- Frierson HF Jr, Moskaluk CA, Powell SM *et al.* Large-scale molecular and tissue microarray analysis of mesothelin expression in common human carcinomas. *Hum. Pathol.* 2003; 34; 605–609.
- Ordonez NG. Application of mesothelin immunostaining in tumor diagnosis. Am. J. Surg. Pathol. 2003; 27; 1418–1428.

## Tuberous sclerosis complex presenting as a pulmonary solitary nodule

## DOI: 10.1111/j.1365-2559.2006.02363.x

Sir: Tuberous sclerosis complex (TSC) is a rare autosomal dominant disease characterized by hamartomatous lesions in several organs.<sup>1</sup> TSC-related pulmonary manifestations comprise several pathological conditions, such as lymphangioleiomyomatosis (LAM), multifocal micronodular pneumocyte hyperplasia (MMPH), clear cell sugar tumour, angiomyolipoma and micronodular/interstitial clear cell LAM-like proliferations: they may involve the lung singly or in different combinations,  $^{2-6}$  but none of them *per se* is diagnostic of TSC. LAM and MMPH, although rare, are the most common features of TSC in the lung. They generally present on imaging as thin-walled cystic changes randomly distributed throughout the lungs in LAM and as diffuse or predominantly lower zone micronodules in MMPH. We report a unique case of TSC incidentally diagnosed during the medical work-up for a pulmonary solitary 'coin' lesion morphologically consistent with a hitherto unreported 'macronodular form' of MMPH.

A 49-year-old previously healthy and asymptomatic, non-smoking female working as a caretaker at an old people's home was incidentally found to have a 25-mm nodule in the right lower lobe of the lung at chest X-ray performed for a doubtful intradermal tuberculin reaction during a routine medical check-up. Chest computer tomographic (CT) scan confirmed the presence of a non-calcified, well-demarcated pulmonary nodule with soft tissue density initially suggesting a pulmonary hamartoma (Figure 1A) without other parenchymal abnormalities or lymphadenopathy. Routine laboratory tests and pulmonary function studies were unremarkable. The patient underwent a thoracotomy with wedge resection of the right lower lobe. The intraoperative finding of small, firm nodules on the surface of the visceral pleura led to a segmentectomy of the right upper and middle lobes.

Grossly, the right pulmonary lower lobe specimen contained a grey-whitish, rounded nodule, 25 mm across, while small, irregularly shaped spots were observed in the lung parenchyma adjacent to the nodule and in the other lobes. At histology, the nodule

consisted of a sharply outlined proliferation of mediumto-large, hyperplastic, polygonal type II pneumocytes lining the alveoli, sometimes displaying nuclear inclusions but lacking cytological atypia (Figure 1B) and positively immunostaining for cytokeratin AE1/AE3 and TTF-1. Several microscopic foci (ranging from 1 to 4 mm in diameter) characterized by the same proliferation of hyperplastic pneumocytes were randomly distributed in the remaining lung parenchyma in all lung specimens. In addition, a few small cystic nodules consisting of a subpleural and perilymphatic proliferation of spindle-shaped, oval-to-rounded cells with a myoid appearance (eosinophilic cytoplasm and blunt fusiform nuclei) were noted (Figure 1C). These cells were immunoreactive for smooth muscle actin, desmin, HMB45 (Figure 1D), oestrogen and progesterone receptors. A diagnosis of nodular and MMPH associated with pulmonary LAM was made. The patient was further investigated for the possibility of other TSCrelated lesions. Cranial magnetic resonance imaging and abdominal ultrasonography showed no evidence of brain lesions or renal abnormalities, respectively. However, dermatological examination revealed several facial angiofibromas in the perinasal area (Figure 1E).

Based on the new TSC Consensus Conference clinical criteria,<sup>7</sup> the presence of two major features (pulmonary LAM and facial angiofibromas) in our patient was considered diagnostic of TSC. The patient, with no history of TSC in her family, had a healthy 25-year-old son.

Finally, a pulmonary high-resolution (HR) CT scan showed the presence of a few thin-walled cysts mainly involving the left upper lobe (Figure 1F). Since the patient has remained asymptomatic, no treatment has been instituted and she is alive and well 14 months after surgery.

TSC is an autosomal dominant disorder characterized by hamartomatous and neoplastic lesions involving multiple organs.<sup>1</sup> In the lung, the most frequent features of TSC are LAM and MMPH, while clear cell sugar tumour, angiomyolipoma and clear cell LAMlike interstitial proliferation occur less frequently.<sup>2–6</sup> Pulmonary LAM consists of HMB45-immunoreactive myoid cells growing around lymphatics and radiologically appearing as thin-walled air-filled cysts diffusely arranged throughout both lungs,<sup>8</sup> while MMPH is a multifocal proliferation of type II pneumocytes appearing as a diffuse micronodular picture on HRCT scan of the chest.<sup>3</sup> Both LAM and MMPH may occur singly or together, as sporadic disease or in patients with TSC. Patients with LAM and/or MMPH are commonly symptomatic at diagnosis suffering progressive dyspnoea on exertion, but Franz et al.<sup>9</sup> prospectively found

<sup>© 2006</sup> Blackwell Publishing Ltd, Histopathology, 48, 764-776.



Figure 1. The chest computed tomographic (CT) scan shows a rounded nodule with soft tissue attenuation at the right lower lobe (A). Histologically, the nodule appears as a type 2 pneumocyte proliferation without cytological atypia (B) consistent with a macronodular form of multifocal micronodular pneumocyte hyperplasia. Small foci of myoid cell growth (C) immunoreactive for HMB45 (D) and suggestive of lymphangioleiomyomatosis were noted. The patient also had facial angiofibromas (E). A high-resolution CT scan shows a few air-filled cysts surrounded by otherwise normal lung parenchyma (F).

G Rossi A Cavazza<sup>3</sup> C Casali<sup>1</sup> A M Cesinaro F Cinquantini<sup>2</sup> U Morandi<sup>1</sup>

Sections of Pathologic Anatomy, <sup>1</sup>Thoracic Surgery and <sup>2</sup>Radiology, Policlinico- University of Modena and Reggio Emilia, Modena, and <sup>3</sup>Operative Unit of Pathologic Anatomy, Hospital St Maria Nuova, Reggio Emilia, Italy

- 1. Gomez MR, Sampson JR, Whittemore VH, eds. *Tuberous sclerosis complex*, 3rd edn. New York: Oxford University Press 1999.
- Bonetti F, Chiodera PL. The lung in tuberous sclerosis. In Corrin B ed. Pathology of lung tumors. London: Churchill Livingstone 1997.
- 3. Muir TE, Leslie KO, Popper H et al. Micronodular pneumocyte hyperplasia. Am. J. Surg. Pathol. 1998; 22; 465–472.
- 4. Flieder DB, Travis WD. Clear cell 'sugar' tumor of the lung: association with lymphangioleiomyomatosis and multifocal micronodular pneumocyte hyperplasia in a patient with tuberous sclerosis. *Am. J. Surg. Pathol.* 1997; **21**; 1242–1247.
- Bonetti F, Pea M, Martignoni G *et al.* Clear cell ('sugar') tumor of the lung is a lesion strictly related to angiomyolipoma. The concept of a family of lesions characterized by the presence of the perivascular epithelioid cell (PEC). *Pathology* 1994; 26; 230–236.
- Pileri SA, Cavazza A, Schiavina M *et al.* Clear-cell proliferation of the lung with lymphangioleiomyomatosis-like change. *Histopathology* 2004; 44; 156–163.
- Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J. Child Neurol. 1998; 13; 624–628.
- Guinee DG Jr, Feuerstein I, Koss MN, Travis WD. Pulmonary lymphangioleiomyomatosis. Diagnosis based on results of transbronchial biopsy and immunohistochemical studies and correlation with high-resolution computer tomography findings. *Arch. Pathol. Lab. Med.* 1994; **118**; 846–849.
- Franz ND, Brody A, Meyer C 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. 2001; 164: 661–668.
- Matsui K, Beasly MB, Nelson WK *et al.* Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. *Am. J. Surg. Pathol.* 2001; 25; 479–484.
- Cancellieri A, Poletti V, Corrin B. Respiratory failure due to micronodular type II pneumocyte hyperplasia. *Histopathology* 2002; 41; 263–265.

## A TFE3+ gastrointestinal tumour: report of a case

DOI: 10.1111/j.1365-2559.2006.02390.x

*Sir*: This report documents an unusual case of a malignant clear cell tumour of the ileum bearing a close histological resemblance to clear cell sarcoma of

nodular lung disease suggestive of MMPH at HRCT in 39% and 43% of asymptomatic women with TSC, respectively. In addition, multinodular lung changes coexisted with cysts in 78% of investigated patients.<sup>9</sup> Based on the percentage of lung parenchyma involved by LAM cells and cysts, Matsui et al.<sup>10</sup> established a grading score [LAM histological score (LHS)], demonstrating a statistically significant difference in survival in patients with pulmonary LAM. In our case, the patient had grade 1 LHS (< 25% of tissue involved) and normal pulmonary function, thus it is not surprising that she had no clinical manifestation of her underlying interstitial lung pathology at presentation and stable disease at follow-up. It is noteworthy that this report illustrates a unique case of TSC presenting as a single lung nodule in an otherwise asymptomatic woman. The nodular lesion which prompted investigation was morphologically consistent with a large and sharply demarcated proliferation of hyperplastic type II pneumocytes identical to that seen in MMPH. a condition generally showing a micronodular pattern at HRCT scan in the TSC pulmonary setting.<sup>3,9</sup> An unusual case of MMPH presenting with bilateral ground-glass opacities and a superimposed micronodular pattern leading to respiratory failure in a young woman without hallmarks of TSC has recently been reported.<sup>11</sup> The nodular appearance of MMPH in our case further expands the clinicopathological spectrum of this rare lung disease and gives rise to some challenging problems in differential diagnosis with other more common benign and malignant conditions involving pneumocytes, such as papillary (PA) and alveolar adenoma (AA), sclerosing haemangioma (SH), atypical adenomatous hyperplasia (AAH) and nonmucinous bronchioloalveolar carcinoma (BAC). Basically, the finding of several foci of MMPH throughout the lung parenchyma tends to exclude PA. AA and SH, which are typically solitary lung lesions. In addition, AA consists of a proliferation of type II pneumocytes and interstitial stromal cells with cystic spaces, while SH is commonly characterized by a combination of several growth patterns (solid, papillary, sclerotic and haemorrhagic). AAH is a preneoplastic lesion < 5 mm in diameter often associated with lung adenocarcinoma or BAC. The lack of frank nuclear atypia or mitoses and the well-circumscribed borders in our case were more consistent with a benign process rather than with malignancy. Finally, the presence of small foci of LAM throughout the lung parenchyma further confirmed the diagnosis of MMPH, underlining the value of extensive sampling in such problematic cases.

evidence of cystic changes consistent with LAM and

<sup>© 2006</sup> Blackwell Publishing Ltd, Histopathology, 48, 764-776.