Case Report

Acute Monoblastic Leukemia with t(10;11)(p12;q23) Presenting with Pulmonary Involvement: A Case Report and Literature Review

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A forty-three-year-old Thai man presented with acute fever and dyspnea for one week with bilateral patchy infiltration, pancytopenia with monoblast. Bone marrow study was consistent with acute monoblastic leukemia. Lung lesions rapidly progressed to acute respiratory failure, which required intubation. Bronchoscopy with bronchoalveolar lavage revealed monotonous monoblast infiltration. Induction chemotherapy with 7 + 3 regimen was administered to halt the progression of leukemic pulmonary infiltration. Although there was clinical improvement, the chest radiograph developed crescent formation in the right upper lung field. Invasive pulmonary aspergillosis was suspected and successfully treated with antifungal agent. After peripheral blood recovery, bone marrow evaluation was performed and complete remission was established. HLA matching was sent to prepare for hematopoietic stem cell transplantation (HSCT). The literature review showed that the appropriate treatment for the patients with t(10;11)(p12;q23) was HSCT, but there was no data concerning correlation of t(10;11)(p12;q23) and pulmonary infiltration. This may be due to the low incidence of leukemic infiltration of acute leukemia patients, which is 0.48% and 3.06% in acute myeloid leukemia and acute monoblastic leukemia, respectively.

Keywords: *Acute monoblastic leukemia, Leukemic pulmonary infiltration, t(10;11)(p12;q23)*

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A forty-three-year-old man presented with high grade fever for 1 week with dyspnea on exertion. Physical examination revealed fever, but no gingival hyperplasia or skin rash. Bilateral coarse crepitation was noted on chest examination. No focal neurological deficit or meningeal irritation sign was detected. The chest roentgenogram revealed bilateral patchy infiltration (Fig. 1). Sputum gram stain and culture were both negative. (Sputum with numerous WBC and few squamous epithelial cells) Complete blood count showed Hb 9.5 g/dL Hct 27.6% MCV 92 fL WBC 3,800/mm^3 N 7% L 28% Mo 2%, Eo 3%, myelocyte 2%, monoblast 32%, promonocyte 24% Plt 81,000/mm^3. Empirical antibiotic for febrile neutropenia were started with meropenem and levofloxacin for coverage of gram negative bacilli and *Pseudomonas aeruginosa*. Bone marrow examination was performed and the aspiration Wright's stain showed markedly hypercellular marrow with decreased megakaryocytes, there was predominance of monoblast > 95%. Acute myelogenous leukemia, FAB classification M5a was diagnosed. The immunophenotype was positive for CD11b, CD15, CD33, CD34, CD117, HLA-DR, TdT, MPO compatible with acute myeloid leukemia of monocytic origin. The Trephine's biopsy showed that the blast had monoblastic and lymphoblastic features, biphenotypic acute leukemia was considered. However, the immunophenotype didn't reach the score for diagnosis of biphenotypic

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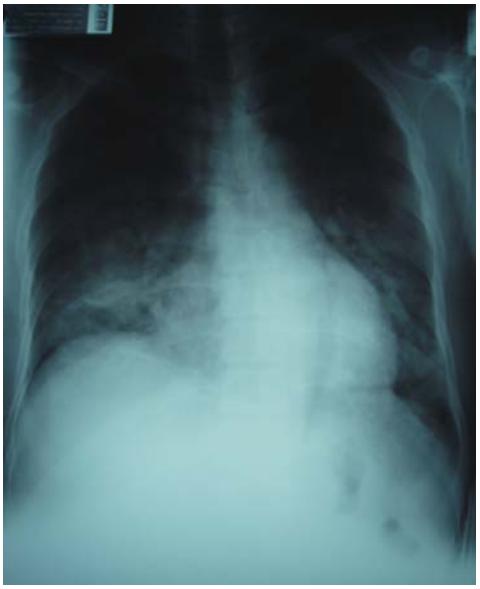

Fig. 1 The patient's chest Roengenogram at presentation showed bilateral patchy infiltration, which was later proved to be pulmonary leukemic infiltration

acute leukemia. Bone marrow cytogenetics showed 46 XY, t(10;11)(p12;q23). This result completed the clinical diagnosis of AML with recurrent aberrant translocation according to WHO classification, which has an unfavorable prognosis. Hemoculture grew within one day: non-drug resistant group D *Salmonella*. Five days after admission he developed progressive dyspnea with subsequent respiratory failure. An endotracheal tube was gently inserted without overt airway trauma. Fiberoptic bronchoscopy was performed. Bronchoalveolar larvage (BAL) showed few red blood cells and numerous white cells. Wright's stain revealed numerous monotonous mononuclear cells with nucleolus, which were compatible with monoblast (Fig. 2). BAL fluid for gram stain was not found, BAL fluid culture was no growth.

Monoblastic infiltration of the lung was diagnosed. Standard chemotherapy was started because the patient had rapidly progressive dyspnea with idarubicin 12 mg/m^2 bolus, intravenously for three days, together with cytosine arabinoside 150 mg/m^2 by continuous intravenous infusion over 24 hours for seven days. Hemorrhage via endotracheal tube occurred a few days after administration of chemotherapy. He was also fully supported with platelets and red cell transfusion. One week after starting chemotherapy the pulmonary infiltrates had not resolved and fever persisted, so empirical antifungal agent was started with caspofungin. On day 14 after initiation of chemotherapy there was gradual clinical improvement. He was subsequently weaned from the mechanical ventilator and extubated a few days later. Neutropenia was terminated on day 24, and the left lung infiltration was gradually improved. However, the right lung infiltration persisted and developed crescent formation (Fig. 3) on day 33. Invasive pulmonary aspergillosis was suspected and voriconazole was started, resulting in clinical and radiographic improvement. Sputum culture was positive for *Aspergillus fumigatus*, serum galactomannan index 1.0 (cut-off index was 0.5). After full peripheral blood recovery on day 29, bone marrow study was repeated. Bone marrow myeloblast was found to be less than 5%. HLA typing of his three siblings did not match. He

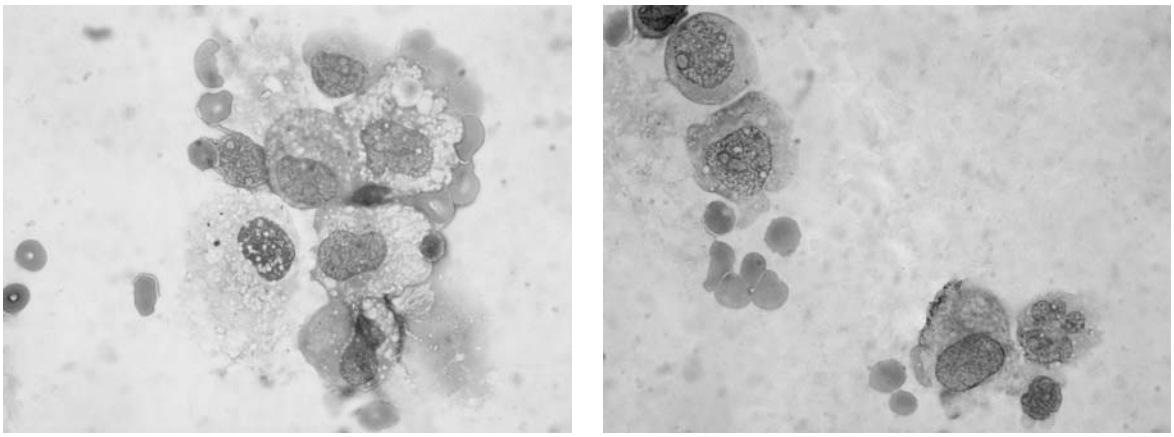

Fig. 2 Bronchoalveolar larvage revealed monotonous proliferation of the monoblasts; large vacuolated mononuclear cell with prominent nucleoli and convoluted nucleus

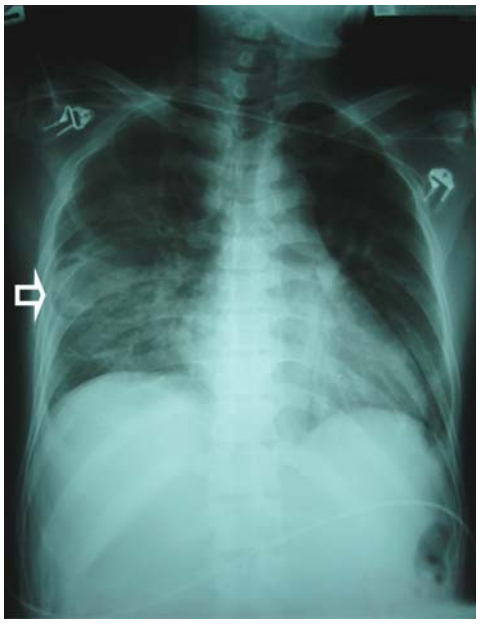

Fig. 3 The chest Roentgenogram after chemotherapy administration the patchy infiltration of left lung was resolved but crescent formation of the right lung (→) was occured

is now waiting in search for matching with unrelated donors. Bridging therapy with intensification post-remission chemotherapy was administered with 3 gram/m^2 cytosine arabinosides infusion intravenously over 3 hours every 12 hours on day 1, 3, and 5. After he received three courses of intensification chemotherapy he still retained complete remission.

Discussion

Acute myeloid leukemia (AML); M4 (myelo-monoblastic;AMMoL) and M5 (monoblastic; AMoL) are known for involvement of extramedullary organs. Organs commonly involved by monoblasts consist of gum, skin, and the nervous system. Many cases were reported proximal renal tubular acidosis due to muramidase (lysozyme) secreted from monoblasts[1]. Pulmonary manifestation is not an uncommon manifestation but pulmonary infiltration documented by BAL is rare in AML[2-5]. Only a few cases have been reported[6-14], Azoulay and colleagues reported an incidence of 0.48% for all AML patients and 3.06% for AMoL patients[14]. Pulmonary manifestation may be classified into 3 groups. The first group is hyperleukocytosis with leukostasis, which is seen in patients with peripheral blast more than 50,000/ml. The patient develops dyspnea due to increased pulmonary blood viscosity, resulting in decreased pulmonary blood flow. The second group is monoblastic infiltration of the lungs. Respiratory manifestations could develop regardless of peripheral blast count, due to the adhesive property to vascular endothelium and extravasating ability of this type of blast[15]. The last group is acute lysis pneumopathy, which usually develops after administration of chemotherapy, and is more commonly associated with acute myelomonocytic leukemia with abnormal marrow eosinophils (AML, M4Eo). The exact mechanism of disease of the last group is not known. Eosinophils may play a major role[8]. Differentiation of the blast to mature granulocyte from chemotherapy administration has also been postulated[9,10].

The t(10;11) is the fusion of 11q23 or MLL and 10p11-13 or AF10 gene. More than half of the patients are AML-M5; the remaining are ALL, AML-M1, M4, M2 and biphenotypic acute leukemia, respectively. Most of the cases of t(10;11) were part of complex abnormalities, found in 60% of the cases[16-20]. According to Lillington et al, survival of patients who received hematopoietic stem cell transplantation (HSCT) was more than 18.9 months, compared with more than 5.5 months in those without HSCT[16] (Table 1). The most appropriate therapy for this group of patients may be HSCT.

There is no previous data on the correlation between t(10;11), which is a common cytogenetic abnormality for AMoL, and pulmonary leukemic infiltration. This may be due to the very small number of cases of acute monoblastic leukemia with pulmonary infiltration. The treatment for these patients is similar to that of AML patients, of which the mainstay induction regimen is the 7 + 3 regimen. Post-remission therapy depends on risk groups according to two large studies from MRC[21] and SWOG/ECOG[22]. The presented patient had t(10;11), which indicated unfavorable prognosis. The most appropriate post-remission therapy is allogeneic HSCT. The presented data corresponds with that of Lillington et al, of which the median survival in the HSCT group was better than chemotherapy alone[17].

Conclusion

Leukemic pulmonary infiltrates can occur regardless of peripheral blast count. The t(10;11)(p11-13;q23) is classified as unfavorable risk because of MLL gene rearrangement itself, and is usually associated with complex cytogenetic abnormalities. This suggests the necessity of HSCT for post-remission period. The

Table 1. Natural history of patients with t(10;11)(p11-13;q23)

Reference	Chaplin et al[18]	Beverloo et al[19]	Lillington et al[17]	Dreyling et al[20]	Total
Number of patients	8	10	20	10	48
AML-M0	0	0	0	10%	2.08%
AML-M1	0	0	5%	30%	8.33%
AML-M2	0	0	0	20%	4.26%
AML-M4	12.5%	10%	5%	0	6.25%
AML-M5	87.5%	90%	55%	30%	62.50%
ALL	0	0	20%	10%	10.42%
Biphenotypic	0	0	5%	0	2.08%
t(10;11) alone	12.5%	10%	20%	30%	18.75%
Complex cytogenetics	62.5%	50%	60%	50%	56.25%
Median OS (mo)	NR	NR	9.1+	11	
OS of HSCT (mo)	NR	NR	18.9+	NR	
OS of non-HSCT (mo)	NR	NR	5.5+	NR	

AML = Acute myeloid leukemia, ALL = Acute lymphoblastic leukemia NR = Not reported, OS = Overall survival, HSCT = Hematopoietic stem cell transplantation

literature also shows that for the patient with t(10;11), survival is better in the HSCT group. However, the relationship between t(10;11) and leukemic pulmonary infiltration was not established. This may be because the lungs are not commonly involved with regards to leukemic infiltration.

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ผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดโมโนบลาสต์ที่มีความผิดปกติชนิด t(10;11)(p12;q23) มีรอยโรคกินเนื้อปอด แม้มีจำนวนเม็ดเลือดขาวในเลือดต่ำ

กานดิษฎ์ ประยงค์รัตน์, มนะพล กุลปราณีต, ประภาพร พานิชชอบ, วรพจน์ ตันติศิริวัฒน์

รายงานผู้ป่วยชายอายุ 43 ปี มาพบแพทย์ด้วยไข้ หอบเหนื่อยเฉียบพลัน พบมี bilateral patchy infiltration, pancytopenia with monoblast ตรวจไขกระดูกเข้าได้กับ acute monoblastic leukemia (AMoL) อาการของปอดมากขึ้นเรื่อย ๆ จนเกิดภาวะระบบหายใจล้มเหลว ใส่ท่อช่วยหายใจ และส่องกล้องหลอดลมพบว่าเต็มไปด้วยเซลล์โมโนบลาสต์ ให้การรักษาด้วยเคมีบำบัดต่อมาอาการทางปอดดีขึ้นแต่พบ crescent lesion ของปอดขวาให้ยาต้านเชื้อราครอบคลุมเชื้อแอสเปอร์จิลลัสรอยโรคลดลงมาก ต่อมาตรวจไขกระดูกพบโมโนบลาสต์น้อยกว่าร้อยละ 5 ได้ทำการตรวจ HLA เพื่อปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดต่อไป เนื่องจากการทบทวนวรรณกรรมพบว่าผู้ป่วยมะเร็งเม็ดเลือดขาวที่มี t(10;11)(p11-13;q23) ซึ่งรักษาด้วยการปลูกถ่ายไขกระดูกมีอัตราการรอดชีวิตที่ดีกว่า อย่างไรก็ดีไม่พบว่ามีรายงาน t(10;11) กับการมีรอยโรคที่ปอด อาจเนื่องมาจากการที่ผู้ป่วยมะเร็งเม็ดเลือดขาวที่มีโรคกินเนื้อปอดมีอุบัติการณ์ต่ำคือร้อยละ 0.48 และ 3.06 ในผู้ป่วย AML และ AMoL ตามลำดับ