Tuberous Sclerosis Complex Complicated by Pulmonary Multinodular Shadows

Hiroyuki Kamiya¹, Kinya Shinoda¹, Nobuyuki Kobayashi¹, Koichiro Kudo¹, Tomokiyo Nomura², Takatomo Morita² and Takeshi Fujii³

Abstract

A 41-year-old woman with a history of epilepsy was referred for multiple nodular ground-glass opacities on a chest computed tomography (CT) scan. They were initially suspected of representing atypical adenomatous hyperplasia or well-differentiated adenocarcinoma. However, the subsequent brain CT and magnetic resonance imaging (MRI) scans revealed a coarse nodular calcification and cortical tubers. A subungual fibroma was also noted. Histological examination of a video-assisted thoracoscopic lung biopsy specimen disclosed multiple nodules of type II pneumocyte hyperplasia with septal thickening. Based on all of these findings taken together, a diagnosis of tuberous sclerosis complex with multifocal micronodular pneumocyte hyperplasia (MMPH) was made.

Key words: tuberous sclerosis complex, multifocal micronodular pneumocyte hyperplasia, video-assisted thoracoscopic lung biopsy

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant hereditary neurocutaneous syndrome in which hamartomas develop in various organs, including the brain, skin, and kidney. Pulmonary involvement is rare, occurring in about 0.1 to 1% of cases, and although the majority of pulmonary lesions have been described as lymphangioleiomyomatosis, recent reports have indicated that multifocal micronodular pneumocyte hyperplasia (MMPH) is the second major form of pulmonary involvement by TSC. This rare lesion is manifested by multiple nodular ground-glass opacities on CT scans, and histologically may resemble atypical adenomatous hyperplasia or other neoplastic lesions. We report a case in which multinodular pulmonary shadows were noted on a CT scan of the chest and the diagnosis was TSC with MMPH.

Case

A 41-year-old Japanese-American woman consulted her physician because of speech and gait disturbances and a convulsion that involved her right arm. At that time abnormal shadows were first noted on a chest CT scan, which was included in the general survey and she was referred to our hospital for admission. The patient had initially presented with clonic seizures at 10 years of age, and she had been treated for epilepsy at a local clinic until her late twenties. The frequency of the seizures gradually decreased thereafter without medication, and she became seizure-free in her thirties. She is mentally retarded and has a fourth-grade intelligence level. She has hyperthyroidism since 38 years of age and has a history of cholecystectomy and hysterectomy for cholecystolithiasis and adenomyomatosis, respectively. There is no clear family history of TSC, but her father had a history of seizures and presented with the same findings in his toes as her.

On admission, she was conscious and slightly febrile

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(37.1°C). No rales or crackles were heard. A diffuse goiter was noted. A subungual fibroma was observed on the left big toe (Fig. 1) and several white macules on her limbs and trunk. There were no abnormal neurological findings. Laboratory data on admission (Table 1) showed slight anemia, but were otherwise normal, including tumor marker levels. She subsequently presented with a convulsion that affected her right upper arm and transient difficulty in speaking. Although we were unable to make a definite diagnosis of a seizure, because no clear spikes were detected on an electroencephalogram, abnormal sharp waves were identified in the occipital lead. A subsequent CT scan of the brain revealed a coarse nodular calcification near the foramen of Monro in the anterior portion of the right ventricle (Fig. 2), and the T2-weighted magnetic resonance imaging (MRI) showed high intensity areas in the right frontal and occipital lobes and in the left frontoparietal lobe, which were thought to represent cortical tubers. This constellation of findings suggested a diagnosis of TSC. The abnormal pulmonary shadows were inconspicuous on the chest X-ray, but multiple nodular ground-glass opacities were seen on a CT scan of the chest (Fig. 3). They were initially suspected of representing atypical adenomatous hyperplasia or well-differentiated adenocarcinoma. A wide range of surveys, including upper gastrointestinal and colorectal fiberscopy, head-and-neck and abdominal CT scans, neck and mammary ultrasonography, and Ga-67 scintigraphy ruled out any extrapulmonary primary

![Figure 1. Subungual fibroma of the left big toe (arrow).](image1)

![Figure 2. CT scan of the brain shows a coarse nodular calcification near the foramen of Monro in the anterior portion of the right ventricle.](image2)

![Figure 3. Chest high-resolution CT scan shows multiple nodular ground-glass opacities (arrowhead) randomly distributed in both lung fields.](image3)

Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 7.4x10^12/μl</td>
<td>AST 14 IU/l</td>
<td>CRP 0.31 mg/dL</td>
</tr>
<tr>
<td>Neu 69.0 %</td>
<td>ALT 6 IU/l</td>
<td>CEA 1.1 ng/ml</td>
</tr>
<tr>
<td>Lgm 28.0 %</td>
<td>LDH 188 IU/l</td>
<td>ProGRP 15.8 pg/ml</td>
</tr>
<tr>
<td>Mem 2.0 %</td>
<td>T-Bil 0.4 mg/dl</td>
<td>CYFRA &lt;0.3 ng/ml</td>
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<tr>
<td>Eo 1.0 %</td>
<td>ALP 102 IU/l</td>
<td>TSH 0.74 μU/ml</td>
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<tr>
<td>Base 0.9 %</td>
<td>BUN 8 mg/dl</td>
<td>FT3 7.4 pg/ml</td>
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<tr>
<td>RBC 4.2x10^12/μl</td>
<td>Cr 0.39 mg/dl</td>
<td>FT4 6.9 mg/ml</td>
</tr>
<tr>
<td>Hb 11.3 g/dl</td>
<td>Na 140 mmEq/l</td>
<td>TRAb (−)</td>
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<tr>
<td>Ht 33.9 %</td>
<td>K 3.6 mmEq/l</td>
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<tr>
<td>PIt 17.6x10^12/μl</td>
<td>Cl 108 mmEq/l</td>
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</tr>
<tr>
<td>ESR 5 mm/h</td>
<td>TP 6.3 g/dl</td>
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<tr>
<td></td>
<td>Alb 4.1 g/dl</td>
<td></td>
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<tr>
<td></td>
<td>Glu 94 mg/dl</td>
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<td></td>
<td>Oxygenation (room air)</td>
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<td></td>
<td></td>
<td>pCO₂ 41.0 torr</td>
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<td></td>
<td></td>
<td>pO₂ 91.0 torr</td>
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<tr>
<td></td>
<td></td>
<td>HCO₃ 25.8 mmEq/l</td>
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</table>

No significant abnormalities were detected in the blood gas analysis (room air).
Figure 4. Microscopic view of the specimen shows a well-demarcated nodular growth of bland-looking type II pneumocytes along the fibrously thickened alveolar septa containing an increase in elastic fibers. (A: HE staining, ×75, B: elastica-van Gieson staining, ×75, C: HE staining, ×400).

lesion. Video-assisted thoracoscopic biopsy of the left lower lobe (S6) of the lung was performed to examine the lung lesions, and histological examination revealed multiple well-demarcated nodules up to 10 mm in greatest diameter that consisted of type II pneumocytes with minimal cellular atypia growing along thickened alveolar septa (Figs. 4A, 4B, 4C), suggesting a diagnosis of MMPH.

Discussion

TSC is an autosomal-dominant hereditary neurocutaneous syndrome that is characterized by the presence of hamartomas in various organs, including the brain, skin, and kidney (1, 2). The causative genes responsible for TSC are located on chromosome 9q34 (TSC1) and chromosome 16p 13.3 (TSC2) (3, 4). A sporadic form also occurs, and accounts for about two-thirds of the cases. The patient in this case has no clear family history of TSC, but it may have been inherited from her father since he had a history of seizure and presented with the same findings in his toes.

The prevalence of TSC is about one per ten to fifteen thousand population (5) and angiofibroma, mental retardation, and epilepsy are known as the classic Vogt’s triad of TSC, although few cases present with all of the triad (6). The definite diagnosis of this case was not made for many years, which might be due to the fact that most physicians see this triad as an absolute diagnostic criterion. Meanwhile, a new criterion for TSC was proposed based on the hamartomas detected in each organ by Gomez (7) in 1991, and it was approved at the TSC consensus conference (6) in 1998.

Pulmonary involvement occurs in about 0.1 to 1% of cases, and in the majority it is associated with lymphangiomyomatosis (LAM) (8, 9), however, other forms of pulmonary involvement by TSC have also been described. Popper et al (10) reported MMPH associated with TSC in 1991, and Guinee et al (11) reported it in 1995, but only a few dozen of reports have focused on it since then. MMPH may coexist with other pulmonary TSC lesions, such as LAM (11), angiomyolipoma (12) and clear cell tumor (sugar tumor) (13), but each lesion is considered an independent event in these cases, because MMPH is negative for HMB-45, whereas the other three lesions are immunoreactive for HMB-45 (14, 15).

MMPH is histologically characterized by the presence of multicentric well-demarcated nodular growth of bland-looking type II pneumocytes along alveolar septa that exhibit fibrous thickening, increased elastic fibers, and aggregated alveolar macrophages (10, 11, 16). Atypical adenomatous hyperplasia and well-differentiated adenocarcinoma must be included in the differential diagnosis (17). There tend to be more interstitial changes in MMPH, and cellular atypia and destruction of the lung structure are not prominent. The prognosis is unclear (18), but it is unlikely to result in malignancy.

We have reported a case of MMPH as pulmonary involvement associated with TSC. MMPH and LAM are the pulmonary lesions of TSC. MMPH rarely occurs sporadically, and some cases of MMPH in males have been reported (17), whereas LAM (8) occurs almost exclusively in females. It will take further research to determine their pathogenesis.

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References


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