Breast and ovarian recurrence of acute lymphoblastic leukaemia after allogeneic peripheral blood haematopoietic stem cell transplantation

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ABSTRACT

Breast recurrence of acute lymphoblastic leukaemia (ALL) after stem cell transplant is uncommon, with less than 20 reported cases in the literature. In the majority of cases, the lesions developed without simultaneous involvement of other sites or graft-versus-host disease (GvHD). We describe the first case of simultaneous bilateral breast and ovarian relapses after allografting in ALL, occurring in an 18-year-old female Chinese patient while she was having oral and hepatic chronic GvHD, persistent haematological remission and donor haematopoiesis. She received radiotherapy and chemotherapy, which resulted in resolution of the breast and ovarian lesions, and remained disease-free ten months after the onset of the relapse. This case suggests that there may be different mechanisms for bone marrow vs. extramedullary relapses and a complex relationship between GvHD and graft-versus-leukaemia.

Keywords: acute lymphoblastic leukaemia, allogeneic peripheral blood haematopoietic stem cell transplantation, breast leukaemia relapse, graft-versus-host disease, ovarian leukaemia relapse

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INTRODUCTION

Extramedullary (EM) relapse of acute lymphoblastic leukaemia (ALL) in the breast or ovary is uncommon after either allogeneic haematopoietic stem cell transplantation (allo-HSCT) or chemotherapy (CMT).[1] There have been 15 reported cases of breast relapse in ALL after stem cell transplant (SCT).[2] They all occurred within 24 months of transplantation. In 11 cases, the breast lesions were unilateral, and in six, there were prior or simultaneous bone marrow (BM) involvement. Four cases had simultaneous involvement of other sites.

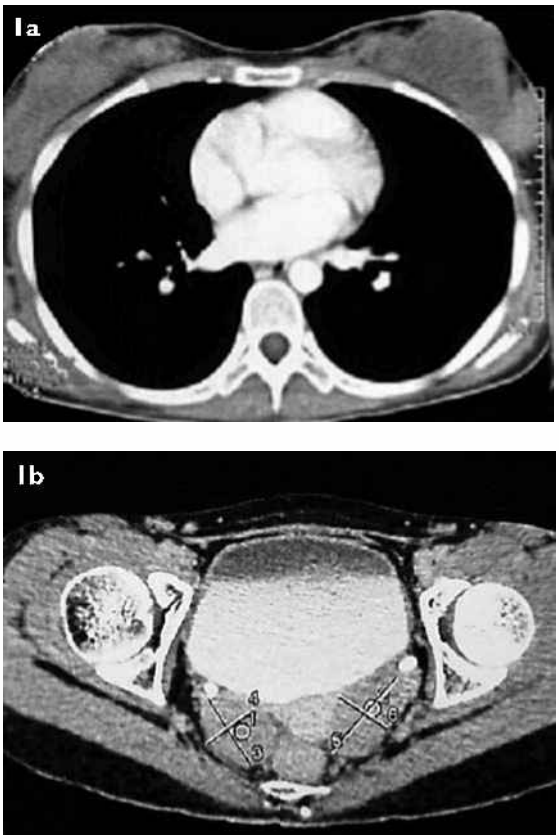

Fig. 1 Axial CT images show (a) diffuse infiltration of the breasts with nodular lesions, and (b) masses in the ovaries (right, 4 cm × 3 cm; left, 6 cm × 5 cm).

None of them had concurrent graft-versus-host disease (GvHD). Following treatment that consisted of either radiotherapy (RT) alone or RT plus CMT with or without donor lymphocyte infusion (DLI), most patients, except two patients who had received the combined therapy (RT/CMT/DLI), relapsed or died.[3] We describe an uncommon case of bilateral breast and ovarian relapse of ALL after allo-SCT, occurring while there were complete donor chimerism and GvHD. The patient responded to treatment (RT/CMT/DLI) and remained well ten months after the onset of relapse.

CASE REPORT

In September 2005, an 18-year-old female Chinese

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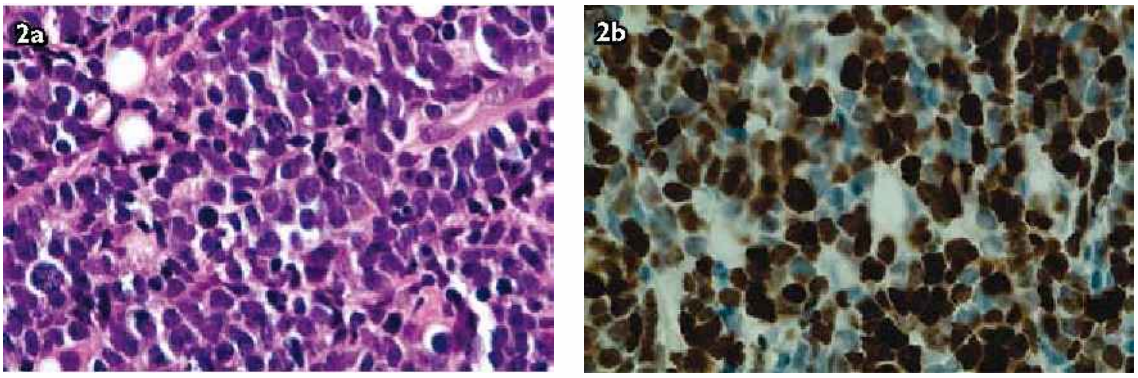

Fig. 2 Photomicrographs of the breast mass show (a) malignant cells exhibiting oval nuclei with scanty cytoplasm and an absence of breast acini (Haematoxylin & eosin, × 40), and (b) over 90% of the malignant cells expressing Ki-67 (Ki-67, × 40).

patient presented with fever and hyperleucocytosis (leucocyte count 229 × 10^9/L). Her BM was packed with lymphoblasts expressing CD10, CD19, CD34 and TdT, which was consistent with a diagnosis of B-precursor ALL. The cytogenetic study was unremarkable. The patient was treated with a high-risk ALL CMT protocol and achieved haematological remission in November 2005. In March 2006, she underwent allogeneic peripheral blood HSCT during her first complete remission. Cyclophosphamide 120 mg/kg and total body irradiation 12 Gy were used as conditioning regimen, while cysclosporin, methotrexate and prednisolone were given as GvHD prophylaxis. She received granulocyte colony-stimulating-factor–mobilised peripheral blood stem cell (4.5 × 10^6 $CD34^+$ cells/kg) collected from a human leucocyte antigen-identical female sibling donor. The patient achieved neutrophil engraftment on Day 21 after SCT. Grade I oral GvHD that was treated with mouthwash and mild hepatic GvHD appeared on Day 160. On Day 172, she presented with a 2 cm × 1 cm lump in her left breast, and two months later, the lumps had increased in size, involving both breasts. Physical examination revealed hard masses measuring 3–6 cm in the breasts, and dryness, atrophy and lichen planus-like lesions in the oral cavity, which were consistent with chronic GvHD. The patient requested to delay further investigations and treatment, but was readmitted at Day 270 post-SCT, with diffuse enlargement and an "orange peel" appearance of her breasts.

The haemoglobin on admission was 13.6 g/dL (normal red cell indices), leucocyte count 5.8 × 10^9/L (normal differential counts) and platelets 195 × 10^9/L. The liver enzymes and serum lactate dehydrogenase (LDH) were twice the normal range. Computed tomography (CT) showed multiple nodular lesions in the breasts, lobulated masses in the ovaries (3–4 cm) and lymph node enlargement in the axillae (Fig. 1). Fine needle aspiration cytology of the breast masses revealed tumour cells, and histological examination confirmed pre-B ALL (Fig. 2). Simultaneously, there was no blast in the peripheral blood. Short tandem repeat-polymerase chain reaction study showed that the patient's BM cells were 100% of donor origin (complete donor chimerism). She underwent RT (40 Gy) of the breasts, resulting in a partial resolution of the breast lesions. Then she received CMT (mitoxantrone and cytosine arabinoside), followed by 10 × 10^6/kg donor lymphocytes, resulting in a normalisation of the serum LDH, a near-complete remission of the breast lesions and a total resolution of the ovarian masses. The oral and hepatic GvHD remained well-controlled with conservative treatment. Approximately two years after the diagnosis of ALL and ten months after the onset of relapse in the breast, the patient was still alive and free of disease.

DISCUSSION

EM recurrences following allo-SCT for ALL usually occur in the "sequestered sites", i.e. the testis and central nervous system.[4] However, the breast is being reported with increasing frequency among female patients with acute leukaemia having a first EM relapse after SCT.[5] In all 16 cases, including our patient, the breast relapse occurred within 24 months of transplant, and the time after the original diagnosis of ALL ranged 12–65 months.[2] Simultaneous involvement of other EM sites in patients with breast relapse after allo-SCT is uncommon, and has been reported in the skin, bone, bladder and pancreas.[2] However, involvement of the ovaries, as in our patient, has not been described.

Risk factors for breast leukaemia cannot be determined from the limited data available, but it is apparent that patients with various levels of white blood cell count, various karyotypes and immunophenotypes have experienced these lesions. Being in the

premenopausal age range may be significant, as 90% of female patients were reported to be younger than 50 years of age.[2] Additionally, breast recurrences without haematological relapse occurred in about 40%–50% of cases. This data suggests that there may be different pathogenetic mechanisms for BM vs. EM relapse after allo-SCT.

Interestingly, our patient had concomitant GvHD, complete donor chimerism and haematological remission of the BM, when she had a relapse of ALL in her breasts and ovaries. There was one other case of breast relapse of ALL that occurred despite hepatic GvHD and haematological remission after allografting in a B-ALL patient.[6] This illustrates an intriguing point that GvHD and graft-versus-leukaemia may have complex interactions, since EM relapses of ALL had occurred despite GvHD and the persistence of donor haematopoiesis. Several reports have suggested that the GvL effect at EM sites might be less prominent than in the BM.[7] Lee et al have shown that in 194 patients with acute leukaemia, GvHD after allo-SCT had an anti-leukaemic effect, which prevented BM relapse; however, it may be less effective in preventing EM relapse.[8]

Regardless of whether the BM is in morphologic remission, a breast lesion signifies systemic leukaemia. Once disseminated, EM disease is typically resistant to therapy. Although the optimal type and duration of therapy cannot be determined, owing to the small numbers of cases reported, surgery and RT alone have been inadequate treatments for breast leukaemia, which is rarely truly a unilateral or localised disease. Among the six patients who had received RT alone, one died and five relapsed (two in the BM, two in the breasts and one in the cerebrospinal fluid). One patient who had received only CMT experienced breast relapse a year later.[2] All four patients who were treated with RT plus CMT developed central nervous system, skin and systemic relapses. Among the patients who had received the combined therapy (RT/CMT/DLI), two died of GvHD after achieving complete remission, and two survived 51 and 70 months after the onset of breast relapse, respectively.[3,4] Four patients underwent a second allo-SCT and none achieved lasting remissions. One died of toxicity and three relapsed in the BM at 12 months.[1,3] Our patient received RT of the breasts followed by CMT and DLI, resulting in significant resolution of the breast and ovarian lesions, and was leukaemia-free ten months after the onset of the relapse. It appeared that intensive systemic treatment may be required for disease eradication and that the exact roles of RT, DLI and a repeat allo-SCT need to be investigated in future reports. Importantly, upon completion of induction therapy, it is essential to closely monitor the patients with mammograms, CT scans or functional imaging studies and BM biopsy, in view of the potential for local and systemic relapse.

To the best of our knowledge, simultaneous bilateral breast and ovarian relapses without marrow involvement after allografting in ALL have not been previously described. Premenopousal women who had received CMT or SCT for ALL should be monitored closely for recurrence in the breast and ovaries. Because the biological and clinical characteristics of breast relapse of ALL are currently unknown, further study is required before optimal treatment can be determined. Nonetheless, prompt initiation of intensive CMT combined with RT and DLI, assuming occult site involvement, should increase the potential for disease eradication.

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