savani 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.

4 | CONCLUSIONS

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.

ACKNOWLEDGMENT
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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
YK involved in supervision. HM involved in conceptualization. TN involved in conceptualization. KT involved in project administration. TK involved in resources, writing-review and editing. MO involved in resources.

ETHICAL APPROVAL
Because this report involves no experiment, ethic approval is waived.

CONSENT
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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