Case report

Uterine relapse of Philadelphia chromosome-negative acute lymphoblastic leukemia

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The relapse of acute lymphoblastic leukemia (ALL) usually involves the bone marrow, with the central nervous system being the most frequent extramedullary site.   The relapse of ALL in the female genital organs, particularly the uterus, is markedly rare.   We report such a patient who developed relapse in the bone marrow and uterus.   The uterine lesion, which presented as abnormal uterine bleeding, consisted of a mass on MRI and proliferation of ALL cells on histology.   MRI revealed a heterogeneous high-intensity mass (T2-WI/D-WI) with a diameter of 6.8 cm, a notable decrease in the apparent diffusion coefficient (ADC), and mild enhancement by contrast enhancement study.   Histological findings of the uterine cervix demonstrated the infiltration of ALL.   The patient achieved remission by allogeneic haplo-identical hematopoietic stem-cell transplantation, but died of complications of the transplantation.   This case suggested that attention should be paid to the uterus as a site of extramedullary relapse.   In addition, abnormal uterine bleeding, which is a common sign of hormonal imbalance and hormone replacement therapy after chemotherapy, may be an initial sign of extramedullary recurrence.   To confirm uterine relapse as an intractable disease, the accumulation of more cases is required.

Keywords: Philadelphia-negative B-ALL, uterine relapse, MRI features, refractory clinical course

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a hematological malignancy characterized by clonal proliferation of abnormal lymphoblasts in the bone marrow.[1-3]   The relapse of ALL usually involves the bone marrow, but occasionally involves extramedullary sites.   Most extramedullary relapse involves the central nervous system,[1-3] and that in the female genital organs, particularly the uterus, is markedly rare.[4-8]

We describe an ALL patient with relapse in the bone marrow and uterus after cord blood stem-cell transplantation (CBT).   The importance of this case is discussed.

CASE PRESENTATION

Case: A 46-year-old woman with fever and petechiae visited her family doctor, and was transferred to our hospital because of anemia and thrombocytopenia.   Laboratory findings included a hemoglobin concentration of 4.9 g/dL, platelet count of 19 x 10^9/L, and white blood cell count of 3.81 x 10^9/L with 4% blasts.   In addition, bone marrow examination demonstrated the proliferation of abnormal lymphoid blasts (91%) with a phenotype of CD19+, CD10+, HLA-DR+, CD24+, cyCD79a+, cyCD22+, CD15+, CD65+, CD13-, CD33-, and myeloperoxidase (MPO)-.   Chromosomal analysis by G-banding revealed a normal karyotype without

the Philadelphia chromosome. Other molecular analyses revealed negative findings regarding PML-RARA, AML1-MTG8, CBFB-MYH11, NUP98-HoxA, ETV 6-AML 1, E2A-HLF, SIL-TAL-1, MLL-AF4, MLL-AF6, MLL-AF9, and MLL-EML. No extramedullary mass lesions were found on whole-body CT. Based on these findings, the patient was finally diagnosed with Philadelphia chromosome-negative B-ALL. At the initial diagnosis, the extramedullary lesion was not present on CT examination. The patient was treated by the protocol of MRD 2008[9] and achieved complete remission (CR).

However, after 18 months, the patient developed the first relapse in the bone marrow (41% abnormal lymphoid blasts). No extramedullary lesion was observed at that time. The patient received two courses of hyper-CVAD/MA therapy[10] and achieved second CR. As the patient had no HLA-identical donor among related or unrelated individuals, she received allogeneic CBT from a two HLA loci-mismatched cord blood (NCC 2.96 x 10^7 cells/kg and 1.07 x10^5 CD34+ cells/kg), with a conditioning regimen consisting of cyclophosphamide (120 mg/kg) and total-body irradiation (TBI, 12 Gy). Engraftment was achieved at day 17. The main complications were pre-engraftment immune reaction (PIR), human herpesvirus 6 (HHV-6) DNAemia, cytomegalovirus (CMV) antigenemia, and acute graft-versus-host disease (GVHD) (grade 2 by skin biopsy). Thus, the patient achieved second CR, and by controlling transplantation-related complications, she was discharged from the hospital on day 90.

Six months later, the patient suddenly presented with abnormal vaginal/uterine bleeding. CT revealed a large mass in the uterine region (Figure 1A, B), but no masses were found in other regions of the body. Furthermore, MRI revealed a heterogeneous high-intensity mass (T2-WI/D-WI) with a diameter of 6.8 cm, a notable decrease in the apparent diffusion coefficient (ADC) (0.4 x 10(-3) mm^2/s), and mild enhancement by contrast enhancement study (Figure 1C-F). Biopsy of the uterine cervix revealed small aggregates of atypical lymphoid cells with round nuclei, some distinct nucleoli, and scant cytoplasm in the hemorrhagic and edematous background (Figure 2A). Immunohistochemically, these lymphoid cells were positive for CD79a and TdT (Figure 2B, C), but negative for CD20, cCD3, CD5, CD34, and MPO. Reactive T cells (cCD3+/CD5+) were intermingled in the background. Bone marrow examination demonstrated 81% blasts. Based on these findings, the patient was judged to have secondary relapse involving the bone marrow and uterus. Subsequently, two courses of hyper-CVAD/MA therapy were performed, which led to the third CR according to the response criteria of the International Working Group of Acute Leukemia (2003).[11] Furthermore, extramedullary uterine lesions of ALL were not detected by CT or MRI. However, the third relapse was observed five months later. Bone marrow examination demonstrated 40% blasts and PET/CT revealed a mass in the uterus. Thus, she underwent the second transplantation from an HLA-haploidentical donor (her daughter) with a conditioning regimen consisting of

fludarabine (Flu) (150 mg/mm^2), busulfan (Bu) (12.8 mg/kg), melphalan (MEL) (100 mg/mm^2), anti-thymocyte globulin (ATG) (5 mg/kg), and TBI (2 Gy). The second transplantation led to the fourth CR without extramedullary uterus lesions by PET/CT, but she died on day 166 because of severe hemorrhagic cystitis (BK) (grade 3) and sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) (grade 4). Permission for autopsy was not granted.

DISCUSSION

We presented a rare case of B-ALL with uterine relapse in which the patient presented with abnormal vaginal/uterine hemorrhage after CBT. Subsequent MRI examination was useful. Previously reported cases of ALL with uterine relapse and our case are listed in Table 1 in order to discuss the clinical features and treatment outcome after chemotherapy and HSCT.

First, initial clinical signs, such as vaginal/uterine hemorrhage (four cases, Table 1), and the use of MRI may be important to diagnose the uterine relapse of ALL. Although uterine bleeding is a common sign of hormonal imbalance, uterine leiomyoma, adenomyosis, uterine cancer, or hormone replacement therapy after chemotherapy, it is necessary to pay attention to the condition for a long period of time because uterine relapse of ALL can develop even several years later. Furthermore, abdominal pain as a sign of relapse, which was observed in two cases (Table 1), should be carefully followed up. At present, MRI is useful for distinguishing cancer from benign disease, staging, and treatment response.[12] Furthermore, in female genital organs, including the uterus and ovaries, MRI is useful for the clinical diagnosis of many diseases by distinguishing benign disease, cancer, and lymphoma.[13,14] In malignant lymphoma, MRI demonstrates T2 high intensity with Gd enhancement and a decrease in ADC.[15,16] For the diagnosis of uterine relapse of ALL, MRI was effective in two previously reported cases and ours, and its common findings, i.e., T2 high intensity with Gd enhancement and the marked decrease in ADC, may be useful to differentiate the lesion from primary uterine cancer.

Second, regarding the treatment outcome, ALL with uterine relapse may follow a refractory clinical course. Almost all reported patients were refractory to chemotherapy, with only two being alive. Although there are no established guidelines for extramedullary relapse after allo-HSCT due to limited previous reports, systemic chemotherapy, repeated allo-HSCT, DLI, and focal irradiation may be effective.[17,18] In our case, bone marrow relapse occurred at the same time as uterine relapse after CBT, thus systemic treatment was required. Although there were repeated recurrences in the uterus, PET demonstrated remission after the haploidentical transplantation. Radiation therapy for uterine was not carried out because of expected GVL effects by haploidentical transplantation. Thus, intensive immunotherapy, including a combination of chemotherapy and allo-HSCT from HLA-mismatched donors, may be needed to cure ALL with uterine
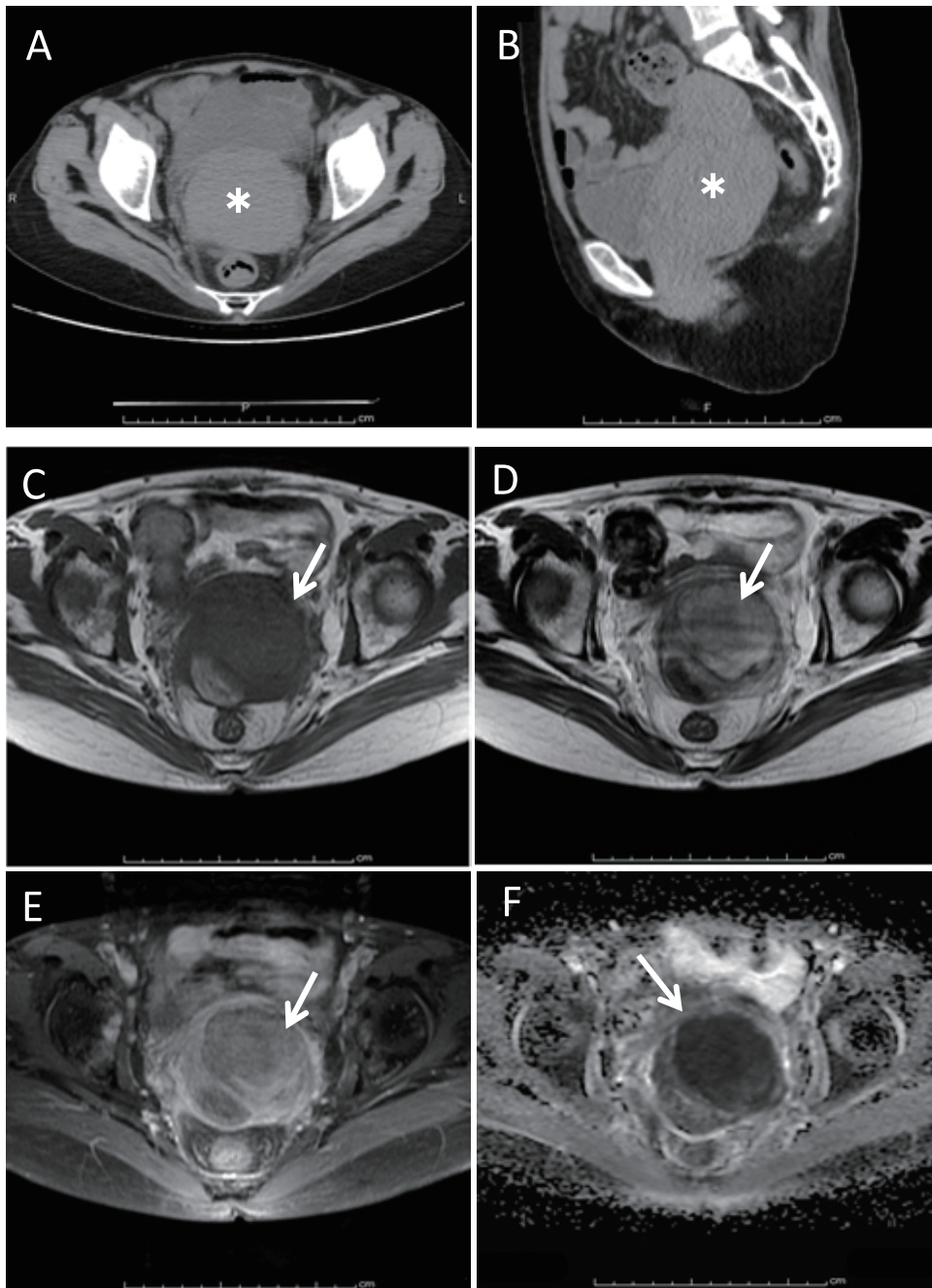
Fig. 1. CT/MRI findings in the lower abdomen.
A; Horizontal section (CT), *B*; Sagittal section (CT), *C*; T1 high-intensity lesions (MRI), *D*; T2 high-intensity lesions (MRI), *E*; Apparent diffusion coefficient (ADC) (MRI), *F*; Gd enhancement (MRI). Asterisks and arrows indicate the uterus and uterine mass, respectively.
1*A* and 1*B*. CT findings of extramedullary uterine relapse. The uterine lesion was not detected at the time of initial diagnosis, but was evident as a mass at the time of the second relapse.
1*C*-1*F*. MRI findings of uterine relapse. MRI revealed a 6.8-cm uterine mass having heterogeneous high intensity (T2-WI/D-WI), marked ADC decrease ($0.4 \times 10(-3)$ mm^2/s), and a mild to moderate degree of enhancement (CE study).

relapse. Regarding prognostic factors for the outcome of ALL, age at diagnosis (greater than 35 years) is an important factor in B-ALL. In addition, leukocyte count (greater than 30,000/μL), presence of t(9;22) or t(4;11), and treatment response for induction therapy were reported as prognostic factors.[19,20] Among these factors, only the age at diagnosis was a factor in three of five reported cases and in ours.

Thus, to clarify the risk factors for the development of extramedullary uterine relapse of ALL, further accumulation of such cases is essential.

Lastly, regarding the pathogenesis of uterine relapse of ALL after CBT, four of five reported cases and ours demonstrated uterine cervical involvement, whereas the remaining reported case included both uterine cervix and corpus
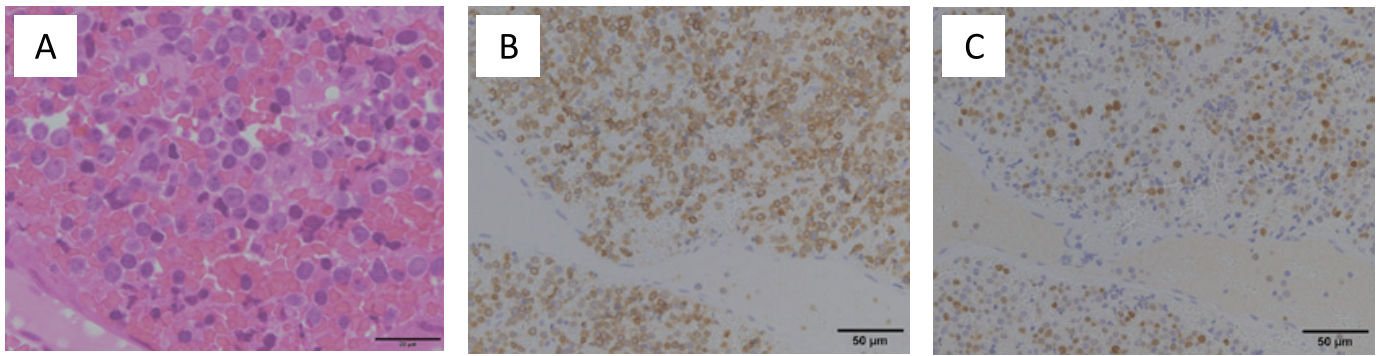
Fig. 2. Histological and immunohistochemical findings of the uterine biopsy.
A; H.E. (x100), *B*; CD79a (x40), *C*; TdT (x40)
2*A*-2*C*. Recurrence of ALL at the uterus was confirmed by biopsy. There were small aggregates of lymphoid cells with medium-sized round nuclei, some exhibiting distinct nucleoli and scant amount of cytoplasm in the endocervical mucosa. Immunohistochemically, these lymphoid cells were positive for CD79a and TdT, but negative for CD20, cCD3, CD5, CD34, and MPO. Reactive T-cells (cCD3-positive) were intermingled in the background. The Ki67-positive rate of these lymphoid cells was approximately 50%. These findings are consistent with ALL cells.

Table 1. Cases of uterine relapse of acute lymphoblastic leukemia

References	Age (yrs) Sex	Ph(+/-) T/B	Leukocyte count (/μL)	Therapy before relapse	Response to therapy	Initial signs at relapse	Time to relapse (years)	Diagnostic Tool (anatomical site of the uterus)	Therapy	Outcome; OS (years) (Cause of death)
Zutter MM	36 female	Ph- B	n.d.	Chemo	CR	Vaginal hemorrhage	2	n.d. (Uterine cervix)	Chemo+RT	Dead; 3 years (relapse)
Tsuruchi M	7 female	Ph- B	1900	Chemo+RT	CR	Abdominal pain	3.6	CT (Uterine cervix)	Chemo	Alive; 4.5 years
Ikuta A	60 female	Ph- B	n.d.	Chemo	CR	Vaginal hemorrhage	2	MRI (Uterine Cervix and corpus)	Chemo	Dead; n.d. (relapse)
Novellas S	15 female	n.d.	n.d.	Chemo	CR	Vaginal hemorrhage	6	MRI (Uterine cervix)	Chemo+RT	Alive; 7 years
Kazi S	59 female	Ph- B	n.d.	Chemo	CR	Abdominal pain	n.d.	CT (Uterine cervix)	Chemo, Allo-HSCT	Dead; n.d. (relapse)
Our Current case	46 female	Ph- B	3810	CThemo+CBT	CR	Vaginal/ uterine hemorrhage	4	CT, MRI (Uterine cervix)	Chemo, Allo-HSCT	Dead: 5 years (HSCT complication)

Abbreviations CBT, cord-blood transplantation; Chemo, chemotherapy; HSCT, hematopoietic stem-cell transplantation; n.d., not described; OS, overall survival; Ph, Philadelphia chromosome; RT, Radiation therapy; T/B,T or B acute lymphoblastic leukemia.

involvement, although both sites have different biological natures. Furthermore, the uterus may not be a target of acute and chronic GVHD.[21] In our case, the uterine relapse may have been due to the uterus being a weak alloreactive target of acute or chronic GVHD and GVL. Thus, the relapse of ALL in the uterus may be explained by the organ not being a target of acute or chronic GVHD and GVL. Further accumulation of such cases is needed to elucidate the pathogenesis of the uterine relapse of ALL.

In conclusion, this case suggests that the uterus should be noted as an organ for extramedullary relapse of ALL. Although reports regarding the uterine relapse of ALL are limited, abnormal vaginal/uterine hemorrhage should be carefully examined for a long period of time during the follow-up of ALL patients with partial or complete remission. Furthermore, MRI may be a useful diagnostic tool in such patients.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest

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