Multifocal Micronodular Pneumocyte Hyperplasia in a Man with Tuberous Sclerosis

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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 lymphangiomyomatosis (LAM) which is related to estrogen and progesterone receptors. (Internal Medicine 44: 462–466, 2005)

Key words: multifocal micronodular pneumocyte hyperplasia (MMPH), tuberous sclerosis, lymphangiomyomatosis (LAM)

Introduction

Tuberous sclerosis is an autosomal dominant disorder characterized by the presence of hamartias and the growth of hamartomas in one or more organs. Although the central nervous system, skin, kidney, heart, retina and lung are the

most commonly involved, nearly any organ in the body can be affected (1). Tuberous sclerosis has a relatively high penetrance (90–95%), and the prevalence has been estimated at 1 : 30,000 individuals under the age of 65 years and 1 : 15,000 under the age of five years (2). According to another study, the prevalence was 1 : 10,000 and the birth incidence 1 : 5,800 (3). Tuberous sclerosis does not occur predominantly in any gender, race or geographical location. With respect to pulmonary involvement, lymphangiomyomatosis (LAM) is found in 1% of cases (4), while multifocal micronodular pneumocyte hyperplasia (MMPH) is extremely rare (5). The majority of tuberous sclerosis patients with MMPH are women of premenopausal age who also have LAM. However, there is a particularly interesting tuberous sclerosis case with MMPH occurring in a male mentioned in a previous report (6, 7). Here, we describe a male with tuberous sclerosis and pulmonary involvement manifested by MMPH without LAM clinicopathologically.

Case Report

A 43-year-old man had been diagnosed as having tuberous sclerosis associated with angiofibroma of the face and bilateral renal angioliipoma. 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

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Table 1. Laboratory Data on Admission

Peripheral blood		Serology	
RBC	438×10 ⁴ /μl	IgG	1,400 mg/dl
Hb	13.2 g/dl	IgA	186 mg/dl
Ht	40.3%	IgM	165 mg/dl
WBC	5,080/μl	IgD	1.1 mg/dl
Seg	70%	IgE	19 I U/ml
Mono	1%	CEA	<1.0 ng/ml
Lym	29%	CA19-9	<5.0 U/ml
Plt	28.6×10 ⁴ /μl	SCC	<0.5 ng/ml
ESR	20 mm/h	SLX	23.8 U/ml
Blood chemistry		TPA	11 U/l
TP	7.9 g/dl	NSE	6.8 ng/ml
BS	82 mg/dl	ProGRP	18.3 pg/ml
Bil (T)	0.5 mg/dl	CYFRA	<1.0 ng/ml
ALP	249 IU/l	SP-D	77.2 ng/ml
Cho	216 mg/dl	KL-6	188 U/ml
γ-GTP	18 IU/l	Canditec	(-)
LDH	149 IU/l	<i>Cryptococcus</i> antigen	(-)
Alb	4.8 g/dl	<i>Cryptococcus</i> antibody	(-)
Glb	3.1 g/dl	<i>Aspergillus</i> antigen	(-)
ChE	385 IU/l	<i>Aspergillus</i> antibody	(-)
GPT	20 IU/l	β-D-glucan	<6.0 pg/ml
GOT	15 IU/l	ANA	(-)
Crn	0.84 mg/dl	CH ₅₀	39.9 U/ml
BUN	22 mg/dl	β ₂ -microglobulin	1.9 μg/ml
UA	5.4 mg/dl	Ccr	97.0 ml/min
Amy	67 IU/l	Pulmonary function test	
CRP	0.10 mg/dl	%VC (VC)	109.6% (4.42 l)
Na	143 mEq/l	FEV _{1.0} % (FEV _{1.0})	82.5% (3.72 l)
K	4.5 mEq/l	%DLco	102.0%
Cl	103 mEq/l	PPD	0×0
P	4.4 mg/dl		16×10
Ca	9.8 mg/dl	Urine	
Mg	2.2 mg/dl	Protein	(-)
		Sugar	(-)
		Blood	(-)
		Stool Blood	(-)

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 thorascopic 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 specimens showed four white firm nodules of varying sizes ranging from 1mm to 3mm in diameter, scattered in the lung parenchyma.

Histopathologically, these several nodules had a compara-

tively 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 varies 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-

Figure 1. Chest CT on admission showing multiple micronodules (arrowhead) in the lung fields bilaterally (A) and the magnification of micronodule in the segment 3 of the right lung (B).

Figure 2. Low-power view showing micronodule (arrowhead) which had a comparatively clear margin and were composed of a proliferation of type II pneumocytes. The center of the micronodule showing papillary or trabecular growth pattern (A) (HE staining, $\times 10$). High-power view showing the 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. A mild infiltration of lymphocytes in the thickened alveolar septa and aggregations of macrophages in the alveolar lumens (B) (HE staining, $\times 200$).

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 hyper-

plastic 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)

Figure 3. Proliferating alveolar epithelial cells were intensely stained by cytokeratin immunohistochemically (Immunoperoxidase, $\times 50$).

associated LAM. However, little attention has been focused on the true nature of these peculiar lesions. Though the study of Popper et al (10) suggested a hamartomatous proliferation of type II pneumocytes, this conclusion was based on limited morphological and ultrastructural data. However, in the present study, the positive immunohistochemical staining for cytokeratin in the proliferated cells confirmed epithelial differentiation. As well positive staining for surfactant apoprotein A and B provided additional evidence of type II pneumocyte origin (14). HMB-45 is recognized as a marker for LAM that is immunohistochemically distinct from other pulmonary smooth muscle proliferation (15). The findings in LAM (16, 17) are different from those in MMPH. In fact, the studies so far have reported no immunoreactivity for HMB-45 as well as negative results for estrogen and progesterone receptors in MMPH (13, 16–18). In cases with combined LAM and MMPH, the characteristic manifestation of LAM ended at the edges of the MMPH lesions (6). The negative staining for HMB-45 in the MMPH lesions indicates that the pathogenesis of the MMPH is probably separate from that of the smooth muscle cell proliferation of LAM. Histologically, the most important differential diagnosis for MMPH is atypical bronchioalveolar cell hyperplasia. It is usually found in the parenchyma adjacent to other lung carcinomas, and may represent a precursor to adenocarcinoma (19–21). In this case, there was no malignant lesion on histological finding in the specimen of VATS and proliferating epithelial cells were all negative for p53 or CEA immunohistochemically. Unlike atypical bronchioalveolar cell hyperplasia, there is no evidence that MMPH is preneoplastic.

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 hetero-

zygosity (LOH) of the *TSC2* gene preliminarily was detected in a LAM lesion but not in MMPH. Unfortunately however, we could 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 as 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.

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