CASE REPORT

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Acute myeloid leukemia relapse after allogeneic hematopoietic stem cell transplantation presenting as pericardial effusion

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1. INTRODUCTION

Extramedullary leukemic infiltration can occur as a manifestation of relapse. It is, however, rare with fewer than 10 cases of cardiovascular relapse reported in the literature, and it often presents as myeloid sarcoma.[1] We report a case of pericardial effusion presenting as an isolated extramedullary relapse (IEMR) of leukemia after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

2. DESCRIPTION

A 35-year-old female presented in November 2014 with a 10-day history of symptoms consisting of fever, fatigue, and ache in the elbow. Her medical history was significant for acute myeloid leukemia (AML) with normal chromosome karyotype, FAB class M5 at diagnosis. Gene mutation screening was positive for FLT3 exon20, ASXL1 exon12, Notch exon 25 and TET exon11. Flow cytometric analyses were positive for CD64, HLA-DR, CD33, CD13, CD56, CD36, and CD4 in the blastic cell population. Fluorescent in situ hybridization (FISH) reveals 95% MLL rearrangement. The patient achieved complete remission (CR) after induction chemotherapy containing homoharringtonine, cytarabine, and daunorubicin. She received 3 cycles of consolidation chemotherapy, also of homoharringtonine, cytarabine, and daunorubicin. She stayed in molecular CR. Consolidation was performed with allogeneic peripheral blood HSCT in March 2015, with cytarabine, fludarabine, cyclophosphamide, and busulfan conditioning. The donor was her 10/10 HLA-matched sister with the same ABO and Rh blood group. Grafts contained a $CD34^+$ cell count of 2.16×10^6/kg, and mononuclear cell count (MNC) of 9×10^8/kg. She achieved neutrophil and platelet engraftment 12 days post stem cell infusion. By 6 months posttransplantation, the patient had relapsed with bone marrow containing 20% blasts. Donor chimerism by short tandem repeat (STR) analysis showed that 80.23% of the bone marrow cells were from the donor. FISH revealed 4.2% MLL-positive signals. Donor peripheral blood stem cell infusion (MNC 1.94×10^8/kg, $CD34^+$ 0.47×10^7/kg) was followed by chemotherapy containing mitoxantrone, cytarabine, and cyclophosphamide immediately after relapse. This patient's course was complicated by acute graft-versus-host disease (aGVHD) of the skin (grade II) 3 weeks following the infusion. She was treated with cyclosporine and methylprednisolone, which ceased soon after her symptoms resolved. Her bone marrow achieved CR 7 months post-HSCT (1 month after the second infusion), and STR revealed 98.99% bone marrow cells from the donor. Subsequent treatment included a first donor lymphocyte infusion (DLI) (MNC 1.59×10^8/kg, $CD3^+$T 7.67×10^7/kg) 9.5 months post-HSCT and a second DLI (MNC 1.77×10^8/kg, $CD3^+$T 8.6×10^7/kg) 11.5 months post-HSCT; her bone marrow then remained in CR. The patient subsequently presented with progressive chest tightness and suffocation 15 months after HSCT, and pericardial effusion was diagnosed by echocardiogram. This showed an echoless area of 2.39, 1.5, and 1.2 cm behind the left ventricle, cardiac apex, and right ventricle, respectively. Chest computed tomography (CT) confirmed the diagnosis of pericardial effusion and eliminated the possibility of pneumonia and pneumothorax (Fig. 1A). Pericardiocentesis was performed which produced a grossly bloody effusion. Histological analysis with Wright-Giemsa of the pericardiocentesis specimen showed 95% immature monocytes (Fig. 1B). This was later confirmed by flow cytometry with 95% immature monocytes, and FISH analysis of the pericardiocentesis specimen revealed 94% positive MLL rearrangement cells. Chromosomal analysis of effusion cells showed 44~48, xx, add(1)(p36), del(2)(p15),-4,-9,-9, del(11)(q23),del13) (q14q31), -14, -15, -16, -17, +5~8mar, inc [cp20] and was only 9.44% from the donor confirmed by STR. Meanwhile, bone marrow was in CR and was confirmed by STR 99.79% coming from the donor, negative MLL signals, and no leukemia cells by flow cytometry. Peripheral blood count was nearly normal presenting as white blood cell count (WBC) 5.83×10^9/L, hemoglobin (HGB) 99 g/L, and platelet (PLT) 114×10^9/L. A pericardial window was performed and kept in place for roughly 2 weeks to complete drainage of the effusion. Whole-body positron emission tomography (PET)-CT

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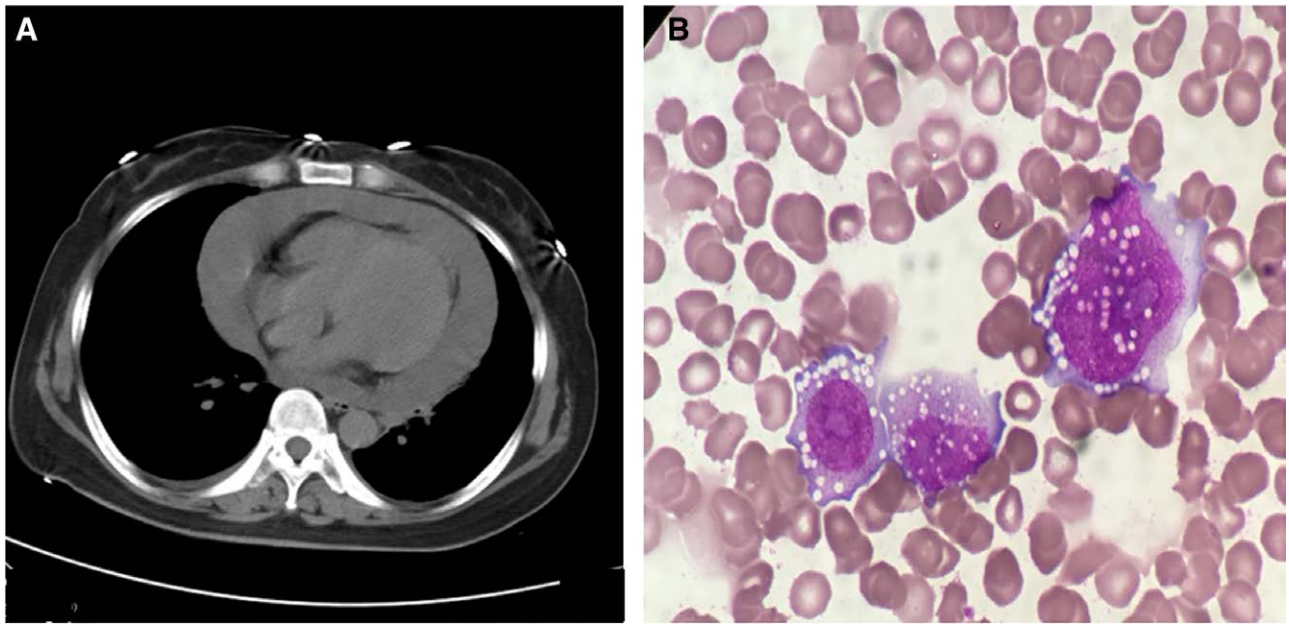

Figure 1. CT and pericardial effusion slides 15 months post-HSCT. (A) CT showed large pericardial effusion and eliminated the possibilities of pneumonia, large pleural effusion, or pneumothorax. (B) The first isolated pericardial relapse. Wright-Giemsa staining on pericardial effusion slides showed 95% immature monocytes. CT = computed tomography, HSCT = hematopoietic stem cell transplantation.

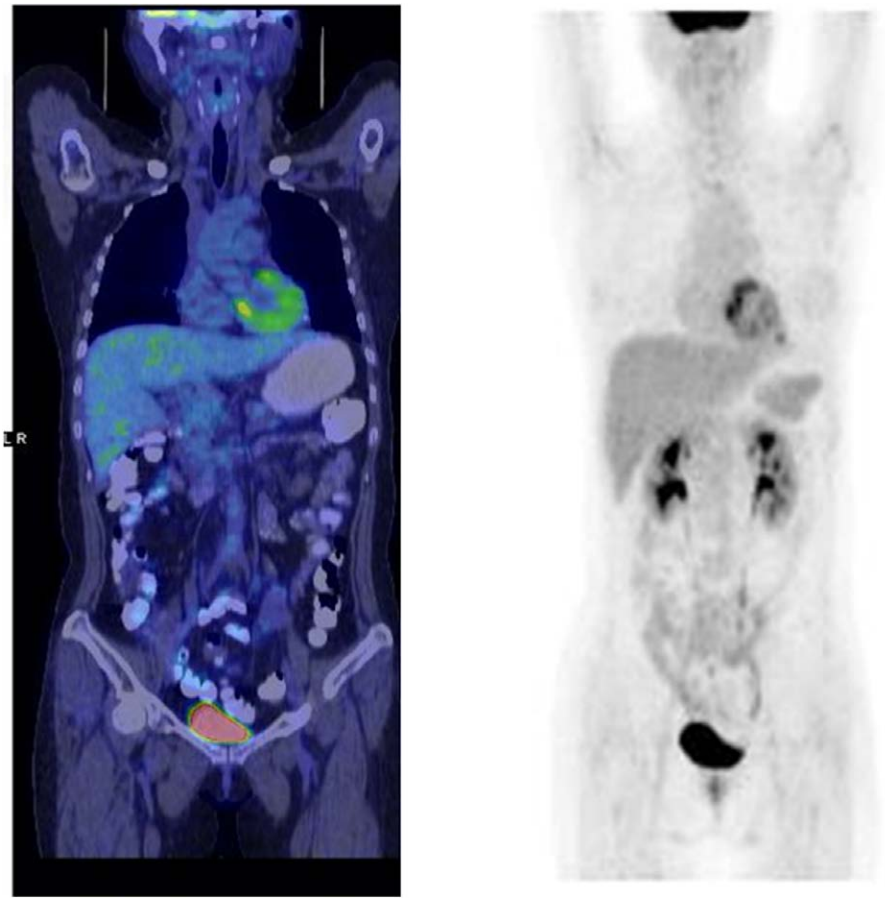

Figure 2. ^{18}F-FDG PET-CT showed no other extramedullary involvement after cardiac effusion drainage at first isolated relapse 15 mo post-HSCT. CT = computed tomography, HSCT = hematopoietic stem cell transplantation, ^{18}F-FDG = ^{18}F-fluorodeoxyglucose.

was performed after drainage of cardiac effusion and showed no activity outside the pericardium, indicating isolated pericardial involvement (Fig. 2). The patient rejected chemotherapy or radiation at this point. She afterward developed chronic GVHD (cGVHD) of the skin and did not receive any immunosuppressant. She remained asymptomatic before experiencing a third

relapse which presented as an IEMR 29 months post-HSCT and chest tightness. Chest CT showed pleural effusion, and beside the left ventricle, a mediastinum mass of size 5.8 cm × 3.7 cm and CT values of 25 to 28 HU. Pleural effusion analysis revealed cells that were 41.68% from the donor were confirmed by STR. Flow cytometry of the pleural effusion revealed 83.27% immature monocytes. The patient's bone marrow again showed molecular CR. For this second extramedullary relapse (EMR), the patient received mediastinal irradiation to reduce tumor burden. However, her status was worsened by the following large pericardial effusion.

The patient chose not to have further examinations or therapies and accepted palliative care. She died 32 months post-HSCT.

3. DISCUSSION

The incidence of EMR in acute leukemia after allo-HSCT varies among transplantation centers, ranging from 6% to 20% in single-center reports with poor survival.[2,3] For AML patients, the incidence of post-HSCT EMR was only 0.65% in a retrospective European Group for Blood and Marrow Transplantation (EBMT) survey.[4,5] IEMR, defined by a history free of leukemia, myelodysplastic syndrome, or other myeloproliferative neoplasms and a negative bone marrow biopsy, has been described in limited case reports. EMR emerges from cells invading sanctuary sites protected from the effects of chemotherapy and the innate immune system and defines an important type of relapse after allo-HSCT.[6–8] Commonly reported sites of post-HSCT EMR of AML patients include central nervous system (CNS), testis, skin/soft tissue, bone, lymph nodes, nasopharynx, and peritoneum.[2] This entity is more common in patients who survive with cGVHD and in patients treated for more advanced disease, including with a second transplant and DLI.[7] Because the bone marrow is protected from the graft-versus-leukemia (GVL) effect, however, whether the extramedullary sites are affected by GVL remains controversial.[9] Previous publications have reported that leukemia can metastasize to the heart after bone marrow transplantation.[10] Isolated cardiac relapse after allogeneic peripheral blood HSCT is rarely reported, with only scattered cases in the literature, mostly presenting as solid myeloid sarcoma or myocardial hypertrophy and constrictive cardiac physiology.[11–13] The patient in this case presented with an isolated cardiac effusion without evidence of myeloid sarcoma or involvement outside the cardiovascular system during her first IEMR. In some studies, it was reported that IEMR has a better prognosis than bone marrow relapse,[7,9] which seems consistent with our case. However, more studies are needed to elucidate this. Limited therapy is available for IEMR; this includes systemic chemotherapy, irradiation, or a second HSCT. There have been no established guidelines for treatment options regarding EMR after HSCT. Not only systemic chemotherapy but also DLI and second transplant have been reported to have limited effects.[14] Although there is a high CR rate in patients receiving local irradiation, this did not contribute to the survival because most patients developed systemic relapse.[15] Despite advanced therapies and the achievement of hematologic CR, the prognosis is still poor.[15] In a Chinese report, in patients with extramedullary involvement post-HSCT, the mortality rate was 70.59%.[16] This case gives us a clue that pericardial effusion can be a special type of extramedullary leukemia relapse after HSCT, and when an AML patient is encountered with cardiac effusion post-HSCT, leukemic involvement should be considered in addition to cardiotoxic drugs, GVHD, and infection.

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AUTHOR CONTRIBUTIONS

Author contributors supervised by S.F. The patient was under the care of D.Y. and J.S. The report was written by Y.S.

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