Multifocal Micronodular Pneumocyte Hyperplasia in a Man with Tuberous Sclerosis

Yoshihiro Kobashi, Kouichiro Yoshida, Naoyuki Miyashita, Yoshihito Niki, Toshiharu Matsushima and Tutomu Irei*

Abstract

We report a peculiar case of multifocal micronodular pneumocyte hyperplasia (MMPH) occurring in a 43-year-old man with tuberous sclerosis. Computed tomography of the chest demonstrated multiple micronodules, measuring up to 5 mm in size, present bilaterally in the lung fields, with no cystic change. Histologically, a proliferation of type II pneumocytes without the typical nuclear atypia lined the thickened alveolar septa in an adenomatoid pattern. Proliferation of immature smooth muscle cells suggestive of LAM was not observed. The characteristic findings of the positive immunohistochemical stains for cytokeratin and surfactant apoprotein A and B, and negative stains for HMB-45, alpha-1 smooth muscle actin, desmin, p53 and carcinoembryonic antigen confirmed the presence of alveolar lining cells in each MMPH lesion. Since the MMPH was observed in a male and did not appear to possess malignant potential, the MMPH appears to be a hamartomatous proliferation occurring in a male with tuberous sclerosis that is separate from lymphangioleiomyomatosis (LAM) which is related to estrogen and progesterone receptors.

Case Report

A 43-year-old man had been diagnosed as having tuberous sclerosis associated with angiofibroma of the face and bilateral renal angiolipoma. He was admitted to our hospital because of abnormal findings on computed tomography (CT) of the chest done as a systemic screening examination for tuberous sclerosis. The patient had no family history of tuberous sclerosis, no respiratory symptoms and did not smoke. He had been diagnosed as having epilepsy five years previously and manifestation of his tuberous sclerosis. However, he had mental retardation. Physical examination including a neurological examination revealed no abnormalities. Laboratory data on admission are shown in Table 1. There were no abnormal laboratory tumor marker findings. Chest X-ray on admission showed almost normal findings. No emphysematous changes, interstitial fibrosis, increased lung volume, or pleural effusions were found. Chest CT revealed...
multiple micronodular shadows smaller than 5 mm in diameter in the lung fields bilaterally (Fig. 1). However, cystic changes suggestive of LAM were absent. To obtain a histopathological diagnosis, we performed a thoracoscopic procedure and specimens were resected from the right upper lobe of the lung. Magnetic resonance imaging (MRI) of the head revealed a subependymal tumor extending bilaterally into the lateral brain spaces. Screening abdominal echogram revealed several tumors corresponding to angiomyolipomas encroaching bilaterally into the kidneys.

Thoracoscopy showed multiple small white nodules up to 5 mm in diameter, which were scattered in the subpleural parenchyma in each lobe of the right lung. The lung surface showed no cystic lesions suggestive of LAM. A resected specimen showed four white firm nodules of varying sizes ranging from 1 mm to 3 mm in diameter, scattered in the lung parenchyma.

Histopathologically, these several nodules had a comparatively clear margin, the largest nodule measuring 3 mm in diameter (Fig. 2A), and were composed of a proliferation of type II pneumocytes. The center of the small nodules showed papillary or trabecular growth pattern. The stroma of these nodules showed a fibrous thickening of the alveolar septa of the elastosis. The type II pneumocytes were enlarged and varied in shape from flattened to cuboidal or round, sometimes with clear nucleolus, but demonstrated no intranuclear inclusion bodies. They lacked marked nuclear atypia or mitotic figures. A mild infiltration of lymphocytes in the thickened alveolar lumens and aggregations of macrophages in the alveolar lumens were also observed (Fig. 2B). A proliferation of immature smooth muscle cells suggestive of LAM was not observed, in any area including the thickened alveolar septum or the area around the pulmonary arteries and bronchioles. Further, emphysematous lesions as seen in cases of LAM were not observed.

Immunohistochemical investigations revealed that all pro-

---

**Table 1. Laboratory Data on Admission**

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Serology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC 438×10⁴/µl</td>
<td>IgG</td>
<td>1,400 mg/dl</td>
</tr>
<tr>
<td>Hb 13.2 g/dl</td>
<td>IgA</td>
<td>186 mg/dl</td>
</tr>
<tr>
<td>Ht 40.3%</td>
<td>IgM</td>
<td>165 mg/dl</td>
</tr>
<tr>
<td>WBC 5,080/µl</td>
<td>IgD</td>
<td>1.1 mg/dl</td>
</tr>
<tr>
<td>Seg 70%</td>
<td>IgE</td>
<td>191 U/ml</td>
</tr>
<tr>
<td>Mono 1%</td>
<td>CEA</td>
<td>&lt;1.0 ng/ml</td>
</tr>
<tr>
<td>Lym 29%</td>
<td>CA19-9</td>
<td>&lt;5.0 U/ml</td>
</tr>
<tr>
<td>Plt 28.6×10³/µl</td>
<td>SCC</td>
<td>&lt;0.5 ng/ml</td>
</tr>
<tr>
<td>ESR 20 mm/h</td>
<td>SLX</td>
<td>23.8 U/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood chemistry</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TP 7.9 g/dl</td>
<td>TPA</td>
</tr>
<tr>
<td>BS 82 mg/dl</td>
<td>NSE</td>
</tr>
<tr>
<td>Bil (T) 0.5 mg/dl</td>
<td>ProGRP</td>
</tr>
<tr>
<td>ALP 249 IU/l</td>
<td>CYFRA</td>
</tr>
<tr>
<td>Cho 216 mg/dl</td>
<td>SP-D</td>
</tr>
<tr>
<td>γ-GTP 18 IU/l</td>
<td>KL-6</td>
</tr>
<tr>
<td>LDH 149 IU/l</td>
<td>Cryptococcus antigen</td>
</tr>
<tr>
<td>Alb 4.8 g/dl</td>
<td>Cryptococcus antibody</td>
</tr>
<tr>
<td>Glb 3.1 g/dl</td>
<td>Aspergillus antigen</td>
</tr>
<tr>
<td>ChE 385 IU/l</td>
<td>Aspergillus antibody</td>
</tr>
<tr>
<td>GPT 20 IU/l</td>
<td>β-D-glucan</td>
</tr>
<tr>
<td>GOT 15 IU/l</td>
<td>ANA</td>
</tr>
<tr>
<td>Crn 0.84 mg/dl</td>
<td>CH₅₀</td>
</tr>
<tr>
<td>BUN 22 mg/dl</td>
<td>β₂-microglobulin</td>
</tr>
<tr>
<td>UA 5.4 mg/dl</td>
<td>Ccr</td>
</tr>
<tr>
<td>Amy 67 IU/l</td>
<td>Pulmonary function test</td>
</tr>
<tr>
<td>CRP 0.10 mg/dl</td>
<td>%VC (VC)</td>
</tr>
<tr>
<td>Na 143 mEq/l</td>
<td>FEV₁₋₅ % (FEV₁₋₅)</td>
</tr>
<tr>
<td>K 4.5 mEq/l</td>
<td>%DLco</td>
</tr>
<tr>
<td>Ca 0.84 mg/dl</td>
<td>PPD</td>
</tr>
<tr>
<td>Mg 2.2 mg/dl</td>
<td></td>
</tr>
<tr>
<td>P 4.4 mg/dl</td>
<td>Protein</td>
</tr>
<tr>
<td>Ca 9.8 mg/dl</td>
<td>Sugar</td>
</tr>
<tr>
<td>Mg 2.2 mg/dl</td>
<td>Blood</td>
</tr>
<tr>
<td>Stool Blood</td>
<td>Slx</td>
</tr>
</tbody>
</table>
liferating alveolar epithelial cells were intensely stained by cytokeratin antibodies (Fig. 3). In addition, these cells were positive for monoclonal antibodies of surfactant apoprotein A and B. However, proliferating epithelial cells and smooth muscle cells in the thickened alveolar septa were negative for CEA, p53, desmin, alpha-1 smooth muscle actin and HMB-45. They were also negative for anti-estrogen and anti-progesterone receptor monoclonal hormonal antibodies.

**Discussion**

There are only a few references in the English language literature to the distinctive micronodular epithelial hyperplastic lesion that is rarely found in the lungs of patients with tuberous sclerosis (8–10). The hamartomatous nature of these peculiar epithelial proliferations has been emphasized by all of the researchers who have identified them, by the use of such as “acinar atypical adenomatoid proliferation of epithelium” (11), “multiple adenomatoid lesions” (12), “micronodular hyperplasia of type II pneumocytes” (10). Recently, based on the number and location of the lesions, as well as their apparent epithelial origin, the term multifocal micronodular pneumocyte hyperplasia (MMPH) has become commonly used (13).

From the few available reports, it would appear that MMPH occurs both in patients with (8, 9) and without (10)
Multifocal Micronodular Pneumocyte Hyperplasia (MMPH)

Concerning the germline mutation analysis using leukocytes of patients, two predisposing genes have recently been found in families affected by tuberous sclerosis; approximately half of the families show linkage to \( TSC1 \) at 9q34.3, and the other half show linkage to \( TSC2 \) at 16p13.3 (22). Murayama et al (23) mentioned that the loss of heterozygosity (LOH) of the \( TSC2 \) gene preliminarily was detected in a LAM lesion but not in MMPH. Unfortunately however, we could be not investigate the germline mutation analysis for this case. It is suggested that MMPH, addition to LAM, could be another pulmonary lesion in tuberous sclerosis patients and that the detection of \( TSC1 \) or \( TSC2 \) gene could be useful for the pathogenesis of MMPH and LAM in tuberous sclerosis patients.

In previous reports (5, 6, 13, 24), most of the tuberous sclerosis patients with pulmonary MMPH involvement were premenopausal women. Although Muir et al (6) first reported that MMPH had been observed in two men with tuberous sclerosis, and then Popper et al reported MMPH in one male case, there were no precise clinicopathological explanations given. Therefore, we have provided a clinicopathological case report of a male with tuberous sclerosis and pulmonary involvement manifested by MMPH without LAM. The present patient had other associated clinical findings including: a subependymal lesion of the brain, angiomyolipoma of kidneys bilaterally and a dermal angiofibroma, in addition to MMPH. The clinical significance of MMPH in patients with tuberous sclerosis is unknown. It does not appear to be potentially fatal and it differs in this respect from LAM. In the present case, there were no respiratory symptoms because only MMPH lesions and no LAM lesions were present, LAM was ruled out on CT of the chest during the follow-up of this patient. In fact, multiple emphysematous areas suggestive of incipient LAM were not shown on CT of the chest. We think that the absence of estrogen and progesterone receptors ass shown by the immunohistochemical investigation suggests that there is no hormonal factor in the atypical epithelial proliferation or the smooth muscle proliferation in MMPH without LAM. Therefore, there are no available hormonal manipulations, including oophorectomy, medroxyprogesterone acetates, or tamoxifen that would be of use (25, 26).

Since the patient had no family history of tuberous sclerosis, the present case is a sporadic case rather than a familial case. There was no association with LAM. The MMPH in the present male case was diagnosed during a surgical procedure using video-assisted thoracoscopic surgery (VATS). It is thought that the prognosis is not poor in male tuberous sclerosis patients with MMPH. Nevertheless, a definitive diagnosis should be made, and therefore we think that a surgical procedure such as VATS is valuable in obtaining a correct diagnosis in a tuberous sclerosis patient showing multifocal micronodular lesions on CT of the chest. However, using genetic and immunohistochemical techniques, the histogenesis of hamartomatous lesions such as MMPH and LAM in tuberous sclerosis patients should be clarified in association with the \( TSC1 \) or \( TSC2 \) gene in the future in order to determine appropriate treatment for MMPH and LAM in tuberous sclerosis.

Acknowledgements: The authors are grateful to Dr. M. Nakata, an Associate Professor in the Department of Thoracic Surgery, Kawasaki
Medical School, for his kind assistance regarding the surgical division in this study.

References

1) Castro M, Shepard CW, Gomez MR, Lie JT, Ryu JH. Pulmonary tuber-
2) Lindor NM, Greene MH. The Mayo Familial Cancer Program, Special
article: The concise handbook of family cancer syndrome. J Natl
Pathology of the lung tumors. Churchill Livingstone, New York, 1997:
225–239.
5) Yamanaka A, Kitaichi M, Fujimoto T, Hirai T, Hori H, Konishi F.
Multifocal micronodular pneumocyte hyperplasia in a postmenopausal
6) Muir TE, Leslie KO, Popper H, et al. Micronodular pneumocyte
7) Popper HH. Micronodular hyperplasia of type II pneumocytes (letter).
8) Lie JT, Miller RD, Williams DE. Cystic disease of the lungs in tuber-
ous sclerosis: clinicopathologic correlation, including body plethysmo-
1043–1053.
10) Popper HH, Juetten-Smolle FM, Pongratz MG. Micronodular hyper-
plasia of type II pneumocytes —a new lung lesion associated with tu-
11) Corrin B, Liebow HH, Friedman PJ. Pulmonary lymphangioleiomy-
12) Okamura H, Yamauchi H. Pulmonary manifestations of tuberous sclero-
sis: its relationship to pulmonary lymphangioleiomyomatosis. Jpn J Chest
13) Guinee D, Singh R, Azumi W, et al. Multifocal micronodular pneumo-
cyte hyperplasia: a distinctive pulmonary manifestation of tuberous
14) Kuroki Y, Dempo K, Akino T. Immunohistochemical study of human
pulmonary surfactant apoprotein with monoclonal antibodies. Patho-
32, 1986.
15) Bonetti F, Chiodera PL, Pea M, et al. Transbronchial biopsy in lymph-
16) Chuah KL, Tan PH. Multifocal micronodular pneumocyte hyperplasia,
lymphangioleiomyomatosis and clear cell micronodules of the lung in a
Chinese female patient with tuberous sclerosis. Pathology 30: 242–246,
1998.
17) Flieder DB, Trvis WD. Clear cell “sugar” tumor of the lung: associa-
tion with lymphangioleiomyomatosis and multifocal micronodular
18) Lantuejoul S, Ferretti G, Negoescu A, Parent B, Brambilla E.
Multifocal alveolar hyperplasia associated with lymphangioleiomyo-
19) Weng SY, Tsuchiya E, Satoh Y, Kitagawa T, Nakagawa K, Sugano H.
Multiple atypical adenomatous hyperplasia of type II pneumocytes
20) Weng SY, Tsuchiya E, Kasuga T, Sugano H. Incidence of atypical
bronchioloalveolar cell hyperplasia of the lung: relation to histological
subtypes of lung cancer. Virchows Arch A Patholl Anat Histopaathol
21) Nakanishi K. Alveolar epithelial hyperplasia and adenocarcinoma of
22) Povey S, Burley MW, Attwood J, et al. Two loci for tuberous sclerosis:
pneumocyte hyperplasia and lymphangioleiomyomatosis in tuberous
24) Kawashima M, Kobayashi H, Tominaga M, Yathunami J, Hayashi S.
A case of micronodular pneumocyte hyperplasia, lymphangioleiomyo-
matosis associated with tuberous sclerosis. Nihon Kokyuki Gakkai
lymphangioleiomyomatosis responsive to progesterone. N Engl J Med
26) Tomasian A, Greenberg MS, Rumerman H. Tamoxifen for lymph-