Pulmonary Lymphangiomyomatosis; Unusual Radiological Manifestation of Multiple Large Nodules

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Abstract

A 44-year-old woman was admitted to our hospital in August 1999 for multiple large nodules detected on chest roentgenogram in an annual health check. Chest CT scans showed bilateral large nodules (>10 mm in diameter) with irregular margins and multiple thin walled cystic lesions. From these radiologic examinations, we suspected pulmonary Langerhans cell histiocytosis. Histological examination of the biopsy specimen by video-assisted thoracoscopy revealed a marked proliferation of the spindle cells, which were immunologically positive for alpha-smooth muscle actin and HMB-45, in the cyst walls and lung parenchyma. The large nodules consisted of proliferation of the smooth muscle cells surrounded by a dense layer of hemosiderin-laden macrophages. During the two years subsequent to these 1999 examinations, the opacities have gradually diminished and the patient was found to have pulmonary lymphangiomyomatosis. This case exhibited rare radiologic manifestations of multiple large nodules mimicking Langerhans cell histiocytosis.
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Key words: lymphangiomyomatosis, hemorrhage, Langerhans cell histiocytosis

Introduction

Pulmonary lymphangiomyomatosis (PLAM) is a rare disease, characterized by the non-neoplastic proliferation of atypical smooth muscle cells within the lung parenchyma, a predominantly peribronchovascular proliferation of the cells associated with airway and vascular obstruction, progressive loss of lung function and ultimately death (1). The radiological abnormalities of PLAM are consistent with ground-glass opacities and multiple cystic lesions accompanied by small nodules whose average size is under 5 mm (2).

Pulmonary Langerhans cell histiocytosis (LCH) is also a rare lung disease characterized by lung infiltrates composed of Langerhans' histiocytes (3), and the radiographic appearance of LCH consists of cystic lesions and multiple nodular opacities ranging on average from 1 to 5 mm, the largest being 10 mm in diameter (4, 5).

Both PLAM and LCH have similar pulmonary cysts, which are defined as air-containing lesions surrounded by thin walls that are not shared, but in general parenchymal large nodules, when present, are helpful in distinguishing LCH from PLAM (6). We describe a case of PLAM with an unusual presentation of large nodular lesions, mimicking LCH.

Case Report

A 44-year-old woman, current smoker, was admitted to our hospital in August 1999 for evaluation of pulmonary nodules found on chest X-ray film in an annual health check. She had undergone an operation to remove her uterus, but not her ovaries, for uterine cervical cancer in 1993. On admission she was 152 cm tall and weighed 76 kg. Her radial pulse rate was 84/min and regular. There was no abnormality in her physiological findings including auscultation of the lung. The liver and renal function tests were both within normal limits except for the high level of serum γ -GTP. Serum tumor markers were all within normal limits except that carbohydrate antigen 125 was 21.0 U/ml (normal <18.0). Arterial blood gas study in room air showed PaO₂ 84.8 Torr, PaCO₂ 34.1 Torr, and pH 7.427. Pulmonary function test was performed but there were slight changes (Table 1). Chest roentgenograms on admission revealed bilateral nodular shadows (Fig. 1) and chest CT scans showed multiple thin walled cystic lesions and multiple nodules (10 to 15 mm in diameter) in both lungs (Fig. 2). No pleural effusion was found. And abdominal CT scans showed no abnormal findings except that her uterus had been removed. From these radiologic examinations, we suspected this case as having LCH or even metastatic lung cancer considering that she had undergone an operation for uterine cervical cancer. To confirm the diagnosis, video-assisted thoracoscopic biopsies from the left

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Table 1. Laboratory Data on Admission

Hematology		Serology	
RBC	423×10 ⁴ /mm ³	CRP	0.36 mg/dl
Hb	13.0 g/dl	IgG	1,330 mg/dl
WBC	8,700 /mm ³	IgA	228 mg/dl
Neut	58%	IgM	90 mg/dl
Lymp	30%	Tumor markers	
Mon	7%	CEA	2.4 ng/ml
Eos	5%	SCC	0.6 ng/ml
Plt	26.6×10 ⁴ /mm ³	SLX	23.8 U/ml
ESR	16 mm (1 h)	CYFRA-21	<0.5 ng/ml
Biochemistry		CA125	21.0 U/ml
TP	6.8 g/dl	Blood gas analysis (room air)	
AST	19 IU/l	PaO ₂	84.8 Torr
ALT	26 IU/l	PaCO ₂	34.1 Torr
LDH	324 IU/l	pH	7.427
ALP	123 IU/l	Pulmonary function test	
γ-GTP	65 IU/l	VC	3.37 l
BUN	16 mg/dl	%VC	126.2%
Cr	0.6 mg/dl	FEV ₁	2.76 l
Na	138 mEq/l	FEV ₁ %	84.9%
K	3.8 mEq/l	TLC	5.03 l
Cl	104 mEq/l	%TLC	125.8%
FBS	87 mg/dl	RV	1.66 l
		%RV	116.9%
		%DLco	84.2%

S⁵ and S⁸ were performed, and histological examination of the biopsy specimens revealed that the large nodules consisted of a marked proliferation of spindle cells and cyst walls covered with the same kind of cells. In the immunohistological examination these cells stained positively for alpha-smooth muscle actin and HMB-45. Additionally, the nodular lesions were surrounded by a dense layer of hemosiderin-laden macrophages (Figs. 3A, B and 4). From these results she was found to have PLAM.

Because she was asymptomatic and she would soon be postmenopausal, she received no specific treatment for PLAM. Although the cystic lesions in the lung fields are worsening, the nodules have markedly diminished in the last 2 years (Fig. 5).

Discussion

The characteristic CT finding of LAM consists of numerous air-filled cysts surrounded by normal lung parenchyma (1, 2). And rarely a few small nodular opacities can be seen (7). Nodules in LCH consist of several types of inflammatory cells including Langerhans' cells, and the majority of them measure 1 to 5 mm in diameter (5). It is suggested that the presence of these parenchymal nodules is helpful to distinguish LCH from PLAM (6, 8). Recently, Keyzer et al (7) described a case of PLAM that mimicked LCH by demonstrating cavitary nod-

Figure 1. Chest roentgenogram on admission shows bilateral large nodules in the middle and lower lung fields.

Figure 2. Chest CT scan on admission shows multiple nodules ranging from 10 to 15 mm in diameter, ground-glass opacities, and cysts.

ules ranging from 3 to 4 mm in diameter and thin-walled cysts, but to our knowledge, there has been no case report of PLAM presenting multiple large nodules of more than 10 mm in diameter. In this case, histological examination of the biopsy specimens revealed a large nodule composed of PLAM cells surrounded by a thick layer of hemosiderin-laden macrophages. The size of the nodule has decreased in the 2 years since the biopsy. In ordinary PLAM cases, hemorrhage is common and radiological findings reveal ground-glass opacities. Additionally, minute (1 to 3 mm) nodules consisting of type II cell hyperplasia on CT scans are revealed in some patients with PLAM (9, 10). However, there were no such pathological find-

A

B

Figure 3. A: Biopsy specimens demonstrate a marked proliferation of the spindle cells in the wall of cyst, which surrounded by macrophages (HE stain, $\times 34$). **B:** Immunohistochemical study shows positive reactivity of the proliferating cells for HMB-45 ($\times 340$).

Figure 4. A large focus of proliferated smooth muscle cell is surrounded by a dense layer of hemosiderin-laden macrophage stained as blue (Iron stain, $\times 9$).

Figure 5. Chest CT scan 2 years after thoracoscopy shows that the nodules nearly disappear in spite of the fact that the cystic lesions are increasing.

ings in the present case. We could not elucidate the reason why so many hemosiderin-laden macrophages remained in existence for such a long time. There has been no case report presenting bilateral large nodules as a radiological manifestation of PLAM.

The abnormal smooth muscle cells in LAM are immunophenotypically distinct in that they express a melanogenesis-associated antigen recognized by HMB-45 and also frequently express estrogen and progesterone receptor proteins (11–13). In the present case the smooth muscle cells were showed positive for HMB-45, therefore this patient was diagnosed as having PLAM. However, before the biopsy the radiologic findings led us to suspect LCH or even metastatic lung cancer.

PLAM is an uncommon disease characterized by patchy proliferation of smooth muscle cells unique to this disease. But

the cause and pathogenesis of LAM are not known yet. There is a significant overlap between LAM, angiomyolipoma, and the syndrome of tuberous sclerosis (14). It has been shown that the smooth muscle found in PLAM is similar histologically and immunohistochemically to that found in angiomyolipoma (11). The suggestion that PLAM is a *forme fruste* of tuberous sclerosis is strengthened by the findings that patients with LAM also have angiomyolipoma (15). But in the present case, renal angiomyolipoma was not seen on CT scans.

The pulmonary function pattern of LAM is generally typical of obstruction resembling that of pulmonary emphysema. Total lung capacity, vital capacity and residual volume are usually normal or increased, and DLco is contrary reduced (16). But this case had a slight increase of total lung capacity and a normal DLco value, and these parameters did not change even

after 2 years. Based on these results, the present case might be considered an early stage of PLAM.

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