

# Isolated Extramedullary Relapse of Acute Myelogenous Leukemia as a Uterine Granulocytic Sarcoma in an Allogeneic Hematopoietic Stem Cell Transplantation Recipient

Hoyoung Maeng<sup>1</sup>, June Won Cheong<sup>1</sup>, Seung Tae Lee<sup>1</sup>, Woo Ick Yang<sup>2,3</sup>, Jee Sook Hahn<sup>1</sup>, Yun Woong Ko<sup>1</sup>, and Yoo Hong Min<sup>1,3</sup>

Departments of <sup>1</sup>Internal Medicine, <sup>2</sup>Pathology, and <sup>3</sup>BK21 Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea.

We report an unusual case of acute myelogenous leukemia in a patient who showed an extramedullary relapse in her uterus, without bone marrow recurrence, two years after an allogeneic bone marrow transplant. She complained of irregular vaginal spotting, and magnetic resonance imaging demonstrated a uterine mass. A biopsy revealed a massive infiltration of immature myeloid cells. A variable number of tandem repeats (VNTR) based on an examination of peripheral blood cells showed full donor chimerism. After receiving chemotherapy, her uterine mass had completely resolved. She has remained in complete remission for more than 6 months. This case suggests that physicians should be aware of the possibility of a uterine relapse in female bone marrow transplant recipients with acute myelogenous leukemia.

**Key Words:** Acute myelogenous leukemia; relapse; uterus; bone marrow transplantation

## INTRODUCTION

Since the application of bone marrow transplants (BMT) for leukemia treatment, extramedullary (EM) relapses have often been reported. Frequent sites of recurrence are the central nervous system (CNS) and the skin, although EM relapses in other organs have also been found.

However, an isolated EM relapse without a recurrence in the bone marrow is particularly rare. The term 'granulocytic sarcoma' is used to indicate solid aggregates of malignant myeloid blastic cells, and frequently indicates an extramedullary tumor in acute myelogenous leukemia.

We report an uncommon case of an isolated EM relapse in the uterus without evidence of a BM recurrence following allogeneic BMT.

## CASE REPORT

A 30-year-old woman presented with irregular vaginal spotting that had persisted for 2 weeks. She was previously diagnosed as having acute myelogenous leukemia (AML), and a surface marker analysis of bone marrow aspirates showed CD 13 and CD 33 expression, but not CD 7, HLA-DR or CD14 expression. Reverse transcriptase-polymerase chain reaction (RT-PCR) for an AML1/ETO gene rearrangement was positive. She was in complete remission (CR) after the remission induction chemotherapy with cytosine arabinoside 100 mg/m<sup>2</sup> (day 1-7) and idarubicin 12 mg/m<sup>2</sup> (day 1-3), and one course of consolidation chemotherapy. Two months after achieving CR, she received an allogeneic BMT from her HLA and ABO-matched younger brother after conditioning therapy with cyclophosphamide at 60 mg/kg once daily i.v. on days -8 and -7 and total body irradiation (total dosage 1320 cGy in 8 fraction) for

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Reprint address: requests to Dr. Yoo Hong Min, Department of Internal Medicine, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-361-5438, Fax: 82-2-393-6884, E-mail: minbrmnd@yumc.yonsei.ac.kr

4 consecutive days from day -5. After BMT, no acute or chronic graft-versus-host disease (GVHD) developed during follow-up.

She was nulli gravida, nulli para, and denied any sexual activity. Careful palpation of her lower abdomen detected an enlarged uterus similar in size to that of a 6<sup>th</sup> week intrauterine pregnancy. A colposcopic examination revealed a friable mass, showing touch bleeding, protruding from the uterine cervix. The pathological diagnosis of the biopsied mass was of a granulocytic sarcoma (Fig. 1). Magnetic resonance imaging (MRI) of the pelvis showed a diffusely enlarged uterus to a largest diameter of 6.5 cm with destruction of the endometrial zonal anatomy and multifocal heterogeneous low signal intensity lesions from the upper vagina to the right parametrium, which suggested a malignant infiltrative process (Fig. 2A).

With the impression of relapsed acute myelogenous leukemia, she was referred to the hematology department. A complete blood count revealed a white blood cell (WBC) count of  $5.96 \times 10^9/L$ , a hemoglobin of 11.2 g/dL, and a platelet count of  $267 \times 10^9/L$ . Her peripheral blood smear and bone marrow (BM) examination were unremarkable, showing no evidence of a relapse. Her chromosome study using BM cells and the G-banding technique showed 46,XY and her AML1/ETO gene rearrangement test was negative. Complete donor chimerism was documented by variable number of tandem repeat (VNTR)-PCR analysis using peripheral mononuclear cells.

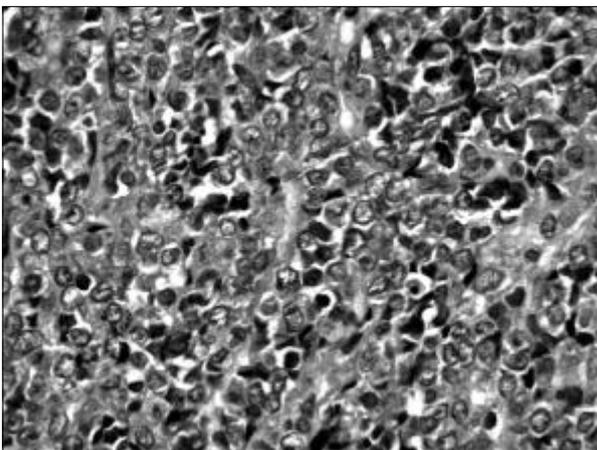


Fig. 1. Cervical punch biopsy showing immature myeloid blastic cell infiltration; a finding compatible with granulocytic sarcoma. (Hematoxylin and eosin,  $\times 400$ ).

Remission re-induction chemotherapy was administered with a combination of mitoxantrone  $10 \text{ mg/m}^2$  and etoposide  $100 \text{ mg/m}^2$  once daily i.v. on days 1 to 3 and cytosine arabinoside  $1,000 \text{ mg/m}^2$  twice daily by i.v. infusion over 2 hours from day 1 to day 5. After 20 days of neutropenia, her hemogram was finally restored. The follow-up MRI taken on 30<sup>th</sup> day of treatment showed that the uterine mass had been resolved (Fig. 2B); moreover, multiple colposcopic biopsies of the uterine cervix revealed a complete disappearance of leukemic cells. She has remained in complete remission for more than 6 months by imaging studies and pathologic examinations.

## DISCUSSION

The incidence of EM relapse following hematopoietic stem cell transplantation (HSCT) appears to be increasing as the number patients and the duration of patient follow-up increase. In a 10-year survey conducted by the European BMT Registry (EBMTR), the incidence rate of EM relapse was 0.65% for AML patients after a BMT in 1988. However, much higher figures of 1.3% to over 20% were reported when the cases of transplant-related deaths was excluded in 1999.<sup>1-3</sup> In addition, with a longer follow-up and more extensive use of donor lymphocyte infusion (DLI), which tends to emphasize the graft-versus-

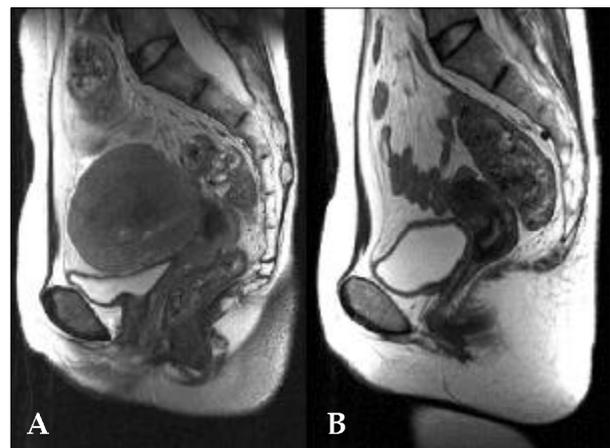


Fig. 2. Pelvic MRI showing the complete disappearance of the uterine mass and the restoration of uterine size. (A) before chemotherapy, and (B) 2-months after chemotherapy.

leukemia (GVL) effect, the incidence of EM relapse is expected to increase in HSCT recipients, and to show relapse patterns that differ from those treated with chemotherapy alone.<sup>2</sup>

The generally accepted definition of an isolated EM relapse is the presence of a new isolated focus of EM leukemia, which occurs during BM remission, but which is not followed by a BM relapse within 30 days.<sup>4</sup> The common sites of EM relapse after HSCT coincide with those of primary granulocytic sarcomas, which include those of the breast, gastrointestinal tract, skin and spine, in addition to the well-known sanctuary sites of the CNS and testis. The other reported sites of an EM relapse are the pancreas, nasopharynx, paranasal sinus, bladder, peritoneal cavity, and pleura.<sup>2,5</sup> However, no report has been issued on uterine granulocytic sarcoma after HSCT for AML, though a single patient with acute lymphoblastic leukemia (ALL) was reported to have developed this disease.<sup>6</sup>

The mechanisms of an EM relapse are unclear. The factors predisposing primary granulocytic sarcoma apply equally to an isolated EM relapse, and include cytogenetic abnormalities such as t(8;21) and inv(16), the MLL rearrangement, and FAB classification M2, M4 and M5 subtype.<sup>2,4</sup> Several suggestions have been made concerning specific tissue predilections. A specific cell surface molecule expression may be one possible explanation and cellular origin of granulocytic sarcoma is sometimes important. We tried to determine whether tumor cells originate from the recipient or from the donor by using a gene rearrangement study or by karyotyping, but failed due to an insufficiency of biopsy material.

One proposed mechanism of isolated EM relapse concerns the continued effect of graft-versus-leukemia (GVL) in the BM, but not at the EM sites previously unexposed to chemotherapeutic agents or anti-leukemic effector cells, or where anti-leukemic effector cells are unable to function due to the presence of a natural barrier or a micro-environmental condition. In a report of 5 assorted cases of isolated EM relapse, only one case had significant (grade 3-4) acute GVHD, and as a consequence, it was suggested that GVHD in itself is important in the development of EM disease.<sup>7</sup> In another report, the presence of extensive

chronic GVHD was observed only in patients with EM relapse, which is in contrast to the findings of a group who found BM relapse only, which suggested that chronic GVHD has a preventive effect on medullary relapse.<sup>3</sup>

The optimal management of isolated EM relapses after HSCT should be individualized. Cumulative anticancer chemotherapeutic agent toxicity or radiation injury before and during HSCT, immune suppressive agents administered to prevent or treat graft-versus-host disease, and imperfect immune reconstitution after HSCT, might negatively affect patient outcome by increasing the treatment related morbidity and mortality of re-induction chemotherapy or of a second HSCT for relapsed AML. Therefore, an EM relapse after HSCT should be treated in a different way to that of a primary isolated granulocytic sarcoma, which is usually treated successfully using combined local and systemic radical therapies.<sup>8</sup> Previous reports have emphasized the use of local treatments including radiation therapy and surgery for this condition, although all agreed that systemic therapy with combination chemotherapy and minimal residual disease (MRD) - targeted therapy, is also important, because a full blown BM relapse may develop even in those who have been under complete local control for 12 months.<sup>4</sup> Radiotherapy is effective at achieving initial control of a granulocytic sarcoma in most cases, and donor lymphocyte infusion (DLI) might be used to control a residual or relapsed leukemia. However, the efficacy and risk-benefits of DLI in EM disease should be investigated.<sup>9</sup> Aggressive treatment with high dose chemotherapy plus stem cell rescue is a therapeutic option in some selected cases. In the present case, the patient was treated using combination chemotherapy at a conventional level, and showed rapid tumor resolution. She has remained in the disease-free status for several months.

Regarding prognosis, post-relapse survival (median 11 months) is shorter than for those who have never relapsed, but longer than for those who have experienced a BM relapse (median 2 months); univariate analysis indicated a longer post-relapse survival with a longer time to relapse from HSCT.<sup>3</sup> However, debate continues as some authors advocate that an 'isolated' EM relapse in

itself does not affect overall survival versus those who have never relapsed.<sup>8</sup>

In conclusion, we suggest that physicians should be aware of the possibility of uterine relapse in female bone marrow transplant recipients with acute myelogenous leukemia.

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