Case Report

Multifocal Micronodular Pneumocyte Hyperplasia Associated with Tuberous Sclerosis: Differentiation from Multiple Atypical Adenomatous Hyperplasia

Yoshihiro Kobashi¹, Tadaaki Sugi¹, Keiji Mouri¹, Tsutomu Irie², Masao Nakata³ and Mikio Oka¹

¹Division of Respiratory Diseases, Department of Medicine, ²Department of Pathology, and ³Department of Thoracic Surgery, Kawasaki Medical School, Kurashiki, Okayama, Japan

Received March 3, 2008; accepted May 3, 2008; published online June 5, 2008

We report a peculiar case of multifocal micronodular pneumocyte hyperplasia (MMPH) in a 54-year-old woman with tuberous sclerosis complex (TSC) diagnosed during antituberculous treatment. Findings were initially detected by chest computed tomography (CT) to check for complication of pulmonary tuberculosis. Chest CT demonstrated multiple small nodules with ground-glass opacity, measuring up to 5 mm diameter, presenting in the bilateral lung fields, without cystic change. Because the differentiation from multiple atypical adenomatous hyperplasia (AAH) was necessary, we finally performed a diagnosis of MMPH based on specimens obtained by video-assisted thoracoscopic surgery. Histologically, type II pneumocytes without nuclear atypia lined the thickened alveolar septa and proliferated papillary structures. There was no proliferation of immature smooth muscle cells suggestive of lymphangioleiomyomatosis. Although immunohistochemical stains for cytokeratin and surfactant apoprotein A and B were positive for alveolar lining cells in each MMPH lesion, those for HMB-45, alpha-smooth muscle actin, p53 and carcinoembryonic antigen were negative. We must consider MMPH as part of the differential diagnosis along with multiple AAH when multiple small nodules with ground-glass opacity were observed on chest CT in patients with TSC.

Key words: multifocal micronodular pneumocyte hyperplasia — tuberous sclerosis complex — video-assisted thoracoscopic surgery

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the triad of mental retardation, seizures and cutaneous lesions (angiofibroma and subungual fibroma). As pulmonary involvement, lymphangioleiomyomatosis (LAM) is found in 1% of cases (1), while multifocal micronodular pneumocyte hyperplasia (MMPH) is extremely rare (2). The majority of patients with MMPH in TSC are women of premenopausal age associated with LAM. In this report, we describe a woman with TSC and pulmonary involvement manifested by MMPH who was detected during antituberculous treatment for cervical tuberculous lymphadenitis and required differentiation from multiple atypical adenomatous hyperplasia (AAH).

CASE REPORT

A 54-year-old woman had been diagnosed as having TSC because of epileptic seizure at the age of 10. Although she had angiofibroma of the face and bilateral renal angioliroma, there was no mental retardation. Menopause occurred at 50 years of age. She had no family history of TSC. She was admitted to our hospital in November 2007 because of cervical tuberculous lymphadenopathy. The cause of left cervical lymphadenopathy was histologically diagnosed as cervical tuberculous lymphadenitis by cervical lymph node resection and...
finally confirmed by bacterial culture of acid-fast bacilli. Antituberculous treatment (isoniazid, rifampicin, ethambutol and pyrazinamide) was administered after the definitive diagnosis was obtained. Although the patient did not have respiratory symptoms, abnormal radiological findings on computed tomography (CT) of the chest were incidentally detected during a systemic screening examination for tuberculosis infection. Laboratory data at diagnosis of cervical tuberculous lymphadenitis is shown in Table 1. Slight anemia, elevation of erythrocyte sedimentation rate, positive response to purified protein derivatives and QuantiFERON TB-2G test were recognized due to tuberculosis infection. However, there were no abnormal findings on other laboratory data including tumor marker levels. Chest radiograph showed almost normal findings. Chest CT demonstrated multiple micronodular ground-glass opacities, <5 mm in diameter in the bilateral lung field (Fig. 1). However, there were no cystic changes suggestive of LAM. We initially suspected multiple AAH. To obtain a histopathological diagnosis, we performed video-assisted thoracoscopic surgery (VATS) and specimens were resected from the right upper lobe of the lung. Magnetic resonance imaging (MRI) of the head demonstrated a subependymal tumor extending bilaterally into the lateral brain spaces. Abdominal echogram demonstrated several tumors corresponding to angiomyolipomas encroaching bilaterally into the kidneys.

Thoracoscopy did not show any cystic lesions suggestive of LAM. Resected specimens showed several small white nodules of varying sizes, ranging from 3 to 5 mm in diameter, scattered in the lung parenchyma. Histopathologically, these several small nodules showed comparatively clear margins with alveolar collapse and were composed of a proliferation of type II pneumocytes along the alveolar septa. The type II pneumocytes were enlarged and varied in shape from flattened to cuboidal or round, sometimes with clear nucleoli, but demonstrated no intranuclear inclusion bodies. The cells lacked nuclear atypia or mitotic figures. The stroma of the small nodules showed a fibrous thickening of the alveolar septa due to an increase of elastic fibers. A mild infiltration of lymphocytes in the thickened alveolar septa and aggregations of macrophages in the alveolar lumens were also observed (Fig. 2). There was no proliferation of immature smooth muscle cells suggestive of LAM in the area, including the thickened alveolar septum or around the pulmonary arteries and bronchioles. There were no emphysematous lesions typically seen in cases of LAM.

Immunohistochemically, all proliferating alveolar epithelial cells were positive for cytokeratin, surfactant apoprotein A and B. However, these cells were negative for carcinoembryonic antigen (CEA), p53, desmin, alpha-smooth muscle actin (α-SMA), HMB-45, estrogen and progesterone receptors. Microvessels within the thickened alveolar septa were positive for α-SMA and desmin, but negative for HMB-45.

**DISCUSSION**

Pulmonary involvement occurs in about 0.1–1% of cases with TSC, and is associated with LAM in the majority (3,4). Popper et al. (5) reported MMPH associated with TSC in 1991, and Guinee et al. (6) reported MMPH with TSC in 1995. The pathology of MMPH has been reported previously, but the radiological findings have not been reported. MMPH is a hamartomatous process of the lung that exhibits multiple small nodules. Chest CT in MMPH demonstrates small nodules measuring 1–10 mm in diameter, which diffusely scattered throughout the lung in a random distribution

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>$333 \times 10^{9}/μl$</td>
</tr>
<tr>
<td>Hb</td>
<td>10.8 g/dl</td>
</tr>
<tr>
<td>Ht</td>
<td>3.30%</td>
</tr>
<tr>
<td>WBC</td>
<td>5750/μl</td>
</tr>
<tr>
<td>Seg</td>
<td>64%</td>
</tr>
<tr>
<td>Mono</td>
<td>4%</td>
</tr>
<tr>
<td>Lym</td>
<td>32%</td>
</tr>
<tr>
<td>Plate</td>
<td>$17.7 \times 10^{4}/μl$</td>
</tr>
<tr>
<td>ESR</td>
<td>75 mm/h</td>
</tr>
<tr>
<td>PPD</td>
<td>15 \times 15/30</td>
</tr>
</tbody>
</table>

PPD, purified protein derivative; QFT, QuantiFERON TB-2G; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; WBC, white blood cell; Plate, platelet; ESR, erythrocyte sedimentation rate.

**Figure 1.** Chest CT during the course of antituberculous treatment. Multiple small ground-glass opacities were shown in the bilateral lung fields (arrow).
with regard to the secondary lobules (7). In this case, MMPH was visualized as comparatively well-defined small nodules (1–5 mm) with ground-glass opacity on chest CT. Ground-glass opacity on chest CT was correlated with decreasing alveolar air spaces due to hyperplastic proliferation of type II pneumocytes and infiltration of macrophages into alveoli. Radiologically, important differential diagnoses of MMPH on chest CT are multiple AAH. Kushihashi et al. (8) described CT findings of AAH demonstrating small nodules with ground-glass opacity. This appearance resembles that of MMPH, making differentiation by chest CT difficult. However, AAH tends to coexist with adenocarcinoma. In this case, multicentric lesions were observed. Multicentric lesions are not common in AAH.

We obtained a definitive histological diagnosis using VATS. To date, the development of thoracoscopy has contributed markedly to the diagnosis of pulmonary diseases that demonstrate a diffuse distribution of shadowing. In fact, recent reports of MMPH cases often described the use of thoracoscopy to obtain a diagnosis (9). MMPH is histologically characterized by the presence of multicentric well-demarcated nodular growth of type II pneumocytes along with alveolar septa that exhibit fibrous thickening, alveolar collapse due to the increase of elastic fibers into alveolar septa and aggregated macrophages into alveolar spaces (5,6,10). However, AAH typically consists of epithelial cells, showing occasional immunoreactivity for CEA and p53, with nuclear atypia and a high nuclear-to-cytoplasmic ratio and shows alveolar structure with fewer intraalveolar macrophages than MMPH and with a slight alveolar collapse due to the increase of collagen fibers into alveolar septa. In this case, because of the presence of multicentric well-demarcated nodular growth of hyperplastic type II pneumocytes (no p-53 positive cells) along alveolar septa, fibrous thickening with alveolar collapse due to the increase in elastic fibers and aggregation of alveolar macrophages into the alveolar spaces, we were able to distinguish MMPH from AAH. The natural history of MMPH is unclear (11), but it is unlikely to progress to malignancy.

Concerning the immunohistochemical findings, the epithelial cells strongly expressed cytokeratin, EMA, and surfactant A and B, but not CEA, desmin or HMB-45. MMPH that does not show invasion into blood or lymphatic vessels (5,12) or immunohistochemical reactivity for p53 or CEA is not considered to possess malignant potential. HMB-45 is recognized as a marker for LAM immunohistochemically distinct from other pulmonary smooth muscle proliferation (13). Negative staining for HMB-45 in MMPH lesions indicates that the pathogenesis of MMPH is probably separate from smooth muscle cell proliferation of LAM (12,14). Otherwise, because estrogen and progesterone receptors were also negative in patients with MMPH unlike that in LAM (12,14), MMPH is unrelated to hormonal abnormality.

The relationship between MMPH and TSC is clearly emphasized in the recent literature, and a correlation with LAM is also evident. However, there were two reports describing patients with MMPH who did not have either TSC or LAM (7,15). In these patients, there was no pulmonary comorbidity and the lesions were asymptomatic. The problem in determining the disease is the non-TSC type or incomplete type of TSC. Kobashi and Watanabe (16) reported a patient with MMPH with the sporadic incomplete type of TSC who was diagnosed as having MMPH during the surgical procedure and did not have any obvious clinical findings indicating TSC. We suggest that the incidence of patients with MMPH of the non-TSC type or incomplete type of TSC has been increasing.

In conclusion, we report a case of MMPH related to TSC that required differentiation of multiple AAH. Findings were incidentally detected during antituberculous treatment for cervical tuberculous lymphadenitis, and the patient was diagnosed using VATS. The thorascopic procedure may have played an important role in the diagnosis of pulmonary lesions in this patient. We must consider MMPH as part of the differential diagnosis along with multiple AAH when multiple small nodules with ground-glass opacity are observed on chest CT in patients with TSC.

Conflict of interest statement
None declared.
References