Multifocal micronodular pneumocyte hyperplasia (MMPH) in a patient with tuberous sclerosis—evidence for long term stability

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Multifocal micronodular pneumocyte hyperplasia (MMPH) is rare entity seen mostly in patients with the tuberous sclerosis complex (TSC). We present the case of a 50 year old woman with TSC (confirmed TSC2 mutation) found to have multiple ground glass opacities with an upper lobe predominance on a screening chest CT. No abnormalities were detected in other viscera. A thoracoscopic lung biopsy obtained from right upper lobe confirmed the diagnosis of MMPH. There were no lesions suggestive of lymphangioleiomyomatosis (LAM) either on the chest CT or lung biopsy. A repeat CT chest obtained on follow up 9 years after initial diagnosis continued to show stability of all MMPH ground glass lesions. This case highlights the distinct patterns of lung involvement in TSC, with MMPH having a benign and stable nature as compared to LAM which is often relentlessly progressive with associated lung function decline.

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1. Case report

A 38 year old Caucasian female evaluated during pregnancy was found to have multiple hypo pigmented lesions all over her skin and small periungual fibromas. A diagnosis of Tuberous Sclerosis Complex (TSC) was eventually confirmed in both mother and baby with detection of a missense mutation of the TSC2 (Tuberin) gene. (C > T transition mutation; nucleotide position 3598 & codon position 1200; amino acid change Arginine > Tryptophan). None of the patient’s family members had any symptoms or signs to suggest TSC. In addition, two of her four siblings tested negative for TSC gene mutations suggesting that this was a de-novo mutation. The patient was completely asymptomatic. A screening CT chest revealed multiple bilateral ground glass opacities (GGOs) in an upper and mid lung field distribution. The average GGO was 5–6 mm in diameter (range 2–8 mm) with a well-rounded smooth border (Fig. 1). A total of 60–70 GGOs were present through both lungs with the highest density of lesions seen in both upper lobes. No cystic lesions typical of lymphangioleiomyomatosis (LAM) were noted in the lungs. Brain MRI was consistent with a diagnosis of Tuberous Sclerosis with multiple foci of T2 signal hyperintensity involving the subcortical white matter and to a lesser extent the cortex of both cerebral hemispheres. Other abnormalities were a 2 cm cystic lesion in the right ovary (which resolved on subsequent ultrasound imaging done 2 months later) and a small cyst in left hepatic lobe. Lung function showed a mild decrease in total lung capacity. Due to the unusual lung findings and lack of histological diagnosis, the patient underwent video assisted thoracoscopic surgical (VATS) lung biopsy of the right upper lobe at an outside facility. The biopsy was initially read as ‘alveolar cell carcinoma’. However a 2nd opinion was obtained at our center from an experienced lung pathologist, and the diagnosis was confirmed as multifocal micronodular pneumocyte hyperplasia (MMPH). There were no histologic features of LAM on the lung biopsy, and HMB 45 staining was negative (see Figs. 2 and 3).

The patient continued follow up at our center and remained completely asymptomatic. A repeat chest CT obtained 9 years after the initial diagnosis showed stable findings in the lung, with no increase in size, density, or number of lesions.

2. Discussion

TSC is a rare autosomal dominant neurocutaneous disorder characterized by the presence of skin lesions (hypopigmented macules, Shagreen patches, angiofibromas and subungual fibromas)
along with benign hamartomas & tumors in multiple organ systems (most commonly brain, lung, kidney and liver) [1–3]. TSC is diagnosed using the Gomez criteria with the classic Vogt’s triad (mental retardation, seizures and facial angiofibromas) being seen in less than 1/3rd of TSC cases [2]. Lung involvement in the form of LAM & MMPH can occur in up to 50% of TSC cases and its prevalence increases with age [1,3].

LAM is a progressive cystic lung disease that occurs almost exclusively in women with TSC. It is characterized and defined by the presence of greater than 10 rounded, thin-walled air filled cysts [2]. LAM can also occur sporadically in non-TSC patients (young, premenopausal women) and tends to be more severe in those cases [2]. It is a progressive disease with increasing airflow limitation, air-trapping and occurrence of spontaneous pneumothoraces. The management of LAM has been transformed by the introduction of mammalian target of rapamycin (mTOR) pathway inhibitors (sirolimus, everolimus) [4]. These drugs slow the relentless progression in LAM with stabilization and even improvement noted in lung function. They are also effective in treating other TSC manifestations such as subependymal giant cell astrocytoma (SEGA) and renal angiomyolipomas [4].

MMPH is a hamartomatous process that is less frequent than LAM, and is characterized by the proliferation of type II pneumocytes along the alveolar septa [2,5,6]. The hyperplastic type II pneumocytes are enlarged but have preserved nuclear to cytoplasmic ratios, and show bland ovoid nuclei with occasional intranuclear vacuoles. There is an associated increase in alveolar macrophages and mild fibrotic interstitial thickening and mild lymphocytic infiltrates in some cases [2]. These morphologic features have some overlap with atypical adenomatous hyperplasia (AAH) and pulmonary adenocarcinoma in situ (AIS), so the multifocal nature and history of TSC are very helpful features to support the diagnosis of MMPH. The histologic features of MMPH are quite distinct from LAM, which is characterized by cystic lesions lined by a proliferation of immature smooth muscle cells which usually express HMB-45 by immunohistochemistry. Thus, it seems the pathogenesis of MMPH is markedly different from the smooth muscle cell proliferation classic of LAM [2].

Radiologically, MMPH presents as multiple discrete lung nodules (Fig. 1). The chest CT in our patient showed GGOs ranging from 1 to 8 mm in diameter without a solid component (pure ground glass lesions). The GGOs correlate pathologically to the hyperplastic proliferation of type II pneumocytes and alveolar infiltration by macrophages. It is always important to think about AAH and AIS in the differential diagnosis, because AAH and AIS can also present on CT as small nodules with a ground glass density [5,7]. AAH however, tends to co-exist with lung adenocarcinoma and does not present with multi-centric lesions like MMPH [2]. AAH and AIS usually have other features more characteristic of neoplasia, including high

Fig. 1. Multiple rounded ground glass opacities (GGOs) of MMPH in both lung fields.

Fig. 2. Micronodular pneumocyte hyperplasia (H&E, 40x). A well-demarcated nodule of hyperplastic pneumocytes is present (arrows), abruptly transitioning from normal lung parenchyma (lower right).

Fig. 3. Hyperplastic type 2 pneumocytes (H&E, 200x). Cytologically, the hyperplastic type 2 pneumocytes are enlarged but have preserved nuclear to cytoplasmic ratios, and show bland ovoid nuclei with occasional intranuclear vacuoles. There is an associated increase in alveolar macrophages and mild fibrotic interstitial thickening.
nuclear to cytoplasmic ratios, nuclear crowding/overlap, and nuclear atypia [2, 8]. The initial pathology report in our case was ‘alveolar cell carcinoma’, which highlights the overlap in radiologic and histological features between AAH/AIS and MMPH.

MMPH is seen at a younger age than LAM and does not appear to be associated with any significant pulmonary function abnormalities. It can co-exist with LAM or be the sole pulmonary abnormality in patients with TSC [3, 9]. The natural history of MMPH is not entirely clear, but it does not appear to progress towards malignancy in most cases [2]. This case serves to highlight the benign nature of MMPH, with stability in lesion size and number over 9 years of follow up.

3. Conclusion

We present a unique case of MMPH in an asymptomatic adult patient with TSC that remained completely stable even after 9 years of follow up. MMPH involves proliferation of the type II pneumocytes, and likely represents a hamartomatous process. It is distinct from LAM with unique clinical, radiological and pathological features.

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Disclosure

None for all authors.

References

[1] L.C. Costello, T.E. Hartman, J.H. Ryu, High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex, Mayo Clin. Proc. 75 (6) (2000) 591–594.
[2] H. Maruyama, C. Ohbayashi, O. Hino, M. Tsutsumi, Y. Konishi, Pathogenesis of multifocal micronodular pneumocyte hyperplasia and lymphangioleiomyomatosis in tuberous sclerosis and association with tuberous sclerosis genes TSC1 and TSC2, Pathol. Int. 51 (8) (2001) 585–594.
[3] F. Di Marco, S. Terraneo, G. Imeri, et al., Women with TSC: relationship between clinical, lung function and radiological features in a genotyped population investigated for lymphangioleiomyomatosis, PLoS One. 11 (5) (2016) e0155331.
[4] P. Curatolo, M. Bjornvold, P.E. Dill, et al., The role of mTOR inhibitors in the treatment of patients with tuberous sclerosis complex: evidence-based and expert opinions, Drugs 76 (5) (2016) 551–565.
[5] D. Guinee, R. Singh, N. Azumi, et al., Multifocal micronodular pneumocyte hyperplasia: a distinctive pulmonary manifestation of tuberous sclerosis, Mod. Pathol. 8 (9) (1995) 902–906.
[6] T.E. Muir, K.O. Leslie, H. Popper, et al., Micronodular pneumocyte hyperplasia, Am. J. Surg. Pathol. 22 (4) (1998) 465–472.
[7] H. Maruyama, K. Seyama, J. Sobajima, et al., Multifocal micronodular pneumocyte hyperplasia and lymphangioleiomyomatosis in tuberous sclerosis with a TSC2 gene, Mod. Pathol. 14 (6) (2001) 609–614.
[8] K.L. Chuah, P.H. Tan, Multifocal micronodular pneumocyte hyperplasia, lymphangioleiomyomatosis and clear cell micronodules of the lung in a Chinese female patient with tuberous sclerosis, Pathology 30 (3) (1998) 242–246.
[9] D.N. Franz, A. Brody, C. Meyer, et al., 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. 164 (4) (2001) 661–668.