[Case Report]

Two Cases of Tuberous Sclerosis Complex Suggestive of Complicating Multifocal Micronodular Pneumocyte Hyperplasia: A Case Report

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Abstract **:** Multifocal micronodular pneumocyte hyperplasia (MMPH) is pathologically characterized by multifocal nodular hyperplasia of type Ⅱ pneumocyte-like cells. MMPH is usually complicated with tuberous sclerosis complex (TSC). MMPH patients tend to be asymptomatic or only slightly symptomatic. MMPH tends to progress slowly and needs no treatment. We herein describe two cases of MMPH with its characteristic radiological features and clinical manifestations of TSC. Case 1: a 20-year-old female with definitive TSC in infancy. Chest CT at the age of 18 revealed multiple nodular opacities and ground-glass attenuations in a scattered and random distribution in the bilateral lungs. Case 2: a 44-year-old female with probable TSC at 36 years of age. Chest CT at the age of 43 showed random areas of small ground-glass attenuations, predominantly in the upper lung fields. Case 1 and Case 2 have had no respiratory symptoms or radiographic changes in the recent two years and four years, respectively. Although pathological examinations of the lung were not performed because consent for surgical lung biospies was unobtainable, we considered that these pulmonary manifestations were most likely MMPH with TSC because of these characteristic radiographical findings of multiple nodular opacities and ground-glass attenuations of 10 mm or less in size and their scattered distribution, and because there have been no abnormal laboratory data or changes in their chest radiological findings for years. Neither patient is under treatment for pulmonary lesions. Although MMPH is a rare disease, multiple nodules and ground-glass attenuations on lung imaging findings should be considered as pulmonary manifestations in patients with TSC.

Keywords **:** multifocal micronodular pneumocyte hyperplasia, tuberous sclerosis complex, lymphangioleiomyomatosis, lung cancer.

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Introduction

Multifocal micronodular pneumocyte hyperplasia (MMPH) was first reported as a new disease entity by Popper *et al* [1]. MMPH is pathologically characterized by multifocal nodular hyperplasia of type II pneumocyte-like cells, and, similar to pulmonary lymphangioleiomyomatosis (LAM), it is usually complicated with tuberous sclerosis complex (TSC). Relatively few cases of MMPH have been reported thus far, and this disease may be under-recognized and misdiagnosed [2−5].

We herein report two cases suspected of being MMPH complicated with TSC, and a review of the literature.

Clinical report

Case 1

A 20-year-old Japanese woman who had never smoked was referred to our hospital for an evaluation of abnormal findings on chest computed tomography (CT). She had been diagnosed with definitive TSC in infancy [6], with multiple retinal hamartomas, cortical tubers, subependymal nodules (SEN) and subependymal giant cell astrocytomas (SEGA), facial angiofibromas, hypomelanotic macules (more than 3 lesions) and confetti skin lesions, renal angiomyolipomas and multiple renal cysts. She also had epilepsy and mental retardation. Her mother had also been diagnosed with TSC 20 years prior. She had no respiratory symptoms, and her peripheral blood laboratory data showed no abnormal findings. Chest X-ray and body CT (Fig. 1) revealed multiple nodular opacities and ground-glass attenuation in a scattered and random distribution in the bilateral lungs, suggesting MMPH, and brain and renal lesions. There have been no changes in her chest manifestations during the past two years.

Case 2

A 44-year-old non-smoking woman was referred to our hospital for an evaluation of abnormal findings on chest X-ray and CT. She had been diagnosed with probable TSC [6] with subependymal giant cell astrocytoma, multiple non-traumatic periungual fibromas and bone cysts when she was 36 years of age. She had no respiratory symptoms. Chest X-ray and body CT (Fig. 2) showed random areas of small ground-glass attenuations predominantly in the upper lung fields, suggesting MMPH, and cystic lesions with thin walls in the bilateral lung fields, suggesting LAM, and bone lesions. Her previous X-ray films had shown no changes in four years. In addition, a spirometric analysis showed a normal pulmonary function (vital capacity: 3,460 m*l*; vital capacity as percent of predicted: 128%; forced expiratory volume in one second: 2,980 m*l*; forced expiratory volume in one second as percent of forced vital capacity: 84.7%).

We proposed a surgical biopsy for a diagnosis of the lung lesions in both patients, but they did not consent. Without pathological findings of the lung, we considered that these pulmonary manifestations were most likely MMPH with TSC. Both of our cases had no abnormal laboratory data, including an Interferon-Gamma release assay (IGRA), no malignancy in a systemic screening examination, and no changes in chest images in years, characteristic radiographical findings of MMPH and clinical diagnosis of definitive or probable TSC, so we considered that the imaging findings were compatible with MMPH. We therefore followed the patients closely without any therapies.

Discussion

MMPH was first reported in 1991 by Popper *et al* although Okamura *et al* reviewed the pulmonary manifestations of TSC in autopsy cases in a Japanese study in 1978 and described the pathological findings of MMPH [1, 7]. Although several reports have described MMPH in patients with TSC, the exact prevalence of MMPH has not been reported thus far, and MMPH may occur less frequently than LAM as a pulmonary complication of TSC [3]. LAM is reported to be a complication of TSC in around 1% of cases, but pulmonary complications have been reported in 32.3% of autopsied TSC cases [8], so MMPH may be more frequent. There was a report that almost half of TSC patients in Japan (30/59 cases) had characteristic radiographic findings of MMPH [9], but pathological evaluations were not performed. It is speculated that there might be more patients who had MMPH with TSC than has been recognized.

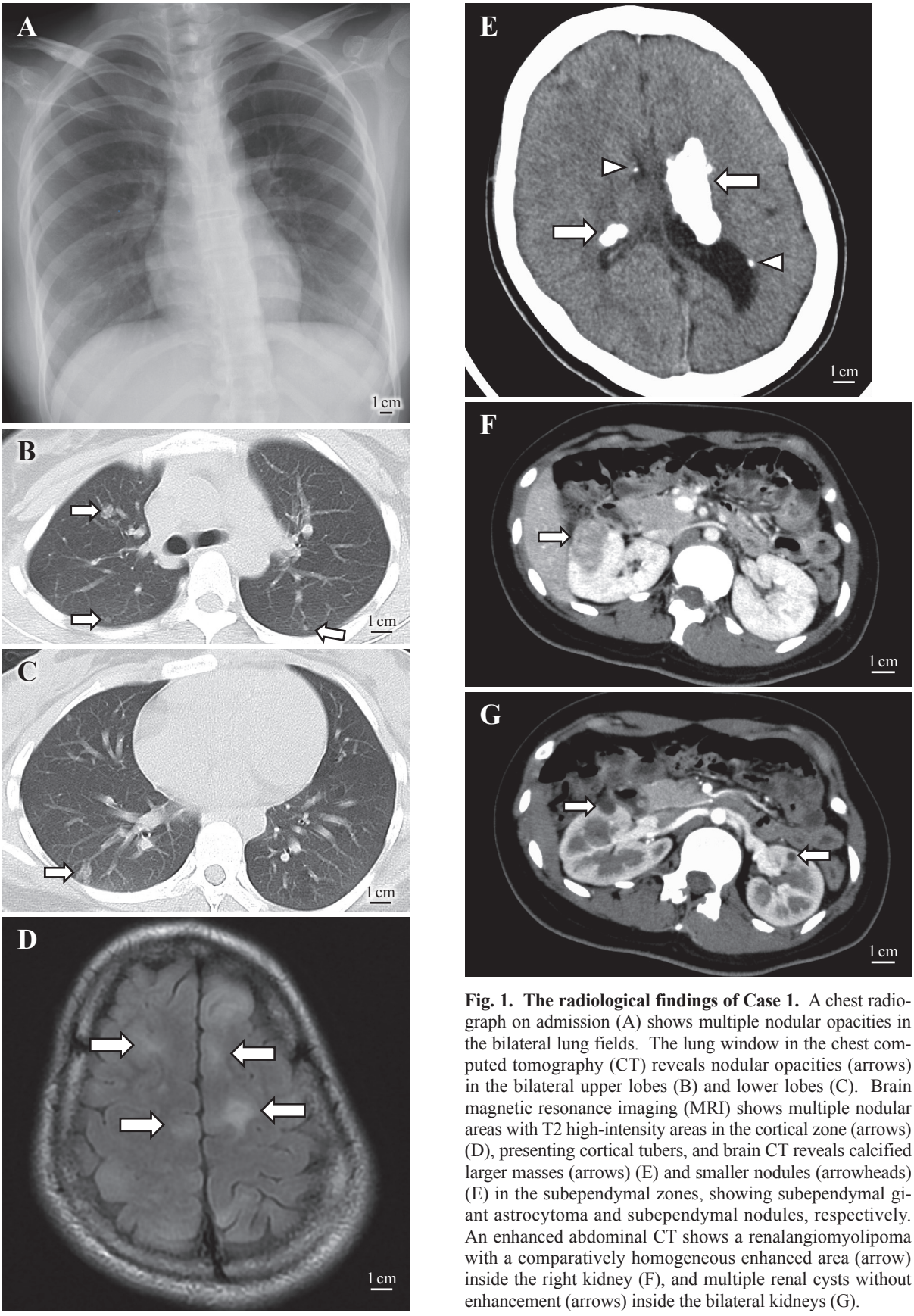

Fig. 1. The radiological findings of Case 1. A chest radiograph on admission (A) shows multiple nodular opacities in the bilateral lung fields. The lung window in the chest computed tomography (CT) reveals nodular opacities (arrows) in the bilateral upper lobes (B) and lower lobes (C). Brain magnetic resonance imaging (MRI) shows multiple nodular areas with T2 high-intensity areas in the cortical zone (arrows) (D), presenting cortical tubers, and brain CT reveals calcified larger masses (arrows) (E) and smaller nodules (arrowheads) (E) in the subependymal zones, showing subependymal giant astrocytoma and subependymal nodules, respectively. An enhanced abdominal CT shows a renalangiomyolipoma with a comparatively homogeneous enhanced area (arrow) inside the right kidney (F), and multiple renal cysts without enhancement (arrows) inside the bilateral kidneys (G).

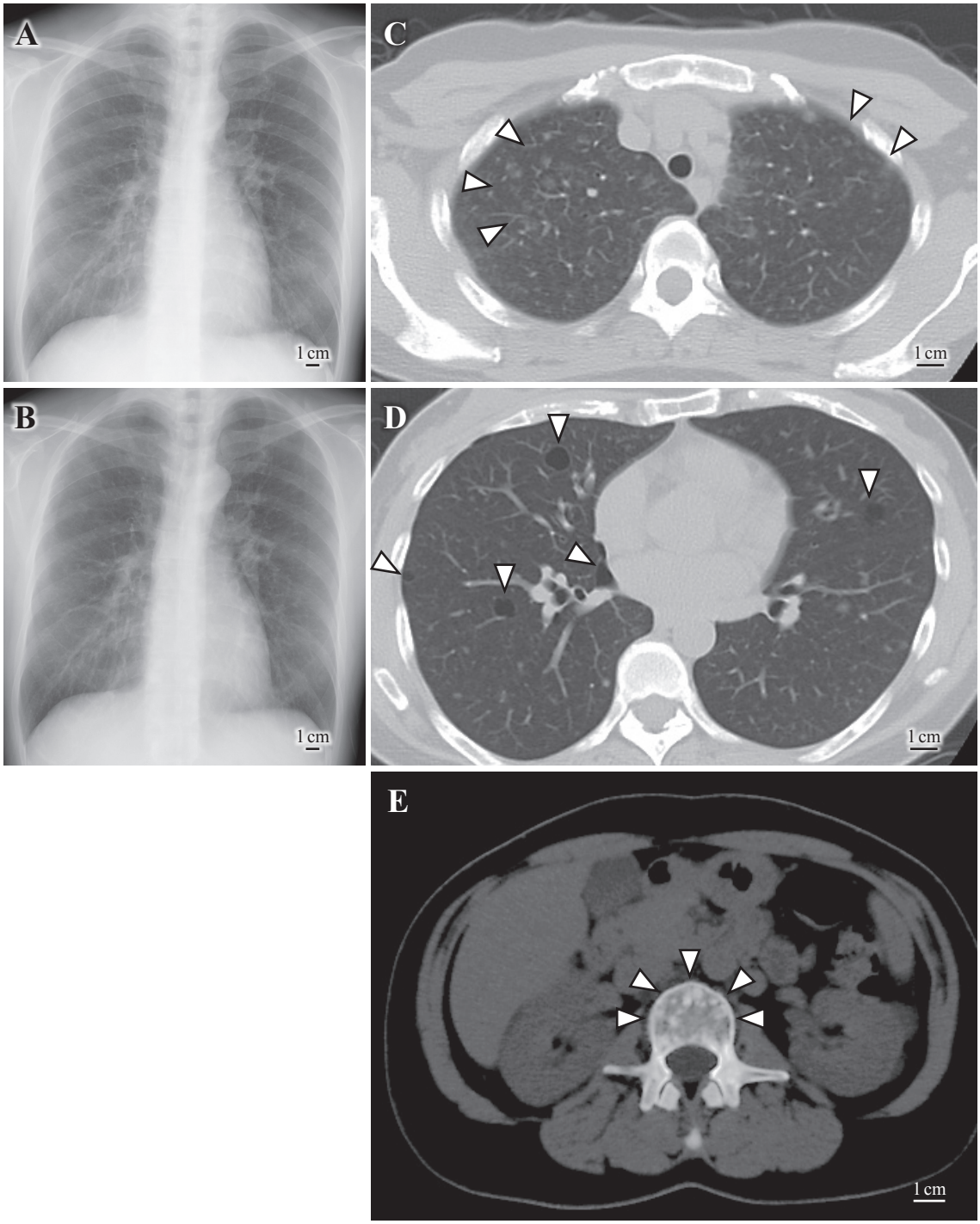

Fig. 2. The radiological findings of Case 2. The chest radiographs on the first visit (A) and four years after the first visit (B) show no remarkable changes. A chest CT shows multiple small ground-glass attenuations (arrowheads) predominantly in the bilateral upper lobes (C) and plural cysts (arrowheads) in the bilateral lungs (D). The bone window image of a chest CT reveals bone sclerosis lesions at L1 (arrowheads) (E) with bone cysts.

Table 1 shows the clinical characteristics of the MMPH cases that have been reported in the English literature as far as our research could determine. There have been 24 reported MMPH cases, including our 2 patients. Most of the reported cases were female (91.7%; 22/24) and relatively young (13−56 years of age). In 87.5% (21/24) of the cases, MMPH was complicated with TSC, and in 20.8% of the cases (5/24), MMPH was also complicated with LAM [2, 10−30].

MMPH patients tend to be asymptomatic or to have only slight respiratory symptoms, such as a cough, and there have been few reports describing the clinical course of MMPH, which tends to progress slowly and is associated with a favorable outcome without a need for treatment [2]. However, two fatal cases have also been reported (Table 1): one due to acute respiratory failure, despite receiving lung transplantation [14], and the other due to a fatal seizure [12]. Both of our patients are alive now without any respiratory symptoms.

The chest radiological findings of MMPH include diffuse and randomly distributed miliary and/or nodular opacities, ground-glass attenuation and reticular opacities without calcifications. Nodular opacities adopt one of two patterns: sporadically distributed nodules 3−10 mm in diameter; and multiple distributions of small granular shadows 1−3 mm in diameter. Both patterns are well-circumscribed [3−5, 17]. The imaging findings of our two patients showed randomly distributed multiple nodules with small granular shadows. Some reports have described these findings as existing predominantly in the peripheral and upper lobes [4, 5], but our investigation of 24 cases revealed no clear trend. The radiological findings of MMPH usually mimic miliary tuberculosis, primary or metastatic lung cancer, atypical adenomatous hyperplasia (AAH) and adenocarcinoma *in situ* (AIS).

Pathologically, MMPH shows clearly defined nodular lesions with fibrous thickening of the alveolar walls and a single layer of slightly enlarged type II pneumocytes on the alveolar surface without atypical changes or any destruction of the alveolar structure [4, 5]. The pathological differential diagnosis of MMPH also includes AAH and AIS, although interstitial changes, such as thickening of the alveolar septa with fibroelastic changes, are more frequently observed in MMPH than in AAH and AIS, and cellular atypia and the destruction of the pulmonary structure are unusual [26]. MMPH is considered to be distinctive from true neoplastic changes because the lesions of MMPH are non-invasive, distractive, or replaceably proliferating and growing. The transformation of MMPH to a malignant tumor is considered to be unusual [12, 18], but lung adenocarcinoma has been reported in association with MMPH complicating TSC [26], and therefore careful follow-up is needed.

There have been several reports of positive and negative relationships between MMPH and mutations of the *TSC* gene. Franz *et al* reported 10 cases of TSC complicated with MMPH who were positive for both *TSC1* and *TSC2* [31]. However, conversely, Maruyama *et al* reported a female patient with TSC complicated with both MMPH and LAM, and a loss of *TSC2* heterozygosity was observed only in the patient's LAM lesions and not in her MMPH lesions [32]. In addition, issues with the low sensitivity of the detection procedures for these genetic mutations have been pointed out [33]. As such, further studies with a higher detection rate of gene mutations may lead to a better understanding of the relationship between MMPH and gene mutations.

In summary, MMPH is a rare disease that is not well-known among physicians. MMPH should be considered in the differential diagnosis of TSC patients with bilateral multiple nodules and ground-glass attenuation on lung CT. Only limited data are available at present, and further clinical data, especially regarding the long-term clinical course of patients, are necessary to understand the clinical aspects of MMPH.

Conflicts of Interest

The authors declare no conflicts of interest in association with the present study.

Table 1. The clinical characteristics of the representative reported cases of MMPH

Case No.	Gender Age	Radiological findings of chest CT			TSC	Family history of TSC	Diagnostic method	Prognosis	Reference
		Distribution	Characteristic	Complication					
1	F, 23	Bilateral, Random	Small nodules	−	+	Unknown	OLB	Survival (9 years)	[2]
2	F, 45	Bilateral, Random	Small nodules	−	−	Unknown	OLB	Unknown	[2]
3	F, 38	Bilateral, Lower lobes dominant	Nodules	LAM	+	Unknown	OLB	Survival (11 years)	[10]
4	F, 24	Bilateral, Lower lobes	Miliary nodules (approximately 1−2 mm)	LAM, Bilateral pneumo-thorace	+	−	OLB	Survival	[11]
5	F, 36	Bilateral, Random	Small nodules (up to 3 mm)	−	+	Unknown	Autopsy	Dead (Seizure)	[12]
6	F, 56	Bilateral, Random	Small nodules (up to 5 mm)	−	a forme fruste, surmised	+	VATS	Survival	[13]
7	F, 16	Bilateral, Lower lobes predominant	GGO, Small nodules	−	−	−	Autopsy	Dead (Respiratory failure due to MMPH)	[14]
8	F, 39	Bilateral, Upper lobes predominant	Small nodules (5−10 mm)	−	+	−	TBLB, VATS	Survival (3 years)	[15]
9	F, 32	Bilateral, Random	Small nodules appearing as GGO (less than 10 mm)	−	+	−	VATS	Survival	[16]
10	F, 51	Bilateral, Random	Small nodules (1−3 mm), Mild intralobular interstitial thickening	−	+	+	TBLB, BAL, VATS	Survival	[17]
11	M, 43	Bilateral, Random	Small nodules (up to 5 mm)	−	+	−	VATS	Survival (3 years)	[18]
12	F, 41	Bilateral, Random	Nodules, GGO (up to 10 mm)	−	+	−	VATS	Survival	[19]
13	F, 38	Bilateral, Random	Small nodules (up to 5 mm)	−	+	Unknown	VATS	Survival	[20]
14	F, 39	Bilateral, Lower lobes dominant	Nodules	LAM, CCTL	+	Unknown	VATS	Unkonwn	[21]
15	F, 49	Bilateral, Random	Small nodules	−	+	Unknown	N.E.	Survival (5 years)	[22]
16	F, 51	Bilateral, Random	Nodules (mostly GGOs) (approximately 10mm or less)	−	+	−	VATS	Survival	[23]
17	F, 21	Bilateral, Random	Nodules (1−8 mm)	−	+	−	VATS	Survival (6 months)	[24]
18	F, 13	Bilateral, Random	Nodules (1−6 mm)	−	+	Unknown	OLB	Survival (1 year)	[25]
19	F, 33	Bilateral, Random	Small nodules	LAM	+	Unknown	OLB	Survival (10 years)	[27]
20	F, 10	Bilateral, Random	Nodules, GGO (30 mm, with reversed halo sign)	−	+	Unknown	CT-guided transthoracic needle biopsy	Unknown	[28]
21	F, 34	Bilateral, Random	Small nodules (1−5 mm)	−	N. E.	+	VATS	Survival (1 month)	[29]
22	M, 38	Bilateral, Random	GGO (1−9 mm)	−	+	−	TBLB, VATS	Survival (16 months)	[30]
23	F, 20	Bilateral, Random	Nodules (up to 10 mm)	−	+	+	N.E.	Survival (4 years)	Our case
24	F, 44	Bilateral, Upper lobes dominant	GGO (up to 10 mm)	LAM, most likely	+	−	N.E.	Survival (2 years)	Our case

BAL: bronchoalveolar lavage, CCTL: clear cell tumor of the lung, CT: computed tomography, GGO: ground-glass opacity, LAM: lymphangioleiomyomatosis, MMPH: multifocal micronodular pneumocyte hyperplasia, NE: not examined, OLB: open lung biopsy, TBLB: transbronchial lung biopsy, TSC: tuberous sclerosis complex, VATS: video-assisted thoracoscopic surgery

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結節性硬化症に伴う多巣性微小結節性肺細胞過形成を呈したと考えられる2症例

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要　　旨：多巣性微小結節性肺細胞過形成（multifocal micronodular pneumocyte hyperplasia（MMPH））は，Ⅱ型肺胞上皮様細胞の増殖からなる多巣性結節性病変で，結節性硬化症（tuberous sclerosis complex （TSC））に併発する疾患である．自覚症状はあっても軽微であり，進行は緩徐で治療を要しないとされている．われわれは，TSCに併発した，特徴的な画像所見を持つMMPHと考えられる2症例を経験したので報告する．症例1：幼児期にTSCと診断された20歳女性．18歳時の胸部CTで両肺に散在する結節影やスリガラス影を指摘された．症例2：36歳時にTSCと診断された44歳女性．43歳時の胸部CTで上葉優位にランダム分布の小さなスリガラス影を認めた．症例1は2年間，症例2は4年間に渡り，呼吸器症状も画像変化も認めない．肺生検の同意が得られず，病理学的な診断ができていないが，血液検査で有意な所見はなく，10 mm以下の結節影やスリガラス影が散在する特徴的画像所見や経年的に不変である経過などから，TSCに伴うMMPHと考えた．2症例とも肺病変に対する治療は行っていない．MMPHは稀な疾患であるが，TSC患者において両肺に多発する結節影やスリガラス影が認められた際にはMMPHである可能性を考慮すべきである．

キーワード：多巣性微小結節性肺細胞過形成，結節性硬化症，リンパ脈管症，肺癌．

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