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Acute myeloid leukemia with t(4;12)(q12;p13) treated with an allogeneic stem cell transplant: A case report and review of the literature

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1. Introduction

The t(4;12)(q12;p13) in acute myeloid leukemia (AML) is a rare finding with less than 30 cases described in the literature. The few cases reported show that this subtype of AML features dysplastic changes in all three cell lines, positivity for CD7, lymphoid appearing myeloblasts, basophilia, and low or absent myeloperoxidase activity [1,2]. Cases have been described in the literature as far back as 1989 [1], but prognosis remains poor with intensive chemotherapy alone. Here, we describe a case of an elderly patient with AML with t(4;12)(q12;p13) with extramedullary involvement who underwent an allogeneic stem cell transplant (alloSCT).

2. Case

The patient is a 70-year-old Filipino female who had been experiencing a cough and intermittent fevers at home over a period of one month. She was treated initially as an outpatient with antibiotics, but showed no improvement. At presentation to our hospital, she had an X-ray proven right pleural effusion. A thoracentesis was performed revealing an exudative effusion with a white blood cell count (WBC) of 1570/μL containing a large population of atypical lymphocytes. Cultures were negative. She remained febrile and had a persistent dry cough despite being on broad-spectrum antibiotics. Bronchoscopy revealed no evidence of infection at the time. The hematology service was consulted for mild neutropenia (ANC 1700/μL) and lymphocytosis (absolute lymphocyte count 5400/μL). Other values included a WBC of 8000/μL, a hemoglobin of 9.0 g/dL, and platelets of 191,000/μL. The peripheral blood smear showed many atypical cells with round to oval nuclei with clumped chromatin, occasional nucleoli and a small to moderate amount of bluish peripheral cytoplasm, initially interpreted as atypical lymphocytes (Fig. 1). Rare target cells, very rare schistocytes, large red blood cells and platelets, and an increased number of basophils were also present. Flow cytometry of peripheral blood showed a large abnormal population of immature cells consistent with myeloblasts (33% of total WBCs) positive for CD7, CD13, CD33, CD34, CD45, CD117, and HLA-DR (Table 1). This population was negative for CD10, CD11b, CD19, CD64, CD79a, TdT, and MPO as well as CD2, CD3, CD5. Bone marrow aspirate showed myeloblasts with agranular cytoplasm and basophils (Fig. 1). Bone marrow biopsy revealed 60% cellularity and an interstitial infiltrate of small to medium sized immature cells consistent with blasts that stained positive for CD34. Megakaryocytes were increased and appeared dysplastic (Fig. 1). Cytogenetics showed an abnormal female karyotype in 20 cells with a translocation between the long arm of chromosome 4 and the short arm of chromosome 12 (Fig. 2). Four cells also had a deletion of the long arm of chromosome 5. Fluorescent in situ hybridization (FISH) testing confirmed the rearrangement of the PDGFRA gene on chromosome 4 and the ETV6 gene on chromosome 12. Molecular studies, including FLT3, were negative. Pleural fluid from prior thoracentesis was subsequently sent for flow cytometry revealing a large population of myeloblasts immunophenotypically similar to those present in the peripheral blood. Previous sputum cultures grew Mycobacterium avium (MAC) and the patient was started on MAC therapy with azithromycin, ethambutol, and rifampin.

The patient underwent induction with 7 + 3 with idarubicin 12 mg/m^2 and cytarabine 100 mg/m^2. Her fevers and cough improved significantly with chemotherapy. The day fourteen bone marrow biopsy showed a markedly hypocellular bone marrow (less than 5% overall cellularity) with persistent blasts (10–15%). Cytogenetics re-demonstrated the t(4;12) and deleted 5q. The patient was given re-induction chemotherapy with fludarabine 30 mg/m^2 and cytarabine 2000 mg/m^2 with g-CSF beginning on day 0 (FLAG regimen). She developed severe thrombocytopenia that was refractory to both single- and pooled-donor platelet transfusions. Her second induction course was discontinued early, due to significant toxicities, leading to a 20% dose reduction. The patient developed worsening pancytopenia and neutropenic fever. She was continued on MAC therapy and broad-spectrum antimicrobials. Her counts slowly recovered and she clinically stabilized; she was discharged on day 30 from her second induction and day 47 from her first.

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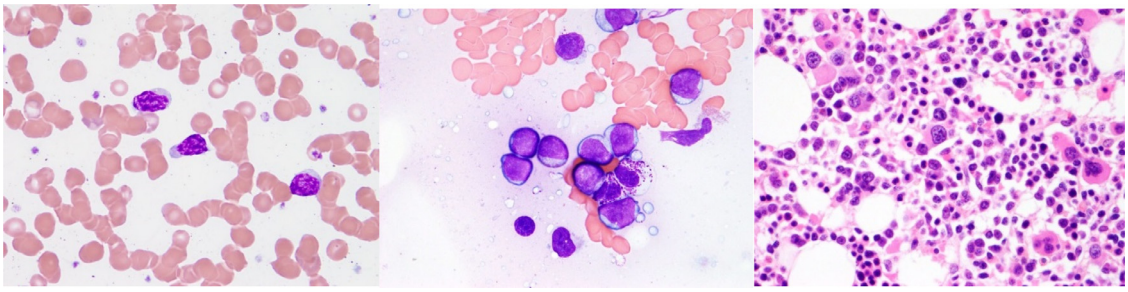

Fig. 1. (a) Peripheral blood showing atypical cells initially interpreted as atypical lymphocytes, (b) Bone marrow aspirate showing myeloblasts with agranular cytoplasm and basophils, (c) Bone marrow biopsy showing many dysplastic megakaryocytes and increased immature cells.

Table 1
Summary of pathologic features of t(4;12) AML.

Pathology	Features
Peripheral smear	Dysplastic features in all three hematopoietic lineages (erythroid, myeloid and megakaryocytic), pseudo-lymphoid/ mature lymphoid morphology, basophilia, low or absent MPO
Flow Cytometry	Myeloblasts: *CD7+, CD 13+, CD33+, CD34+, HLA-DR+
Cytogenetics	t(4;12)
FISH	Rearrangement of PDGFRA gene on chromosome 4 and ETV6 gene on chromosome 12

* t(4;12) may not be restricted to CD7+ [3].

Outpatient bone marrow biopsy, performed on day 59, revealed a hypocellular marrow with trilineage hematopoiesis that was negative for malignancy. Cytogenetics showed a normal female karyotype. She received one cycle of azacitidine 75 mg/m^2 for 7 days while awaiting transplant approval. Her chest x-rays revealed resolution of the pleural effusions.

She underwent a 9/10 matched unrelated donor (MUD) transplant with conditioning regimen busulfan 130 mg/m^2 and fludarabine 40 mg/m^2 and use of bone marrow as the stem cell source. The patient's transplant course was complicated by graft versus host disease with a grade one rash that improved with steroids. She was discharged on day +22 with close follow-up. She is now 13 months from diagnosis and 6 months from transplant. Most recent bone marrow biopsy demonstrates a complete remission.

3. Discussion

The first described case of a patient with t(4;12) AML was in 1989 [1]. Since this initial report, less than 30 cases of this type of AML have been described in literature [3,4]. In many of these cases, the CBC showed an increased absolute lymphocyte count and blasts in the peripheral blood were initially misinterpreted as lymphocytes or atypical lymphocytes, as was the case with our patient. In our patient, this error was rectified by flow cytometry analysis.

In previous reports, less than 50% of cases achieve remission with intensive induction chemotherapy [5]. The reason why this particular AML subtype seems to be inherently resistant to chemotherapy may be related to the fact that it is associated with an immature phenotype as supported by immunophenotypic findings. It has been postulated that abnormal anthracycline distribution may account for natural resistance of immature AML phenotypes to anthracyclines [6]. If morphologic remission is not achieved, patients do not survive beyond six months [7–9] On further review of fifteen cases, only a third of patients achieved a complete remission [10] . Given so few complete remissions and poor survival outcomes with intensive chemotherapy alone, treatment should be aggressive and include an alloSCT when feasible.

On extensive literature review, there are only four reports of patients with this rare AML presentation who underwent an alloSCT. The first was a 54-year-old male who initially achieved a 26-month remission after intensive chemotherapy. At relapse, the t(4;12) was re-identified on cytogenetics. He underwent induction chemotherapy and eventually an alloSCT with last reported survival at 24 months [11] . A

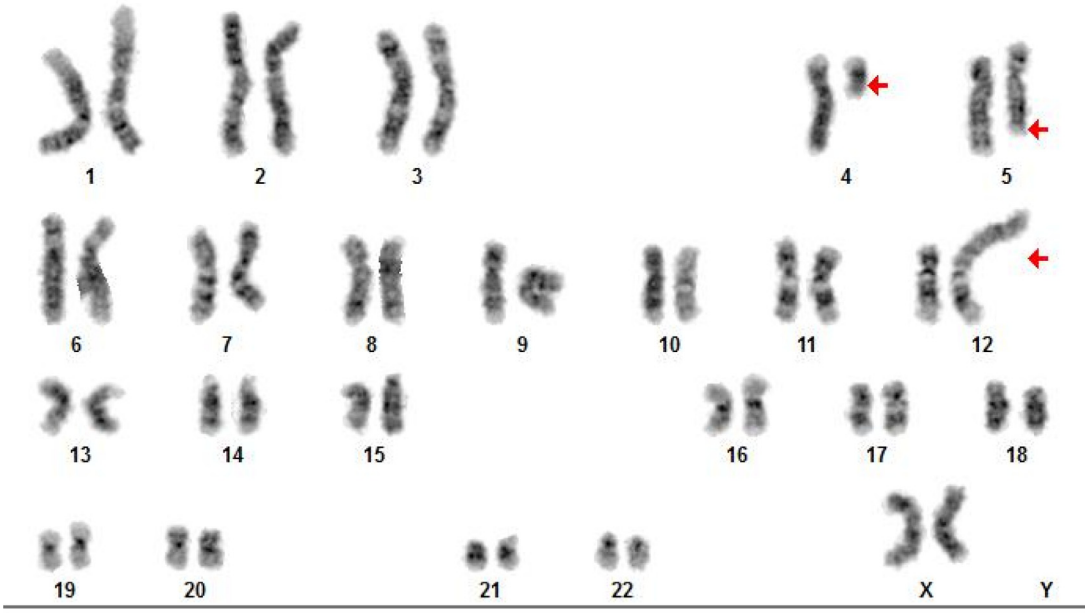

Fig. 2. Karyotype demonstrating t(4;12)(q12;p13) and 5q deletion.

second case described an 18-year-old female in 2009 who failed initial induction chemotherapy with 7 + 3, but achieved a complete hematologic and cytogenetic remission after re-induction with mitoxantrone and cytarabine. She received consolidation chemotherapy and maintained a complete remission until 6 months later when a bone marrow aspirate demonstrated t(4;12) in one of 20 cells evaluated. Subsequently, she underwent more intensive chemotherapy followed by a cord blood transplant [12] . A third case regarded a 57-year-old male patient with history of Hodgkin's lymphoma, at age 25, treated with ABVD. He was diagnosed with secondary AML with t(4;12), achieved a complete remission after 7 + 3 and re-induction with 2 + 5, and received consolidation with Ara-C. He underwent a MUD SCT in 2008 with last reported survival of 24 months in 2010 [5]. Finally, Kim et al, in 2016, described a fourth case of a 53-year-old male with newly diagnosed t (4;12) AML who underwent induction with idarubicin and cytarabine, followed by re-induction with high-dose cytarabine and daunorubicin. He achieved a complete remission and underwent a MUD SCT with a remission of at least 52 months [3].

To our knowledge, our patient is the first case with t(4;12) AML reported in the literature to undergo aggressive treatment with intensive chemotherapy followed by alloSCT at the age of 70 years. Previous reports have suggested that age over 60 years is a poor prognostic marker for non-relapse mortality after alloSCT. A large retrospective analysis proposed the use of a composite comorbidity/age score and assessment of high risk features of primary disease for selection of appropriate patients [13] . In the case of our patient, her excellent performance status and lack of comorbidities allowed for aggressive treatment leading to her prolonged survival.

Furthermore, this case demonstrates the importance of ancillary studies in the diagnosis, prognosis, and treatment of leukemia, including immunophenotyping by flow cytometry and cytogenetic analysis. In our case, misinterpretation of the morphology of abnormal cells in the peripheral blood led to an initial diagnosis of a low grade lymphoproliferative disorder rather than AML. In retrospect, the increase in basophils may have been a diagnostic tip-off, however, the definitive diagnosis of AML was finally made through flow cytometry and cytogenetic analysis.

In conclusion, it is important to have a high suspicion for this type of AML with atypical appearing lymphocytes and basophilia on the peripheral smear. When t(4;12) AML is diagnosed, given the aggressiveness of the disease with few reported complete remissions and poor survival outcomes with chemotherapy alone, patients should be evaluated for early allogeneic transplant.

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