Case Report

Multifocal micronodular pneumocyte hyperplasia in a Chinese man masquerading as miliary tuberculosis

Qi Sun¹, Hou-Rong Cai², Eugene J Mark³, Li-Yun Miao², Hong-Yan Wu¹, Qiang Zhou¹, Jun Chen¹, Wei Zhang⁴, Fan-Qing Meng¹

Departments of ¹Pathology, ²Respiratory Medicine, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, Jiangsu Province, China; ³Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; ⁴Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu Province, China

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Abstract: Multifocal Micronodular Pneumocyte Hyperplasia (MMPH) is a rare and histologically, distinctive pulmonary manifestation of tuberous sclerosis complex (TSC) characterized by numerous and extensive proliferative lesions of type II pneumocytes similar to atypical adenomatous hyperplasia (AAH) or non-mucinous adenocarcinoma in situ (AIS). We reported MMPH in a 38-year-old Chinese man with TSC masquerading for 16 months as miliary tuberculosis and discussed the differential diagnosis.

Keywords: Tuberous sclerosis complex, multifocal micronodular pneumocyte hyperplasia

Introduction

Tuberous sclerosis complex (TSC) is a genetic disease characterized by hamartomatous lesion in various organs [1]. Pulmonary manifestations of TSC include lymphangioleiomyomatosis (LAM) and multifocal micronodular pneumocyte hyperplasia (MMPH). MMPH, as described by Popper in 1991 [2], has multifocal well-demarcated nodular lesions consisting of proliferation of type II pneumocytes with mild fibrous thickening of the alveolar septa particularly when extensive. Active proliferating pneumocytes with atypia can lead to diagnostic problem. We describe MMPH in a Chinese man with TSC, and discuss the clinical, histological and molecular features of MMPH with emphasis on the differential diagnosis.

Case report

Clinical history

A 38-year-old man was admitted to local hospital because of a constant dull chest pain in the sternum for one year. Computed tomography (CT) of the chest revealed multiple bilateral ground-glass opacities ranging from 1 mm to 9 mm in diameter (Figure 1A). No cystic lesions, pleural effusions, or hilar and mediastinal lymph node enlargement were observed. A provisional diagnosis of military tuberculosis was made, and antituberculosis chemotherapy was given for 1 year. CT scans after 6, 12 and 16 months, showed no change. The patient was referred to our hospital for further investigation and treatment.

On admission, the patient had no symptoms. Examination revealed firm slightly elevated yellow-red nodules characteristic of shagreen patchs on his back (Figure 1B). Shagreen patchs suggest TSC, but the patient had no family history of TSC. Brain CT showed multiple subependymal calcifications along the lateral ventricle (Figure 1C). Pulmonary function testing was normal.

Transbronchial lung biopsy (TBLB) was performed. It showed prominent hyperplasia of pneumocytes. The differential diagnosis included atypical adenomatous hyperplasia (AAH) or non-mucinous adenocarcinoma in situ Therefore, video-assisted thoracoscopy (VAT) was
performed during the operation, the surgeon noted white nodules beneath the pleura.

Pathologic findings

Three wedge lung tissues from the upper, middle and lower lobe of right lung were obtained. Lots of white firm tiny and small nodules, ranging from 1 mm to 5 mm in diameter, were found on cut surface.

Microscopically, the nodules without encapsule or defined boundary. They were composed of a proliferation of type II pneumocytes alveolar septa with collapse of alveolar airspace (Figure 2A). The pneumocytes were enlarged and varied in shape from flattened to cuboidal (Figure 2B). No mitoses were present. Elastica van Gieson stain showed an increase of elastic fibers in alveolar septa (Figure 2C). Mild infiltration of lymphocytes in the alveolar septa, and macrophages aggregated in the alveolar space. Pneumocytes showed trabecular or papillary growth pattern in focal area.

Immunohistochemically proliferating alveolar epithelial cells stained for pan-CK (pan-cytokeratin), EMA (epithelial membrane antigen), TTF-1 (thyroid transcription factor-1), and SP-B (Surfactant protein-B), whereas negative for HMB-45, vimentin, desmin, SMA (smooth muscle actin), ER (anti-estrogen receptor antibody), PR (anti-progesterone receptor antibody), CR (calretinin), p53, and CEA (carcinoembryonic antigen). The proliferation rate by ki67 (MIB-1) stain was less than 1%.

Clinical findings

After clinical pathological case discussion and a literature review, a firm diagnosis of MMPH was established. In retrospect, the patient had
two of the major diagnostic criteria for TSC, namely subependymal nodules and shagreen patches [1]. The patient did not have the third part of the triad, namely seizures or mental retardation. Unfortunately, the patient refused to take genetic test for confirming TSC gene mutation.

Discussion

Pulmonary manifestation appears in 1%-2% of patients with TSC and usually associated with LAM [3, 4]. MMPH is an additional and rarer manifestation in TSC patients. It occurs in patients with TSC or with LAM, alone but has been reported in men without TSC or LAM [5, 6]. The negative staining for HMB45, estrogen and progesterone receptors in our cases rule one against LAM and also indicate a pathogenetic difference between MMPH and LAM [7].

Less than 50 cases of MMPH are reported in the pathologic literature. The age range has been 13-64 years old [8, 9]. Only a few cases occurred in men [4, 7, 10]. Clinically, MMPH usually have no respiratory symptoms. Some patients with MMPH present with dyspnea, cough, and mild hypoxemia [10] but most patients have no respiratory symptoms. MMPH presents on x-ray as multiple tiny nodules 1-20 mm in diameter [7, 11], as in this case that are randomly scattered throughout the lung [10].

In our case, VAT played an important role in establishing the diagnosis. MMPH must be histologically distinguished from AAH or NAIS [3-7, 12]. MMPH has been in fact described as alveolar epithelial atypical adenomatous hyperplasia [13]. However, AAH foci are usually less than 5 mm in diameter and often appear in association to lung carcinomas. Although nuclear features play a part in the differential diagnosis of AAH and MMPH [3-7], nuclear atypia can appear in both diseases. However, the cells in AAH comprise a more homogeneous population compared to that seen in MMPH (Figure 3A). The epithelial cells in AAH show immunoreactivity for p53 and CEA while the cases of MMPH do not. Both AAH and MMPH can have thickened alveolar septa with an increase in elastic fibers, but the proliferation of elastic fibers in AAH is often assembled in a...
reticular structure, while in MMPH the elasticity is discontinuous or clumped (Figure 3B). Aggregation of alveolar macrophages in the air spaces and lymphocytic infiltration is common in MMPH.

Clinical history is important, MMPH almost only occur in TSC patients of MMPH produces only tiny nodules of <20 mm in diameter randomly and diffusely throughout the lung, while numerous nodules are less common in AAH or NAIS [3]. Our patient was initially considered to have multiple NAIS. Other considerations histologically included papillary adenoma of type II cells, sclerosing hemangioma and alveolar adenoma. These benign lesions are generally larger solid tumors.

From the molecular standpoint, Hayashi et al. [9] suggested that functional loss of TSC genes and consequent hyperphosphorylation of mTOR-related proteins in MMPH causes the benign neoplastic proliferation of pneumocytes. Their study also revealed that constitu-
tive activation of phospho-Akt (an upstream regulatory protein of mTOR) in both AAH and NAIS was more frequently detected than TSC LOH, suggesting different molecular mechanisms between MMPH and preinvasive lesions of pneumocytes. Although TSC is an autosomal dominant disease associated with gene mutations of TSC1 or TSC2, two-thirds of cases have sporadic mutations [14], which leads to under-diagnosis in TSC patients without the classical clinical triad. Our case, evaluation of the TSC gene mutations was not taken. However, our patient had no family history of TSC, suggesting that this case was sporadic.

The prognosis of MMPH is good. In the literature, 2 patients died of respiratory and heart failure due to bilateral pulmonary nodules of MMPH [5] or progressive cystic changes in other organs [7]. Without any treatment, the lesions in our patient remained unchanged after diagnosis of MMPH for 2 years.

As to our knowledge, MMPH has not been previously reported in the mainland of China. Therefore, it is important to be aware of its existence in TSC patient in order to prevent more aggressive surgery and avoiding other diagnoses including tuberculosis.

Disclosure of conflict of interest
None.

Address correspondence to: Dr. Fan-Qing Meng, Department of Pathology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing, Jiangsu Province, China. Tel: (0086)2583304616-10166; E-mail: fqmeng2004@126.com

References


Multifocal micronodular pneumocyte hyperplasia in tuberous sclerosis complex
