Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Radiology

Multifocal Micronodular Pneumocyte Hyperplasia in Tuberous Sclerosis: an 8-Year CT Follow-Up

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DOI: 10.36347/sjmcr.2022.v10i08.026 | **Received:** 22.06.2022 | **Accepted:** 03.08.2022 | **Published:** 30.08.2022

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Abstract | **Case Report**

Although the most common pulmonary manifestation of tuberous sclerosis complex (TSC) is lymphangiomyomatosis, multifocal micronodular pneumocyte hyperplasia (MMPH) can also be seen in up to half of the patients with TSC. Computed tomography is the modality of choice for diagnosis and follow-up of MMPH which is typically appear as multiple, subcentimeter, randomly distributed solid and groundglass nodules. The awareness of this entity in patients with TSC will avoid unnecessary further work-up for underlying infectious or neoplastic causes.

Keywords: tuberous sclerosis complex (TSC), tomography, groundglass nodules, neurocutaneous disorder.

INTRODUCTION

Tuberous sclerosis complex (TSC) is a rare phacomatosis (neurocutaneous disorder) consisting of the development of hamartomas and benign, or rarely malignant, neoplasms distributed in several organs throughout the body (e.g. skin, eyes, heart, and nervous system) [1]. 50-86% of the cases are secondary to spontaneous mutations while the remainder demonstrate autosomal dominant inheritance [2]. In approximately 80% of the cases, two tumor suppressor genes namely TSC1 or TSC2 are responsible [3]. Common manifestations include cortical tubers, subependymal nodules, white matter abnormalities, retinal abnormalities, cardiac rhabdomyoma, lymphangioleiomyomatosis, renal angiomyolipoma, and skin lesions [1].

The most common pulmonary manifestation of TSC is lymphangioleiomyomatosis (LAM), a hamartomatous cystic lung disease [4]. Multifocal micronodular pneumocyte hyperplasia (MMPH), another hamartomatous pulmonary lesion, has also been described in TSC patients [5]. Although it has been first thought to be a rare manifestation of TSC, recent studies has shown higher prevalence of MMPH, up to 57% and 59% in women and men respectively [6]. This is due to the wide availability of computed tomography (CT) as well as high-resolution algorithms. MMPH can be isolated or coexist with LAM. CT is the choice of modality for diagnosis and follow up of MMPH. In this article, we describe the imaging findings of MMPH in a patient with TSC without LAM on baseline and 8-year follow-up CT.

CASE REPORT

A 54-year-old-female presented for pre-kidney transplant evaluation in setting of TSC, which was associated with end stage renal disease due to bilateral large angiomyolipomas in 2013. Patient was diagnosed with TSC in childhood when her dermatologist noted the presence of cutaneous angiofibromas which involved nasal folds and cheeks. Her tuberous sclerosis was also associated with blindness, seizure disorder, brain lesions, and skin lesions.

A baseline chest CT in 2013 revealed multiple, randomly distributed, solid and ground-glass pulmonary nodules ranging between 2 and 7 mm (Fig 1a & 1b). Patient was asymptomatic with normal exercise capacity and pulmonary function tests. Given the imaging findings and clinical picture those nodules were accepted as multifocal micronodular pneumocyte hyperplasia (MMPH) without a biopsy. Additionally, multiple foci of fat attenuation within the myocardium and papillary muscles consistent with hamartomas/lipomas were identified. The sections through the upper abdomen revealed known large angiomyolipomas in both kidneys.

Patient had kidney transplant in 2014 and on immunosuppression since then. She continued to have annual CT follow up of pulmonary nodules. The last follow up was completed in late 2021 which demonstrated multiple pulmonary nodules without any significant interval change in size, number or configuration since 2013, over 8-years (Fig 2a & 2b). Additionally, no change in exercise capacity or pulmonary function test identified. Despite the cardiac hamartomas, she developed no cardiac symptoms or arrhythmias.

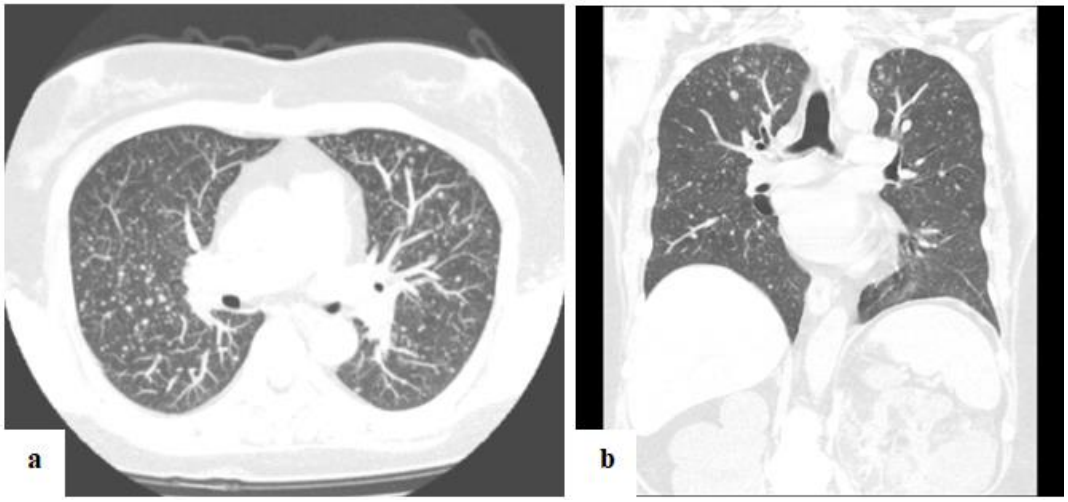

Figure 1: Axial maximum intensity projection (7 mm) (a) and coronal multiplanar reformat images from baseline chest CT obtained in 2013 demonstrated multiple, randomly distributed, solid and ground-glass pulmonary nodules ranging between 2 and 7 mm

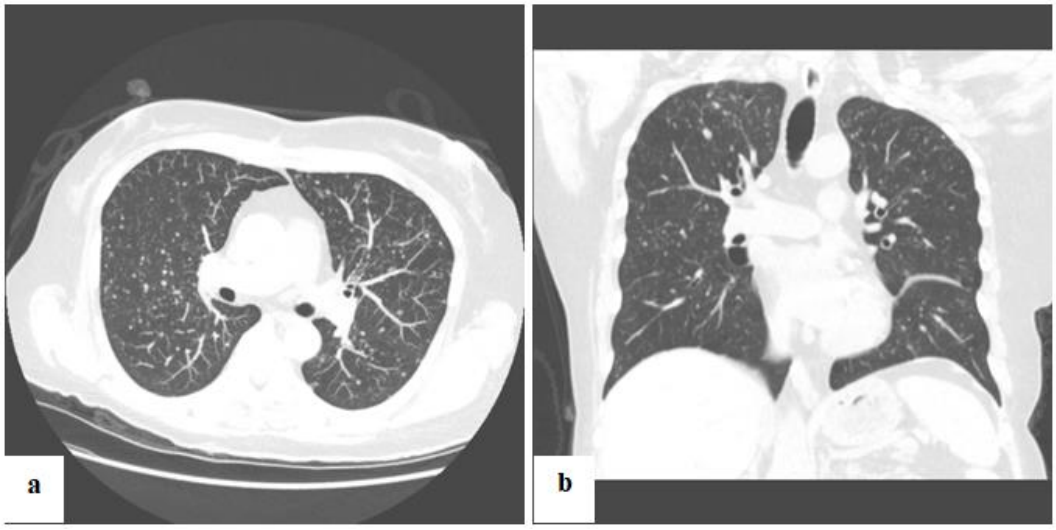

Figure 2: Axial maximum intensity projection (7 mm) (a) and coronal multiplanar reformat images from follow up chest CT obtained in 2021 showed no significant interval change in size, number and appearance of the nodules. Also note that there is no cystic lung disease to suggest LAM

DISCUSSION

MMPH was first described in a patient with TSC in 1991 [7]. It was thought to be a rare manifestation of TSC and more common in women, however recent studies have shown higher prevalence and similar occurrence rates in women and men [6]. MMPH results from an aberrant proliferation of enlarged type II pneumocytes, along the thickened alveolar septa and associated with increase in aggregated alveolar macrophages and interstitial reticulin [5]. Although it is a separate hamartomatous process and not a variance of LAM, they may coexist in the same patient. Similar to other hamartomas associated with TSC, MMPH does not demonstrate any malignant potential.

Although it is commonly asymptomatic, the clinical manifestations of isolated MMPH are dyspnea, cough, and mild hypoxemia. The clinical course is usually not progressive and treatment is unnecessary. When LAM coexists, the clinical presentation is frequently pneumothorax from pulmonary cysts.

CT is the modality of choice for detection and follow up of MMPH. A combination of multiple, randomly distributed, solid and ground-glass pulmonary nodules are the most common imaging findings though ground-glass nodules are more commonly detected than solid nodules alone. The nodules are commonly less than 1 cm in size [6, 8]. Most of the MMPH cases in the literature show no change in nodule size, number or density on follow-up imaging with a maximum follow up period of 4.9 years [6]. Similarly, we observed no interval change in size, number or configuration of the pulmonary nodules over a period of 8 years. Additionally, there was no interval change in patient's exercise capacity or pulmonary function tests.

In summary, the presence of multiple pulmonary nodules in a random distribution in a TSC patient should suggest the presence of MMPH. Nodules can be isolated or in coexistence with LAM. They are usually less than 1 cm in size and remain stable over a longer period of time confirming benign nature and absence of malignant potential.

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