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CASE REPORT

Co-occurrence of giant cell carcinoma and adenocarcinoma of the lung accompanied by multifocal micronodular pneumocyte hyperplasia associated with tuberous sclerosis

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Abstract Multifocal micronodular pneumocyte hyperplasia (MMPH) is a rare pulmonary manifestation of tuberous sclerosis complex (TSC). We report the case of a patient who developed lung giant cell carcinoma and adenocarcinoma accompanied by MMPH associated with TSC. Although she received chemotherapy postoperatively, she died of relapse of the pulmonary giant cell carcinoma 7 months after diagnosis of the lung carcinomas. This case indicates the possibility that MMPH, like atypical adenomatous hyperplasia, can occur as a preneoplastic lesion of lung adenocarcinoma and that a TSC gene mutation might be involved in the pathogenesis. In addition, co-occurrence of these two rare diseases, MMPH and giant cell carcinoma, may facilitate understanding of the pathogenesis of giant cell carcinoma, and suggests involvement of a TSC gene mutation.

Keywords Multifocal micronodular pneumocyte hyperplasia (MMPH) · Tuberous sclerosis complex (TSC) · Giant cell carcinoma · Adenocarcinoma · Lung

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Introduction

Multifocal micronodular pneumocyte hyperplasia (MMPH) is a rare pulmonary manifestation of tuberous sclerosis complex (TSC), characterized histologically by multicentric, well-demarcated nodular growth of type II pneumocytes [1, 2]. A recent molecular analysis revealed that functional loss of the TSC gene, a tumor suppressor gene, causes benign neoplastic proliferation of pneumocytes [3]. Although the histological characteristics of MMPH resemble those of atypical adenomatous hyperplasia (AAH), whether MMPH has the potential for transitioning to neoplasm of the lung remains unclear.

Giant cell carcinoma of the lung is one of five subgroups of sarcomatous carcinoma, and is defined as a group of poorly differentiated non-small cell carcinomas composed entirely of giant cells [4]. Because of its rarity, the pathogenesis of this tumor remains unclear.

Here, we report the case of a patient who developed giant cell carcinoma and adenocarcinoma of the lung accompanied by MMPH. This case indicates the possibility that MMPH, like AAH, can occur as a preneoplastic lesion of lung adenocarcinoma. In addition, the co-occurrence of rare diseases (MMPH and giant cell carcinoma of the lung) in the present case may provide insights into the pathogenesis of giant cell carcinoma.

Case report

A 48-year-old woman was referred to our department following the detection of abnormal shadows on chest radiography. She had been diagnosed with TSC at 9 years old. Examination in our department revealed angiofibroma of the face, subungual fibroma, white spots on the thigh and

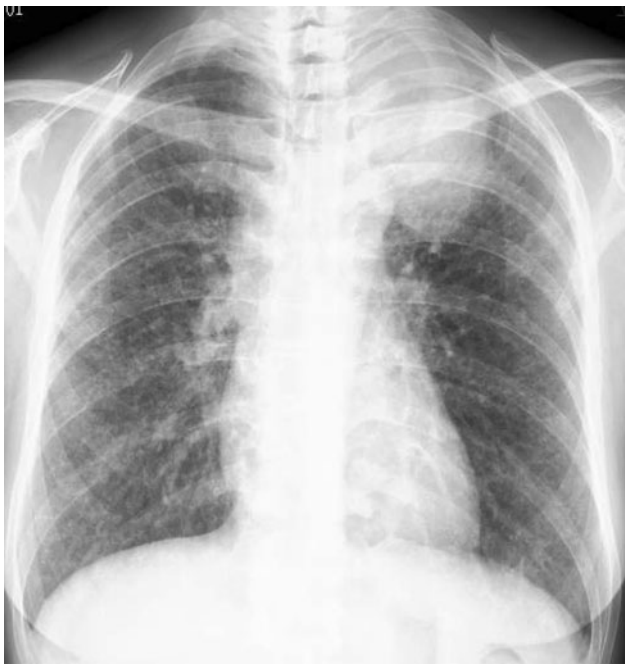

Fig. 1 Chest radiography on admission. A 100-mm tumor is apparent in the left apical lung with extrapleural signs and bilateral diffuse fine nodular opacities

bilateral renal angiolipomas, confirming TSC. High-resolution computed tomograpy (CT) of the chest revealed bilateral diffuse nodular ground-glass opacities extending from the upper to the lower lobes. MMPH was diagnosed histopathologically by transbronchial lung biopsy specimens together with the presence of TSC. The patient had no family history of TSC and a 16-pack/year history of smoking until 37 years old.

Fourteen months after the diagnosis of MMPH, the patient developed left anterior chest pain and high-grade fever. Laboratory data showed: white blood cell count, 4500/μL; erythrocyte sedimentation rate, 27 mm/h; and C-reactive protein level, 0.27 mg/dL. Levels of soluble interleukin-2 receptor and neuron-specific enolase (NSE) were slightly elevated, at 497 U/mL (normal: 0–459 U/mL) and 19.4 ng/mL (normal: 0.0–12.0 ng/mL), respectively. All other results for serum tumor markers were normal (CEA, 5.1 ng/mL; CA19-9, 20 U/mL; SCC, 0.7 ng/mL; CYFRA, 1.5 ng/mL; ProGRP, 32.9 pg/mL). Chest radiography showed a 100-mm tumor in the left apical lung and bilateral diffuse fine nodular opacities (Fig. 1). Chest CT revealed a 90-mm homogeneous mass in the upper-left lobe with extrapleural sign (Fig. 2a), and a

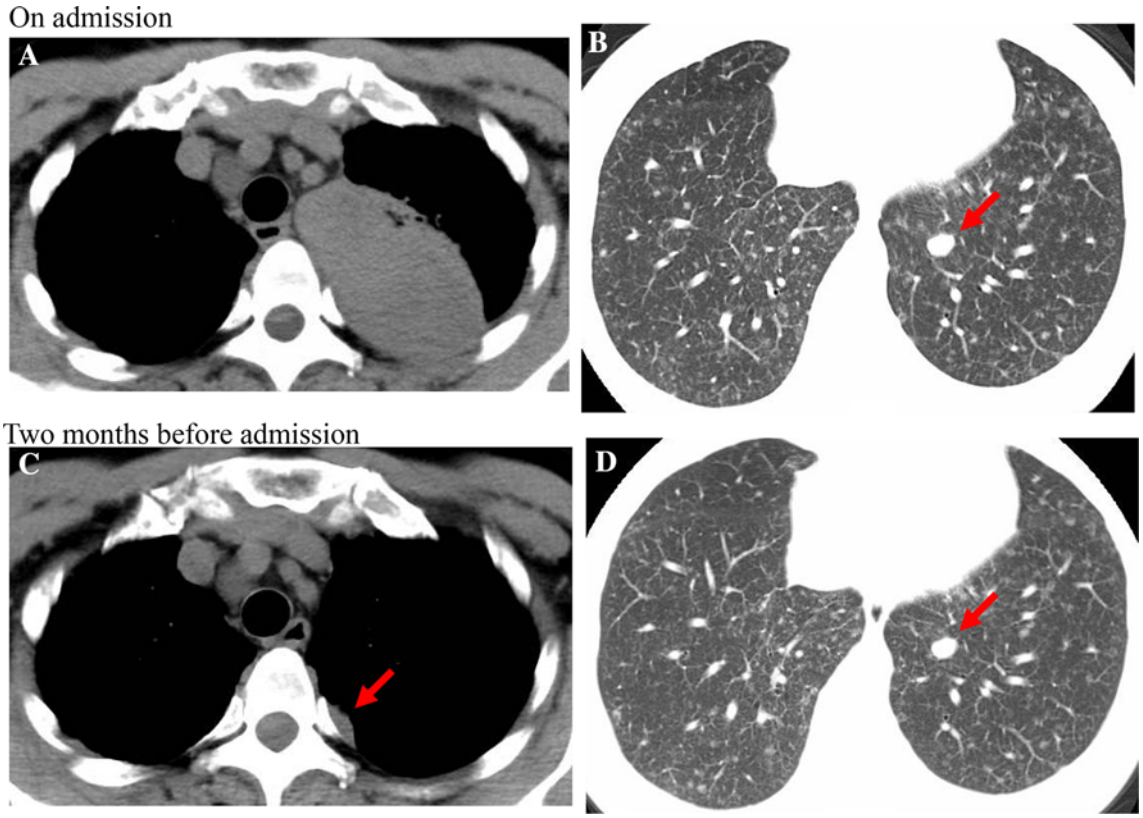

Fig. 2 Chest CT on admission (**a**, **b**) and 2 months before admission (**c**, **d**). The size of the mass in the *upper-left* lobe increased rapidly over the course of 2 months (**a**, **c**). The size of the nodule in the *lower-left* lobe (12 mm) remained unchanged over the same period (**b**, **d**)

12-mm nodule in the left S10 region (Fig. 2b). Chest CT taken 2 months previously showed only slight thickening of the left pleura (Fig. 2c), and the nodule in the left S10 at the same size (Fig. 2d). The size and number of multiple nodular ground-glass opacities had not changed over the intervening 14 months. Positron emission tomography-CT showed high uptake in the mass [standardized uptake value (SUV) max, 23.0] and low uptake in the nodule (SUVmax, 1.8). Magnetic resonance imaging (MRI) did not reveal any invasion of the chest wall or ribs (Fig. 3). Brain MRI and abdominal CT showed no metastatic lesions.

To establish a diagnosis, upper-left segmentectomy was performed with left chest wall resection, left S6 partial resection, and left S10 segmentectomy. The tumor in the upper-left lung was 125 mm × 85 mm × 50 mm, soft, and whitish-brown in color (Fig. 4a). Microscopically, the tumor showed medullary growth without prominent desmoplastic stroma development, and consisted of bizarre, multinucleated giant cells with prominent nucleoli and eosinophilic cytoplasm. These giant tumor cells showed a discohesive manner of growth. Extensive histological observation failed to show tumor elements with either squamous or glandular differentiation in the tumor. Plenty of neutrophils and erythrocyte phagocytosis and emperipolesis were found among tumor cells (Fig. 4b). Immunohistochemical investigations revealed that the tumor cells were more or less positive for TTF-1, AE1/AE3, and EMA, and negative for CEA, calretinin, WT-1, and D2-40, confirming the histopathological diagnosis of giant cell carcinoma of the lung. The nodule in the left S10 was 15 mm × 10 mm in size, solid, and gray-white at the cut surface. Microscopic findings showed adenocarcinoma with mixed subtypes (papillary and bronchioloalveolar) (Fig. 4c). Epidermal growth factor receptor (EGFR) mutations were negative in both the adenocarcinoma and the giant cell carcinoma. Diffuse multiple nodular ground-glass opacities, identified by CT, consisted of a rather uniform proliferation of type II pneumocytes with bland nuclear morphology, along the alveolar septa (Fig. 4d). The alveolar septa also showed fibrous thickening, increased numbers of elastic fibers, and aggregation of alveolar macrophages, suggesting a diagnosis of MMPH when the clinical setting was taken into account. No histopathological findings suggestive of lymphangioleiomyomatosis (LAM) were observed. The final diagnosis was giant cell carcinoma of the lung (pT3N0M0, Stage IIB) and adenocarcinoma (pT1N0M0, Stage IA) accompanied by MMPH. Two months after surgery, CT revealed rapid thickening of the left pleura, suggesting relapse of the giant cell carcinoma. The patient received chemotherapy with carboplatin plus gemcitabine, resulting in progressive disease. Second-line carboplatin plus docetaxel also proved ineffective, and the patient died 7 months after diagnosis of the lung carcinomas.

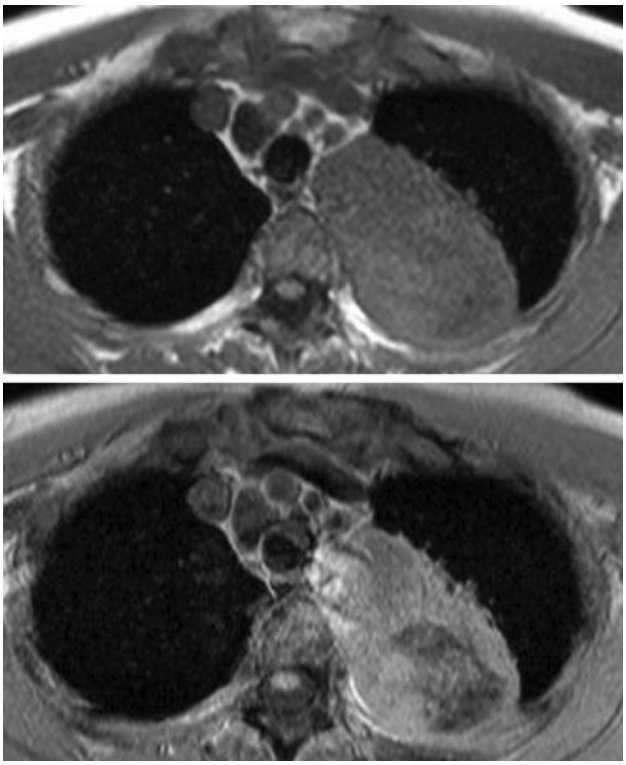

Fig. 3 Chest MRI. The tumor shows no apparent invasion of the chest wall or ribs

Discussion

Multifocal micronodular pneumocyte hyperplasia is a rare lung disease usually found in young or middle-aged women with TSC. High-resolution CT shows small nodules with ground glass opacities throughout the lung parenchyma. The histology is characterized by numerous, hyperplastic lesions of large, type II pneumocytes similar to AAH of the lung and bronchioloalveolar carcinoma [1, 2, 5–7].

Although AAH has been implicated as a preinvasive lesion in lung adenocarcinoma, whether MMPH also has the same potential for transitioning to neoplasm of the lung remains unclear, probably due in part to the rarity of the condition. To the best of our knowledge, only two cases of adenocarcinoma associated with MMPH have been described [3, 8]. Recent genetic studies by Hayashi et al. [3] revealed that functional loss of TSC genes and consequent hyperphosphorylation of mTOR-related proteins in MMPH causes the benign neoplastic proliferation of pneumocytes. The TSC gene is a known tumor suppressor gene, and several studies have shown that chromosome regions related to this gene are involved in the pathogenesis of AAH and lung adenocarcinoma [9, 10]. Although the

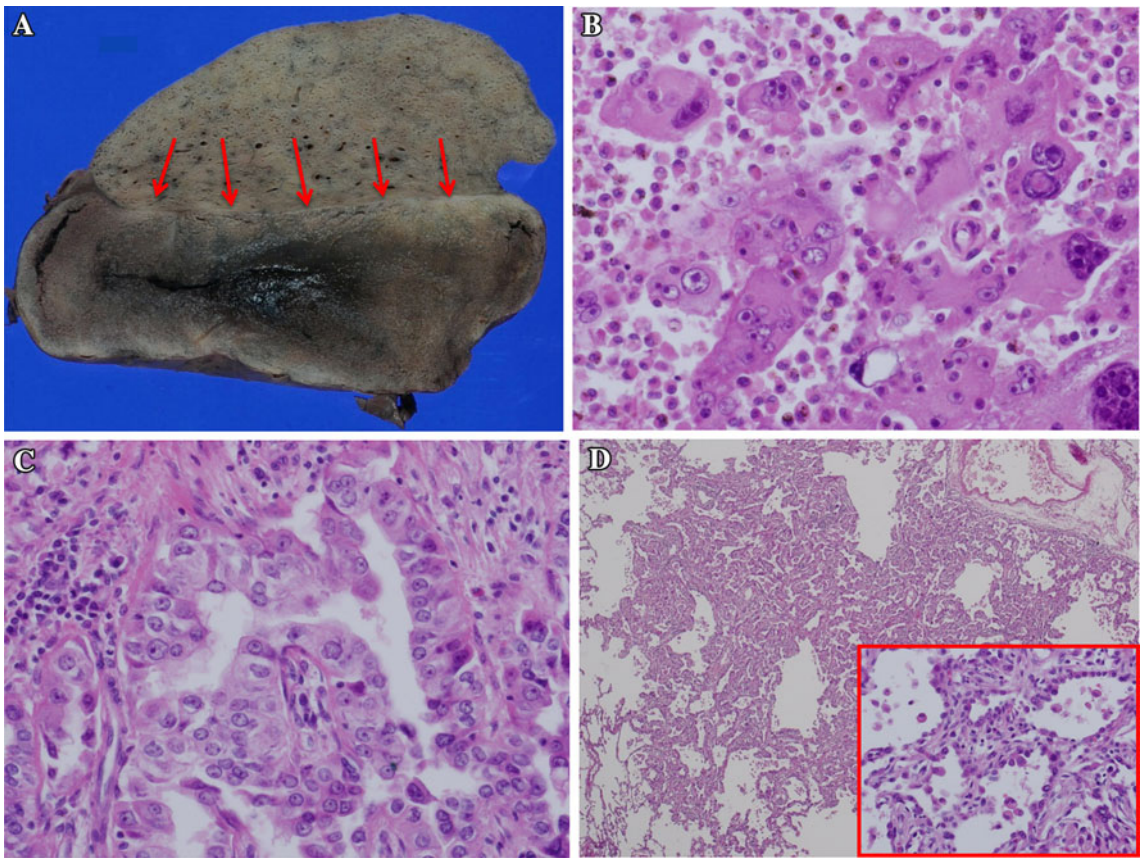

Fig. 4 Pathological examination of the resected specimens. **a** Gross findings of the resected large tumor. **b** Histological findings of the large tumor indicated giant cell carcinoma. HE staining, original magnification, ×400. **c** Histological findings of the tumor located in *left* S10 indicated mixed adenocarcinoma (papillary type and bronchioloalveolar type). HE staining, original magnification, ×400. **d** Histological findings of MMPH, identified by CT. HE staining, original magnification, ×20. *Insets* original magnification, ×400

possibility of coincidental adenocarcinoma and MMPH cannot be ruled out, the current case and previous reports [9, 10] suggest that MMPH may have the same potential as AAH for transitioning into adenocarcinoma of the lung, and a TSC gene mutation may be involved in the pathogenesis of MMPH. Further detailed molecular analyses in MMPH are required to confirm this possibility.

According to the World Health Organization's classification of lung tumors [4], giant cell carcinoma of the lung is one of five subgroups of sarcomatous carcinoma, and is defined as a group of poorly differentiated non-small cell carcinomas composed entirely of giant cells. Sarcomatoid carcinomas of the lung are rare, with giant and spindle cell carcinomas accounting for 0.3 % of all invasive lung malignancies [11], and giant cell carcinoma is extremely rare (0.1–0.4 % of all lung cancers) [12]. Compared with common types of lung carcinoma, genetic studies of sarcomatous carcinomas are limited, and no reports have shown genetic abnormalities in giant cell carcinoma. Similar to adenocarcinoma, the possibility of coincidental giant cell carcinoma and MMPH cannot be ruled out in the present case. However, given the extreme rarity of these pathologies, this possibility seems unlikely. Giant cell carcinoma may thus occur through a loss of heterozygosity (LOH) in the TSC gene, as well as MMPH. Genetic analyses of MMPH, adenocarcinoma, and giant cell carcinoma about LOH or mutations in TSC gene are thus needed. Co-occurrence of two rare diseases, MMPH and giant cell carcinoma, as shown in the present case, may facilitate understanding the pathogenesis of giant cell carcinoma, and suggests that a TSC gene mutation may be associated with this co-occurrence.

Conflict of interest No conflicts of interest for all authors.

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