

Case Report

Therapy-Related Acute Myeloid Leukemia in A Primary Pulmonary Leiomyosarcoma Patient with Skin Metastasis

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ABSTRACT

Primary pulmonary leiomyosarcoma (LMS) is a very unusual tumor. Although LMS has well-known metastatic potential, cutaneous metastasis is a remarkably uncommon. Exposure to cytotoxic agents could lead to "therapy-related myeloid neoplasm" (t-MN). Starting from 2008, the World Health Organization (WHO) has adopted the term to cover the spectrum of malignant diseases previously known as therapy-related acute myeloid leukemia (t-AML), therapy-related myelodysplastic syndrome (t-MDS) and therapy-related myelodysplastic/myeloproliferative neoplasm (t-MDS/MPN). We described the onset of t-MDS and progression to t-AML in one case diagnosed as primary pulmonary LMS with cutaneous metastasis. This patient achieved complete remission (CR) after three courses of IA regimen chemotherapy (idarubicin 5 mg/d, d 1-3; cytarabine 100 mg/d, d 1-5) and 1 course of HA chemotherapy regimen (homoharringtonine 3 mg/d, d 1-3; cytarabine 100 mg/d, d 1-7). This case presents the natural course of therapy-related neoplasm and provides therapeutic experience for t-AML.

Key words: Therapy-related myelodysplastic syndrome; Therapy-related acute myeloid leukemia; Leiomyosarcoma; Metastasis; Skin

INTRODUCTION

Leiomyosarcoma (LMS) is a rare malignancy of smooth muscle origin with an estimated incidence of two per million^[1,2]. LMS is prone to metastasis, but cutaneous metastasis is uncommon^[3]. Primary pulmonary LMS is very rare, and is often misdiagnosed as lung cancer or tumors of mediastinal origin. Reported here is a case of primary pulmonary LMS with cutaneous metastasis. This patient achieved complete remission (CR) after chemotherapy but later developed therapy-related myelodysplastic syndrome (t-MDS) and then progressed to therapy-related acute myeloid leukemia (t-AML).

CASE REPORT

A 62-year-old man came to medical attention for low-grade fever in February 2008. Routine blood test was normal. A computerized tomography (CT) scan of the chest revealed a mass in the left lower lobe and multiple pulmonary nodules (Figure 1A). Tissue biopsy via bronchoscopy revealed a low-grade malignant spindle cell neoplasm (Figure 2A and 2B). The tumor was positive for smooth muscle actin (SMA) (Figure 2C), muscle-specific

actin (MSA), and vimentin (VIM), and negative for cell keratin (CK), CD34, and CD117. Based on the immunocytochemistry results, a diagnosis of primary pulmonary LMS was established. The patient was treated with four courses of chemotherapy (IED; ifosfamide 2 mg/d, d 1-3; etoposide 100 mg/d, d 1-4; cisplatin 120 mg/d, d 1; 28-day off). The patient then developed a painless enlarging mass in the left shoulder. Microscopic examination of the tumor cells (Figure 3A) and immuno-histochemistry (Figure 3B and 3C) showed the same characteristics as the primary lesion in the lungs. The patient was switched to three courses of ID regimen (ifosfamide 2 mg/d, d 1-3; cisplatin 120 mg/d, d 1; 28-day off). Upon completion of the chemotherapy, CT scan revealed significant reduction in the size of the left lower lobe mass, but increased number of nodules in both lungs (Figure 1B). The patient experienced several episodes of leukopenia during and after chemotherapy, and was treated with granulocyte colony stimulating factor (G-CSF). RBC/ hemoglobin and platelet count were within the normal range throughout the disease course. At the first year after the chemotherapy ended, a bone marrow aspirate (WBC: $2.2 \times 10^9/L$) suggested the development of myelodysplastic syndrome. Myeloblast percentage was 5.5% (normal range: 0%-2%). A cytogenetic analysis revealed normal karyotype. Based on the French-America-Britain (FAB) classification, a diagnosis of myelodysplastic syndrome, refractory anemia with excess blasts-1 (MDS-RAEB-1) was made. At this point, the patient refused further treatment except for supportive care.

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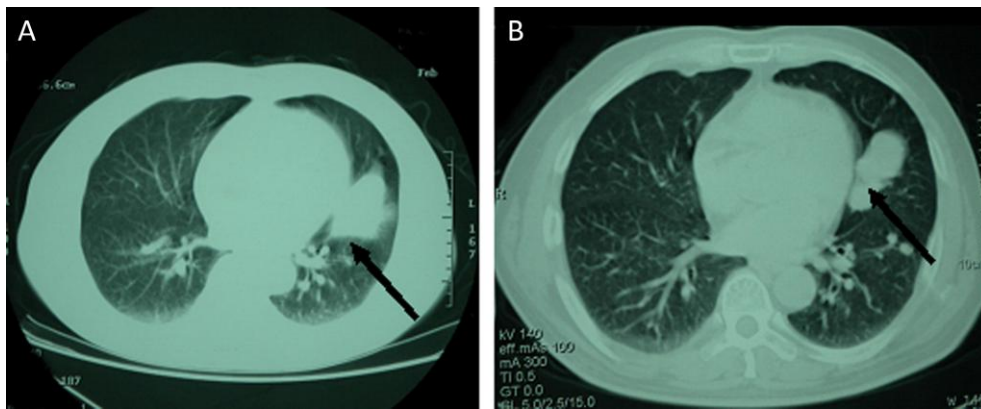


Figure 1. CT scan of the chest. A: Chest CT scan prior to chemotherapy revealing a mass in the left lower lobe (arrow) and multiple pulmonary nodules; B: Chest CT scan after chemotherapy (arrow).

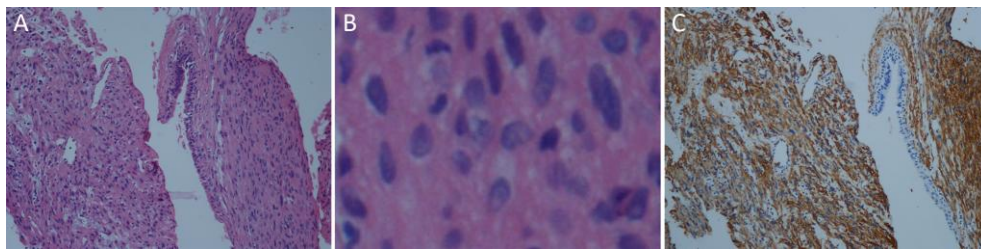


Figure 2. Primary tumor in the lung. A: HE staining ($\times 100$); B: HE staining ($\times 1000$); C: SMA immunohistochemical staining ($\times 100$).

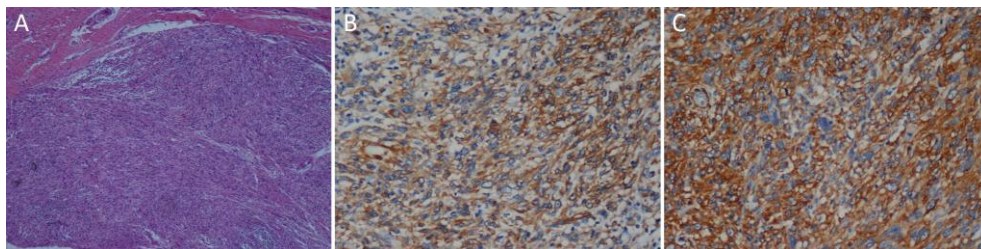


Figure 3. Skin metastasis. A: HE staining ($\times 100$); B: immunohistochemical staining for SMA ($\times 100$); C: immunohistochemical staining for VIM ($\times 100$).

In May 2009, the patient was hospitalized again for thrombocytopenia (platelet count of $17 \times 10^9/L$). Physical examination revealed no lymphadenopathy or hepatosplenomegaly. Hemoglobin and WBC count were 96 g/L and $1.65 \times 10^9/L$, respectively. Bone marrow myeloblast percentage was 24%. A flow cytometry of the bone marrow revealed leukemic cells with the following immunological characteristics: CD117⁺, CD34⁺, DR⁺, CD56⁺, CD13⁺, CD33⁺, MPO⁺, CD15⁺, CD64⁻, CD3⁻, CD4⁻, CD36⁻, CD56⁻, CD41a⁻, CD10⁻, CD7⁻, CD57⁻, CD19⁻, CD8⁻, CD11b⁻, CD20⁻, CD14⁻ and lysozyme⁻. A cytogenetic analysis revealed inv(16)(p13.1q22). Hypercellularity and abnormal location of immature precursor (ALIP) were established upon biopsy. Gomori staining was +++. A diagnosis of t-AML was made. The patient was treated with an IA chemotherapeutic regimen (idarubicin 5 mg/d, d 1-3; cytarabine 100 mg/d, d 1-5; 21-day off). Myeloblast decreased to 18.5% after one course, and the patient continued with 2 additional courses of IA regimen and 1 course of HA regimen chemotherapy

(homo-harringtonine 3 mg/d, d 1-3; cytarabine 100 mg/d, d 1-7; 21-day off). A bone marrow aspirate at this point showed complete remission (CR). One month later, however, a solid painless mass was noticed in the right abdomen. A CT scan revealed a mass involving the femoral vein and bladder. The tumor was deemed unresectable, and the patient left the hospital in December 2009. He died after 2 months, likely for LMS progression.

DISCUSSION

Primary pulmonary LMS is first reported in 1907 by Davidsohn^[4]. It occurs across all ages but with a peak incidence in the fifth and sixth decades. The male/female ratio is 2.5:1. Similar to a previous report^[5], the tumor in this case was positive for SMA, MSA and VIM, and negative staining for CK.

The initial symptom in this case was low-grade fever. The unique feature of this case is metastasis to the skin. In

four out of the 16 previously reported cases of LMS with cutaneous metastases, the primary tumor was in the uterus³. To the best of our knowledge, no cases of primary pulmonary LMS with cutaneous metastasis have been reported.

Another unique feature of this case is the development of t-MDS and then rapid progression to t-AML. T-MDS is a consequence of radiation therapy and exposure to cytotoxic drugs (e.g., alkylating agents, topoisomerase inhibitors and antimetabolites). In 2008, the World Health Organization (WHO) adopted "therapy-related myeloid neoplasm" (t-MN) to cover the spectrum of malignant diseases previously known as t-AML, t-MDS and therapy-related myelodysplastic/myeloproliferative neoplasm (t-MDS/MPN)⁶. Based on latency, two subsets of t-MN are recognized. Patients with relatively long latency (5-10 years after exposure) typically have unbalanced loss of genetic material, mostly involving chromosomes 5 and/or 7, and often present t-MDS plus one or multiple forms of cytopenia. Patients with short latency of 1-5 years are often exposed to topoisomerase inhibitors, and typically have one of the following chromosomal translocations: t(9;11)(p22; q23), t(11;19)(q23; p13), t(8; 21)(q22; q22), t(3; 21)(q26.2; q22.1), t(15;17)(q22; q12) or inv(16)(p13q22)⁷⁻¹¹. Most patients in this subset present overt acute leukemia without a myelodysplastic phase.

The patient in our case was exposed to an alkylating agent (ifosfamide) and a topoisomerase inhibitor (etoposide). Upon the diagnosis of t-MDS, cell karyotype was normal. However, the patient rapidly progressed to AML (within 2 months). It is important to note that t-MDS would not have been identified if this patient did not receive bone marrow examination upon the initial episode of leucopenia. In our view, patients with exposure to cytotoxic drugs and/or radiation should be followed-up with bone marrow aspirate if the routine blood test is abnormal. The low-dose IA

regimen was chosen to manage the t-AML in this case due to pancytopenia. The results (CR after four courses of chemotherapy) indicated that low-dose regimen could be used for elderly t-AML patients with pancytopenia.

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