Progressive Multifocal Micronodular Pneumocyte Hyperplasia in the Lungs of a Patient with Tuberous Sclerosis Complex: A Case Report

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We report a case of multifocal micronodular pneumocyte hyperplasia (MMPH) in a patient with tuberous sclerosis complex, in whom the lung nodules increased in the number and size over the course of 8 years. We diagnosed MMPH following a lung biopsy performed during video-assisted thoracic surgery. In most of the previously reported cases, the number and size of lung nodules is unchanged during the clinical course. Our case is the first report of progressive disease in pathologically proven MMPH.

Key words: Multifocal Micronodular Pneumocyte Hyperplasia, Tuberous Sclerosis Complex, Multiple Ground Glass Opacities

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal-dominant disease caused by a mutation in either the *TSC1* or *TSC2* gene [1, 2]. Hamartomatous lesions develop in various organs such as the skin, retina, kidney, central nervous system, heart, and lungs [3]. Lymphangioleiomyomatosis (LAM) and multifocal micronodular pneumocyte hyperplasia (MMPH) produce cystic and nodular disease, respectively, in the lungs of patients with tuberous sclerosis [4]. The frequency of LAM in females is significantly higher than in males. However, MMPH has no association with gender [5]. In MMPH, multiple pulmonary nodules composed of benign alveolar type II cells are found scattered throughout the lung [6]. In most of the previously reported cases, the number and size of lung nodules remains unchanged during the clinical course [7, 8]. Here, we report a case of MMPH in a patient with tuberous sclerosis complex, in whom the lung nodules increased in the number and size during the course of 8 years.

CASE REPORT

A 35-year-old woman was referred to the pulmonary clinic in Tokai University Hospital for the evaluation of multiple ground glass opacities (GGO) in the lungs. She had a history of epilepsy in childhood. Multiple pulmonary nodules (Fig. 1a) were first identified on the chest computed tomography (CT) at age 27 during systemic evaluation for a uterine tumor of 10 cm in diameter; enucleatic myomectomy following the administration of a luteinizing hormone-releasing hormone analog identified the tumor as a leiomyoma. Multiple papular lesions (hemangioma) in the skin around the alar facial sulcus and neck, dyspigmented lesions in the upper limbs, subependymal nodules in the brain, renal angiomyoleioma, and a pancreatic endocrine tumor were also identified. Based on these findings, as well as family history of Pringle's disease in her father, she was given a definitive diagnosis of TSC.

A lung biopsy was performed 8 years later because the number and size of the pulmonary nodules were increasing gradually on chest CT (Fig. 1). She had no respiratory symptoms prior to the lung biopsy. There were no abnormal finding on physical assessment and no abnormal spirometry and arterial blood gas result were obtained (Table). Two pulmonary specimens were obtained from the lingular division of the left upper lobe and superior segment (S^6) of the left lower lobe during video-assisted thoracic surgery. In the low power view (Fig. 2a), multiple nodular lesions up to 5 mm in size appeared in a random distribution with no apparent tendency to attach to bronchioles or blood vessels. In the high power view (Fig. 2b), the nodular lesions were seen to consist of cuboidal cells with round to irregular nuclei, occasional intranuclear cytoplasmic inclusion, and eosinophilic cytoplasm. These cells proliferated along the alveolar wall without any invasive or destructive growth. Fibrous thickening of the alveolar wall, but not alveolar collapse, was noted in each lesion. Despite the relatively high nuclear-cytoplasmic ratio and some nuclear atypia, the relatively low cellular density and multiple patchy lesions were atypical for a diagnosis of adenocarcinoma. In con-

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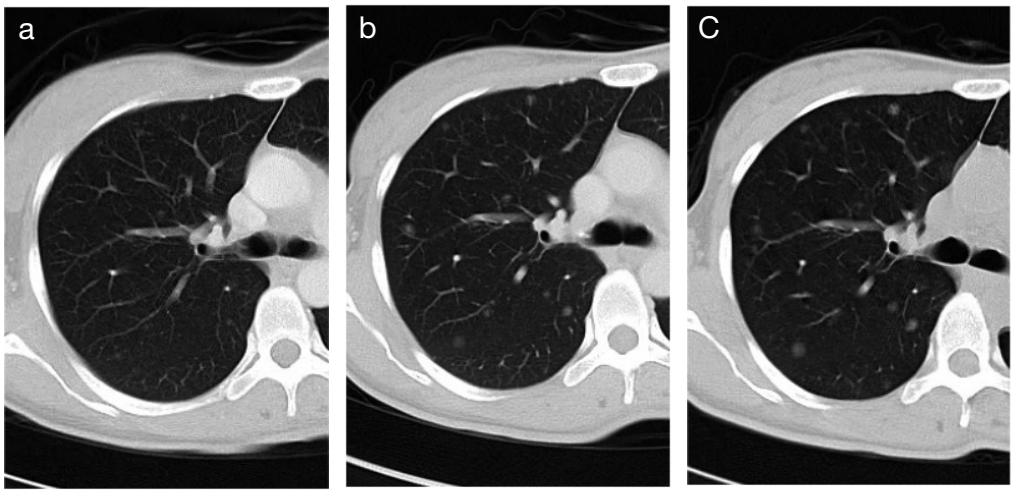

Fig. 1 a) Tiny ground glass opacities (GGOs) were seen on the chest computed tomograph when the patient was 27 years old. b) The number and size of pulmonary GGOs were increased when she was 32 years old. c) The size of the pulmonary GGOs were further increased at 35 years of age.

Table Pulmonary function test

Spirometry		
Vital capacity	3.14	L
Vital capacity, %predicted	94.9	%
FEV_1^*	2.65	L
FEV_1/forced vital capacity	89.2	%
Arterial blood gas analysis		
pH	7.394	
$PaCO_2$	36.0	Torr
PaO_2	92.3	Torr
$[HCO_3^-]$	21.5	mEq/L
$A\text{-}aDO_2$	14.3	Torr

* FEV_1= Forced expiratory volume in one second

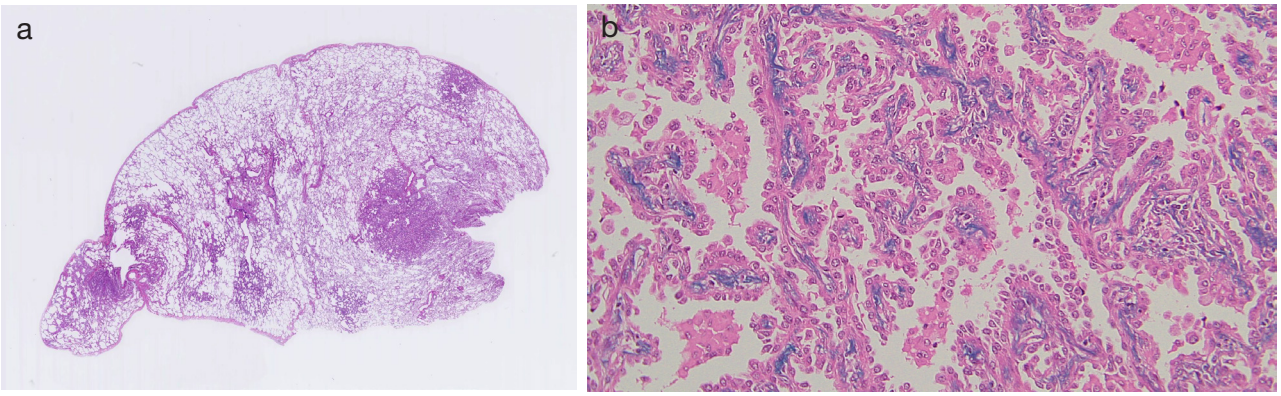

Fig. 2 a) In the low power view with a hematoxylin and eosin (HE) stain, multiple nodular lesions, up to 5 mm in size, appeared in a random distribution with no tendency to attach to bronchioles or blood vessels. b) In the high power view with a HE stain, the nodular lesions consisted of cuboidal cells with round to irregular nuclei, occasional intranuclear cytoplasmic inclusion, and eosinophilic cytoplasm. These cells proliferated along the alveolar wall, without any invasive or destructive growth.

sideration of the histology and clinical features, the pulmonary lesions were diagnosed as MMPH.

The lung nodules increased in number and size. But she is still fine and she has no symptom by no treatment, when she is 39 years old now.

DISCUSSION

We report a case with tuberous sclerosis who exhibited skin lesions, subependymal nodules in the brain, renal angiomyoleioma, a pancreatic endocrine tumor, and multiple lung nodules. The lung nodules were diagnosed as MMPH following biopsy after gradual progression over the course of 8 years.

The time course of disease presentation and progression in tuberous sclerosis varies between the affected organs. Neuropsychiatric lesions are seen from the infancy, with seizures beginning in the first year of life in over 60% of cases [9]. Brain magnetic resonanse imaging shows cortical glioneuronal hamartomas and subependymal nodules in approximately 90% of children with TSC [10]. Renal angiomyoleiomas were present in 37% of the children between 1 and 5 years old and in 41% of boys and 63% of girls after 5 years of age [11]. In contrast, skin lesions tend to increase in size and number through puberty and then tend to be stable over time, although there is considerable variation in the age of expression. Hypomelanic macules and forehead fibrous plaques appear earlier than facial angiofibromas and ungual fibromas [12].

Cystic lesions in the lungs increase with age in the adulthood as in the cases with sporadic LAM, rising by about 8% per year. LAM had a prevalence of 27% in subjects < 21 years old and 81% in subjects > 40 years old [13]. On the contrary, little is known about the development and progression of MMPH lesions. Age at the diagnosis of MMPH has ranged between 13 and 63 years in reportde cases [7, 8], with MMPH identified in the present case identified when the patient was 27 years old. Several reports have examined the progression of MMPH longitudinally. Twenty-two cases with three or more ground glass opacities in the lung showed no change in the number or size of nodules when re-examined 0.9−4.9 years later [8]. Another report followed up 15 Japanese patients for a period ranging from 6 months to 13 years, finding no change in the number or size of MMPH lesions [7]. The only exception is a report of a 33-year-old woman with tuberous sclerosis, whose small nodules in the lung increased in number during pregnancy [14], although the case lacked a definitive pathological diagnosis. Our case is, therefore, the first report of progressive disease in pathologically proven MMPH. It may be possible that MMPH appears and progresses in the second to third decades of life and then stabilizes, similar the skin lesions of TSC.

We reported a rare case of MMPH in a patient with TSC, in whom the lung nodules increased in number and size. However, if instances of MMPH in patients with TSC are observed during a longer period, we may discover other progressive cases. The accumulation of future data is awaited.

REFERENCES

1) The European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of tuberous sclerosis gene on chromosome 16. Cell 1993; 75: 1305−1315.
2) van Slegtenhorst M, de Hoogt R, Hermans C, Nellist M, Janssen B, Verhoef S, Lindhout D, van den Ouweland A, Halley D, Young J, Burley M, Jeremiah S, Woodward K, Nahmias J, Fox M, Ekong R, Osborne J, Wolfe J, Povey S, Snell RG, Cheadle JP, Jones AC, Tachataki M, Ravine D, Sampson JR, Reeve MP, Richardson P, Wilmer F, Munro C, Hawkins TL, Sepp T, Ali JB, Ward S, Green AJ, Yates JR, Kwiatkowska J, Henske EP, Short MP, Haines JH, Jozwiak S, Kwiatkowski DJ. Identification of The Tuberous Sclerosis Gene *TSC1* on Chromosome 9q34. Science 1997; 277: 805−809.
3) Gomez MR. Definition and criteria for diagnosis. In: Gomez MR, Sampson JR, Whittemore VH, eds. Tuberous Sclerosis Complex: Developmental Perspectives in Psychiatry. 3rd ed. Oxford, United Kingdom: Oxford University Press, 1999: 10−23.
4) Franz DN, Brody A, Meyer C, Leonard J, Chuck G, Dabora S, Sethuraman G, Colby TV, Kwiatkowski DJ, McCormack FX. Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. Am J Respir Crit Care Med 2001, 164: 661−668.
5) Wataya-Kaneda M, Tanaka M, Hamasaki T, Katayama I. Trends in the prevalence of tuberous sclerosis complex manifestations: an epidemiological study of 166 Japanese patients. PLoS ONE 2013; 8: e63910.
6) Northrup H, Krueger DA, and on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49(4): 243−254.
7) Kobashi Y, Sugiu T, Mouri K, Irei T, Nakata M, Oka M. Clinicopath- ological analysis of multifocal micronodular pneumocyte hyper- plasia associated with tuberous sclerosis in Japan. Respirology. 2008; 13: 1076−1081.
8) Muzykewicz DA, Black ME, Muse V, Numis AL, Rajagopal J, Thiele EA, Sharma A. Multifocal micronodular pneumocyte hyperplasia: computed tomographic appearance and follow-up in tuberous sclerosis complex. J Comput Assist Tomogr 2012; 36: 518−522.
9) Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010; 51 (7): 1236−1241.
10) Yates JR, Maclean C, Higgins JN, Humphrey A, le Maréchal K, Clifford M, Carcani-Rathwell I, Sampson JR, Bolton PF. The Tuberous Sclerosis 2000 Study: presentation, initial assessments and implications for diagnosis and management. Arch Dis Child 2011 Nov; 96 (11): 1020−1025.
11) Torres VE, King BF, Holley KE, Blute ML, Gomez MR. The kidney in the tuberous sclerosis complex. Adv Nephrol Necker Hosp 1994; 23: 43−70.
12) Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol 1996; 135: 1−5.
13) Cudzilo CJ, Szczesniak RD, Brody AS, Rattan MS, Krueger DA, Bissler JJ, Franz DN, McCormack FX, Young LR. Lymphangioleiomyomatosis screening in women with tuberous sclerosis. Chest 2013; 144: 578−585.
14) Ogawa R, Miyagawa M, Ide K, Akamune A, Ohtsuki Y, Mochizuki T. Exacerbation and remission of pulmonary micronodules with lymphangioleiomyomatosis around the time of childbirth. Jpn J Radiol 2013; 31: 633−636.