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Tuberous sclerosis complex: A rare etiology of multiple subsolid nodules

Dear Editor,

Subsolid nodules (SSN) are increasingly detected due to widespread use of thoracic computer tomography (CT) in regular clinical practice. The most recent Fleischner Society guidelines published in 2017 [1] proposed a specific algorithm for patients with multiple SSN. After an initial follow-up CT examination at 3–6 months that confirms persistence of SSNs, the most suspicious nodules must be identified in order to decide further management. Particularly suspicious SSN are those with a growing solid component, a solid component ≥ 8 mm, or those with lobulated margins or cystic components. These SSN should be investigated by PET/CT, biopsy, or resection (1).

We report herein the case of a woman with tuberous sclerosis complex (TSC) and multiple SSN, the most suspicious of which confirmed to be micronodular pneumonocyte hyperplasia on excisional biopsy.

A 38-year-old woman with a long-standing diagnosis of TSC with inherited TSC2 gene mutation was referred to our department because a chest CT revealed multiple SSNs. Cardiac and dermatologic annual follow up did not find any hamartomatous lesions.

A high resolution volumetric CT performed at our institution confirmed the presence of multiple (n = 24) bilateral pure ground glass nodules (GGN) ranging from 4 to 12 mm, mainly distributed in the upper lobes (Fig. 1). It also showed a large part-solid subpleural nodule within the right lower lobe, measuring 27 × 22 × 15 mm with a 7 mm solid component (Fig. 2 A–C). This nodule was irregular in shape, well delimited and showed internal air bronchiolograms and bubble lucencies. No lung cyst was identified and the abdominal CT did not demonstrate any renal angiomyolipoma or liver hamartoma. The case was discussed at the multidisciplinary meeting with a consensus decision to perform a diagnostic excisional wedge biopsy to rule out a lung adenocarcinoma.

The histological sections showed a well-delimited nodular lesion (Fig. 3A) consisting of a proliferation of type II pneumocytes lining alveolar septa and occasionally forming compact areas with a papillary pattern. The pneumocytes were enlarged, with flattened to cuboidal shape, and occasional hyperchromatic nuclei (Fig. 3B). However, no frank nuclear atypia, mitosis or necrosis was observed. By immunohistochemistry, the pneumocytes expressed EMA, pancytokeratin and TTF1 (Fig. 4A). They were negative for CEA, P40, estrogen and progesterone receptors antibodies. The Ki67 proliferation index was less than 1% (Fig. 4B). A diagnosis of micronodular pneumonocyte hyperplasia was done and the possibility of multifocal micronodular pneumonocyte hyperplasia (MMPH) was suggested based on correlation with clinical and radiologic features. There were no signs of lymphagioleiomyomatosis (LAM).

TSC is an autosomal dominant multisystemic disorder characterized by a neurocutaneous syndrome with the formation of hamartomas and

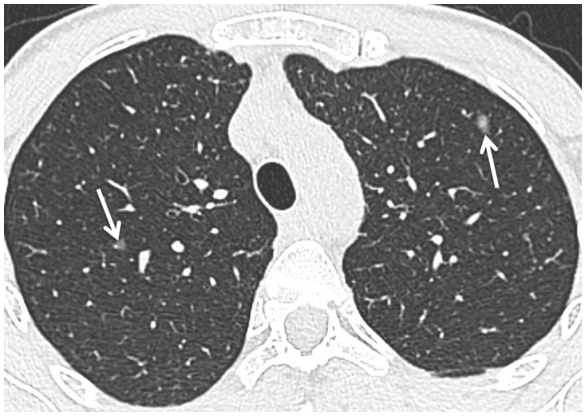

Fig. 1. Transverse high-resolution (0.625-mm section thickness) CT shows multiple bilateral SSN (*arrows*) ranging from 4 to 12 mm in diameter.

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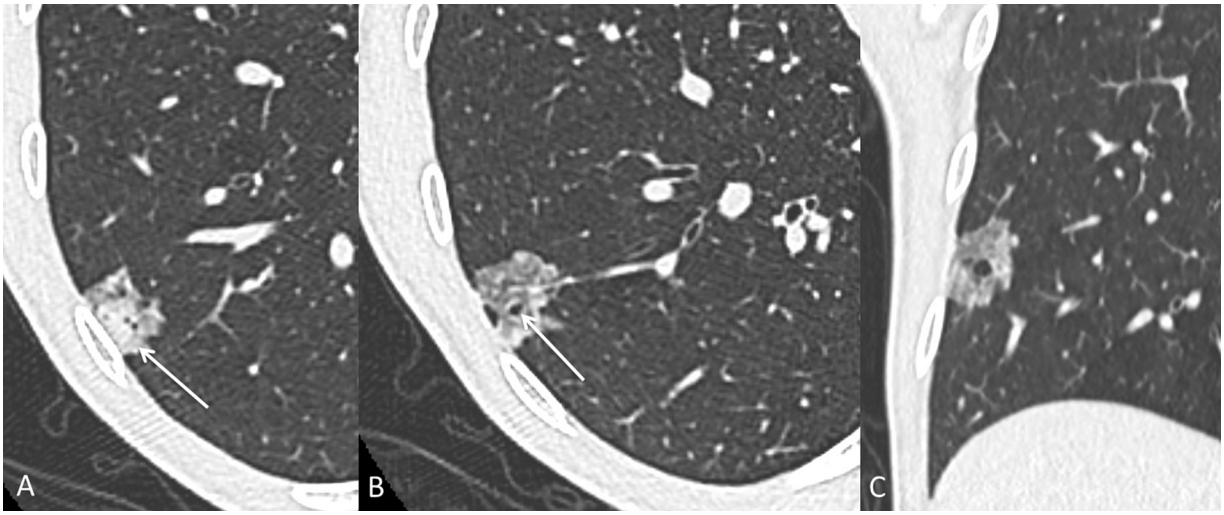

Fig. 2. Part-solid nodule within the right lower lobe. (a): transverse high-resolution (0.625-mm section thickness) CT shows a 7-mm solid component (*arrow*) abutting the pleural as well as air bronchiologram. (b): transverse high-resolution (0.625-mm section thickness) CT shows pure ground glass component with internal bubble lucencies (*arrow*). (c): Coronal reformation shows internal bubble lucencies.

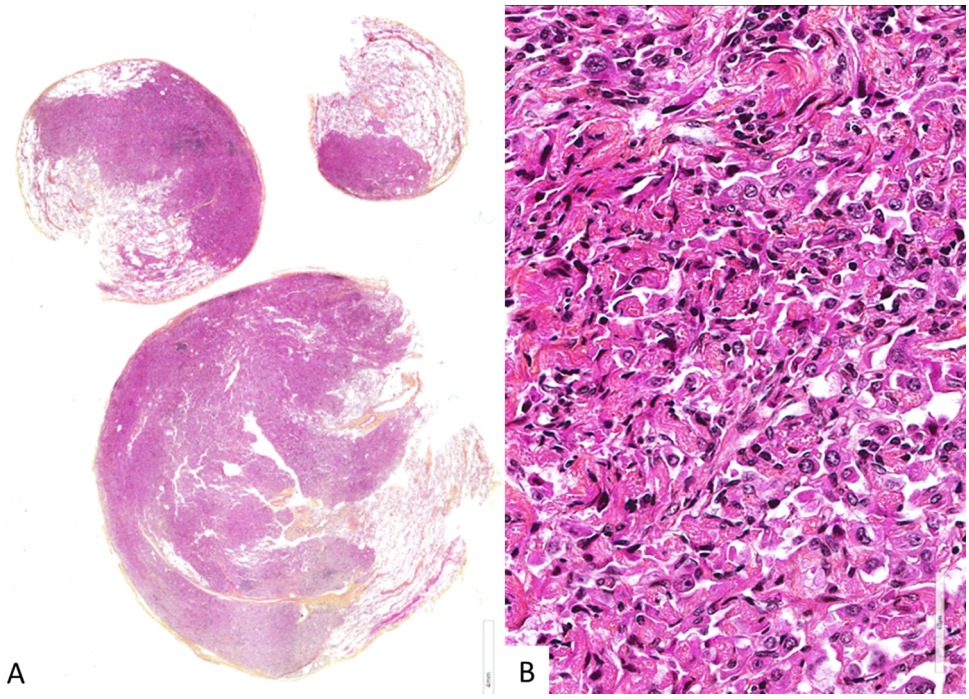

Fig. 3. Histologic analysis revealing. (a): well limited nodule surrounded by normal lung (HES × 1.8). (b): enlarged pneumocytes, from flattened to cuboidal shape, proliferated with papillary patterns (HES × 40).

dysplastic tumors in various organs, such as the skin, brain, kidneys, heart, and lungs.

Pulmonary involvement occurs in only 1% of cases of TSC and is mainly represented by LAM, but also MMPH, and clear cell (sugar) tumor. LAM affects mainly women of childbearing age (34% of women with TSC). Its typical radiological features are randomly distributed and well delimited cysts with thin walls, distributed along lymphatic routes, and sometimes seen in association with thoracic or abdominal chylous effusions. Whereas LAM can also be observed sporadically, MMPH is typically seen in patients with TSC of both sexes, with an estimated

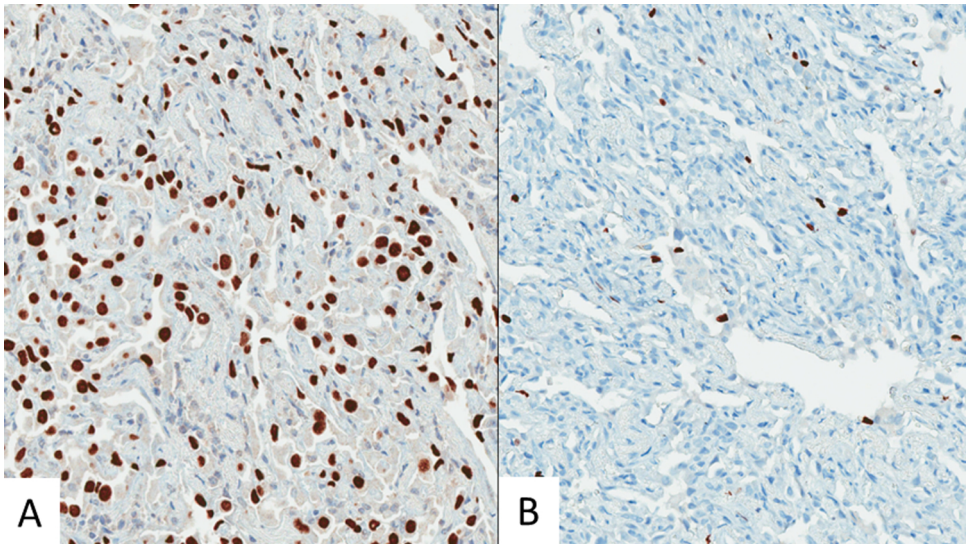

Fig. 4. Immunohistochemistry. (a) TTF-1: nuclear staining. (b) KI67: less than 1%.

prevalence of 40–60% [4], and can occur in the absence of LAM (as in our case). Pathological descriptions of MMPH are rarely reported, with only about fifty cases described in the literature [3]. MMPH is characterized at HRCT by well demarcated SSN, usually ranging from 1 to 14 mm in diameter, with bilateral and randomly distribution within the lungs [2,4]. The majority of MMPH are diagnosed presumptively, without histopathological confirmation.

Follow-up CT examination at 3–6 months showing vanishing SSN indicates an inflammatory or infectious condition [6]. Persistent SSNs more likely correspond to malignant disease. Prolonged CT follow-up is recommended as slow growing SSN are more often preinvasive lesions (atypical adenomatous hyperplasia) or early lung adenocarcinomas, such as adenocarcinoma in situ, minimally invasive or lepidic predominant invasive adenocarcinoma [5]. However, the presentation of lung metastases as SSNs is exceedingly rare.

We demonstrate here that in the context of TSC, small but also large SSN can correspond to MMPH. Although the natural history of MMPH is not well known, it has a very low malignant potential [4]. Awareness of MMPH as a cause of SSN in patients with TCS may prevent unnecessary surgery.

Disclosure of interest

The authors declare that they have no competing interest.

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