Extramedullary Relapse of AML with t(9;11)(p22;q23) Associated with Clonal Evolution from Trisomy 8 into Tetrasomy 8

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Abstract

This report describes a patient with extramedullary relapse of acute myeloid leukemia (AML) without involving bone marrow. A 57-year-old man was diagnosed as having acute monoblastic leukemia with t(9;11) (p22;q23) and trisomy 8. Ten months after achieving complete response (CR) with chemotherapy, masses developed in his left forearm and in the back of his thigh, preceded by enigmatic peripheral neurological symptoms. Aspiration from the forearm showed leukemic relapse, and fluorescence in situ hybridization (FISH) revealed that the majority of the cells had 11q23 anomaly and tetrasomy 8. Bone marrow or meningeal relapse was not observed. To our knowledge, this is the first case report of clonal evolution associated with the development of myeloid sarcoma as a relapse in AML.

Key words: extramedullary relapse, myeloid sarcoma, t(9;11)(p22;q23), trisomy 8, tetrasomy 8

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Introduction

Myeloid sarcoma (MS) is a tumor mass consisting of myeloid blasts with or without maturation occurring at an anatomical site other than the bone marrow (1). It is also known as chloroma, granulocytic sarcoma, or extramedullary tumor, and may precede or coincide with acute myeloid leukemia (AML) (2, 3). Rarely, it also occurs in AML without bone marrow relapse. We report a case of MS as a recurrence of AML without involving the bone marrow after achieving complete response (CR) with chemotherapy alone. Cytogenetic analysis with fluorescence in situ hybridization (FISH) was available at the relapse site and clonal evolution of the leukemic cells was observed.

Case Report

A 57-year-old man was admitted to our hospital in October 2007 as a diagnosis of acute leukemia was suspected when he presented to a clinic with a two-week history of malaise. He had a history of syphilis at the age of 40 and chronic hepatitis C which was cured with alfa-interferon at the age of 52. On physical examination, superficial lymph nodes were not palpated. The liver was palpated 2 cm below the right costal margin and the spleen was not palpated. Several subcutaneous soft masses of less than 1 cm in diameter were palpated in the anterior chest and abdomen. No other abnormal masses were palpated in other part of the body. No neurological deficit was observed at presentation.

The white cell count was 3,300/μL with 4.5% neutrophils, 42.0% lymphocytes, and 53.5% blasts. The hemoglobin concentration was 6.6 g/dL, and the platelet count was 95,000/μL. Results of serum biochemistry tests were normal except for lactate dehydrogenase (LDH) level of 1,414 IU/L (reference range, 115-245). C-reactive protein was 7.29 mg/dL (reference range, ≤0.30). Bone marrow aspiration disclosed that proliferation of agranular blasts without maturation in 95% of all nucleated cells. The blasts were negative for peroxidase staining and positive for non-specific esterase staining. A diagnosis of acute monoblastic leukemia (FAB-M5a) was made. The cell surface marker analysis showed that the
cells were positive for CD4, CD13, CD16, CD33, CD56, and HLA-DR. Chromosomal analysis of the bone marrow cells showed 47, XY, +8, t(9;11)(p22;q23) [20/20]. According to WHO classification, this case was categorized as acute myeloid leukaemia with t(9;11)(p22;q23); MLLT3-MLL (4).

One course of chemotherapy consisting of cytarabine (100 mg/m², day 1-7) and idarubicin (12 mg/m², day 1-3) was started on November 2007, and that induced him into CR. The subcutaneous masses disappeared after the chemotherapy. Though not histologically proven, the masses were considered to be extramedullary infiltrates of the leukemic cells. A chromosomal analysis of bone marrow cells at remission disclosed a normal karyotype 46, XY. He was discharged in May 2008 after four courses of consolidation chemotherapy (consisting of daunorubicin+cytarabine, mitoxantrone+cytarabine, aclorubicin+cytarabine, and etoposide+vincristine+vinodesine+cytarabine, respectively) had been completed. He declined to undergo stem cell transplantation (SCT). A tingling sensation in the right lower extremity developed in the middle of August 2008 followed by pain in the right leg and an occasional muscle cramp in September 2008. Though a magnetic resonance imaging study was performed in another hospital under the suspicion of a diagnosis of disk hernia, no abnormal findings corresponding to his enigmatic neurological symptoms were detected.

He was admitted again in October 2008 due to bulging firm masses in his left forearm (Fig. 2) and right tibial nerve palsy developed. The white cell count was 5,940/cmm³ with normal differential count. The hemoglobin concentration was 13.3 g/dL, and the platelet count was 104,000/cmm³. Results of serum biochemistry tests were normal except for slightly elevated LDH level (433 IU/L). Bone marrow aspiration disclosed no proliferation of the leukemic blasts. Chromosomal analysis of the bone marrow cells showed normal karyotype. FISH analysis of the bone marrow cells showed no split signals with MLL probes. Lumbar puncture showed no meningeal relapse of AML. WT1 mRNA level in the peripheral blood was less than 50 copies/μg RNA, indicating no recurrence of AML in the peripheral blood. Contrast-enhanced CT scan of the left forearm showed enhanced intramuscular masses in the left forearm (Fig. 3). Aspiration cytology at the site disclosed infiltration of blast-like cells (Fig. 4A). The cells were negative for peroxidase staining and positive for non-specific esterase staining (Fig. 4B and 4C). The cell surface marker analysis by flow cytometry showed that the cells were positive for CD4, CD 13, CD16, CD33, CD56, and HLA-DR (Fig. 5). Thus, MS as extramedullary relapse of AML was diagnosed. Chromosomal analysis of the cells was not available because no di-
Figure 3. 3-D images of contrast-enhanced CT of the left forearm.

Figure 4. Aspiration from the left forearm. May-Giemsa staining (A). Myeloperoxidase staining (B). Non-specific esterase staining (C).

Figure 5. Cell surface marker analysis of MS cells by flow cytometry.

Providing cells were obtained. FISH analysis showed that 83% of the cells had split signals with MLL probes, indicating that there was translocation at 11q23 site corresponding to his initial chromosomal abnormality t(9;11)(p22;q23)
Figure 6. FISH analysis. A split signal was observed with MLL probes (A). Three signals were observed with chromosome 8 centromere probe (B). Four signals were observed with chromosome 8 centromere probe (C).

(Fig. 6A). FISH analysis also showed that 9% of the cells had three signals with chromosome 8 centromere probe and 70% of the cells had four signals (Fig. 6B and Fig. 6C), suggesting that the majority of leukemic cells had tetrasomy 8.

After admission, a gradually enlarging round hard mass of 5 cm in diameter in back of the right thigh emerged and the pain in the right lower extremity became agonizing. His neurological symptoms were considered to have been caused by extramedullary relapse of leukemic cells, possibly presenting as nerve root entrapment syndrome as previously reported (5). As the relapse was considered to be multifocal, we chose intravenous chemotherapy rather than local radiation therapy. We selected gemtuzumab ozogamicin (GO) because some promising results for MS had been reported (6, 7). The patient received two doses of GO at 9 mg/m² per dose, with a 14-day interval between doses. Though transient alleviation of the pain after GO administration could be obtained, no apparent regression of the tumors was observed. The pain worsened daily with gradual enlargement of the masses and the patient became cachectic. The patient and his family declined to receive high dose cytarabine therapy and a CAG (low-dose cytarabine and aclacinomycin in combination with granulocyte colony-stimulating factor) regimen was started (8). However, there was no effect on the masses and the pain. He died of disease progression and sepsis while in the state of pancytopenia after the chemotherapy in December 2008. Bone marrow or peripheral blood relapse had not been observed throughout the course.

Discussion

MS usually occurs as a precursor to blastic crisis in myeloproliferative syndrome and myelodysplastic syndrome or during the course of active AML. MS also occurs rarely in patients with normal bone marrow who are in CR from AML as in the present patient. Neiman et al reviewed 50 patients with MS and reported that only three patients had it as a sole marker of AML recurrence (2). Byrd et al reported that only 24 cases had MS as the sole marker of AML relapse out of the more than 400 cases of MS that they reviewed (3). Békássy et al reported isolated extramedullary relapse that occurred after allogeneic stem cell transplantation (SCT) in 20 out of 3,071 AML patients (9). The onset of MS is considered to be almost always followed by bone marrow relapse. Thus, the present case is very rare as having MS as a relapse of AML without bone marrow or peripheral recurrence throughout the course.

Most commonly documented sites of occurrence are the orbits, bones and subcutaneous soft tissues, and other sites have been described; paranasal sinuses, lymph nodes, spine, brain, pleural and peritoneal cavities, breasts, thyroid gland, salivary glands, small bowel, lungs, and testes (1-3, 9, 10). Cases of intramuscular infiltration of MS as in our case have also been reported, however, they were considered to be extremely rare (11, 12). Verra et al reported a case of MS presenting as a recurrent, multifocal nerve root entrapment syndrome after allogeneic SCT (5). The present patient had suffered from enigmatic neurological symptoms, i.e., a tingling sensation with muscle cramp followed by agonizing pain in the right lower extremity associated with the tibial nerve palsy. The symptoms might have been ascribed to nerve root entrapment syndrome due to MS, although we could not have proven it by imaging studies. When enigmatic signs and symptoms develop in a patient with AML in remission, one should suspect the presence of extramedullary relapse as in the present case.

GO is a humanized anti-CD33 monoclonal antibody, conjugated to calicheamicin, a potent anti-tumor antibiotic. Piccaluga et al treated 24 AML patients with GO as a single agent, in 5 cases presenting with MS of the skin and bones (6). The overall CR rate of the AML patients was 21%. Four out of the 5 patients with MS treated with GO showed a regression of the masses; in two cases a clearance of marrow blasts was also obtained. Owonikoko et al also reported a case of isolated extramedullary relapse of AML following allogeneic BMT successfully treated with GO alone (7). The patient had remained in CR for more than 17 months without receiving any further therapy. We selected GO as an initial therapy after relapse in the present case because GO was considered to be promising for MS as relapse of AML. Unfortunately it showed no benefit in our case. However, it should be considered for use in MS as relapse of AML in which leukemic blasts express CD33.

Chang et al reported that extramedullary infiltrates in AML at diagnosis are associated with CD56 expression by leukemic blasts, 11q23 karyotypic abnormalities, low CR rate, and poor overall survival (13). However, there is no established predictor for developing MS as AML relapse. In the setting of isolated extramedullary relapse of AML fol-
lowing allogeneic SCT, the predisposing factors were suggested to be CD56 expression, t(8;21), inv (16), MLL rearrangement, and FAB M4/5 morphology, and t(1;19) (9, 14, 15). In the present case, extramedullary infiltrates at diagnosis was suspected because hepatomegaly and several subcutaneous masses were present. This case might have been in a high risk group of extramedullary relapse because CD56 expression by leukemic blast, 11q23 anomaly (i.e. MLL rearrangement), and M5a morphology were present.

AML with t(9;11)(p22;q23) is composed of 9-12% of pediatric and 2% of adult AML, and is usually associated with monocytic features (4). It is likely to form extramedullary masses by leukemic blast, 11q23 anomaly (i.e. MLL rearrangement, and FAB M4/5 morphology) (9,14,15). In the present case, extramedullary infiltrates at diagnosis was suggested to be CD56 expression, t(8;21), inv(16), MLL rearrangement, and FAB M4/5 morphology (9,14,15). In the present case, extramedullary relapse because CD56 expression by leukemic blast, 11q23 anomaly (i.e. MLL rearrangement, and FAB M4/5 morphology) (9,14,15).

Clonal evolution of the leukemic cells from trisomy 8 into tetrasyom 8 was observed at relapse. Tetrasyom 8 is an extremely rare chromosome abnormality and patients with tetrasyom 8 have a poor prognosis (16). Lessard et al suggested that polysomy 8 (tetrasyom 8 or pentasyom 8) was preferentially associated with monocytic differentiation and might be a particular clonal evolution secondary to 11q23 abnormality (17). To our knowledge, this is the first case report of clonal evolution associated with the development of MS as a relapse of AML. The mechanism of extramedullary relapse of AML without involving bone marrow is yet to be elucidated. Clonal evolution as in our case might be related to conversion of the character of leukemic blasts.

References


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