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Successful treatment of progressive diffuse PEComatosis

To the Editors:

A 43-yr-old, nonsmoking female undergoing gynaecological surgery for menorrhagia was noted to have reduced arterial oxygen saturation and, on direct questioning, reported long-standing, mild, exercise-limiting dyspnoea. Treatment with inhaled bronchodilators had had no effect on her symptoms. Over the succeeding 2 yrs she developed progressive dyspnoea with corresponding deterioration in exercise tolerance. At that time, standard section computed tomography (CT) showed diffuse changes that were considered nonspecific, consisting of difficult-to-characterise opacities without zonal predominance; specifically, there were no conspicuous cysts. The features were suggestive of an infiltrative process and lung function assessment disclosed a forced expiratory volume in 1 s (FEV_1) of 2.12 L (80% predicted), forced vital capacity (FVC) of 2.66 L (88% pred) and transfer factor of the lung for carbon monoxide ($T_{L,CO}$) of 49% pred. A surgical lung biopsy was performed. Ultrasound of the kidneys disclosed no abnormality; specifically, there was no evidence of angiomyolipoma.

Lung histology showed an interstitial proliferation of cytologically bland, mainly rounded cells with predominantly clear cytoplasm (fig. 1a) and without obvious mitotic activity. In areas, these cells formed nodules in the alveolar parenchyma, while elsewhere, the proliferation was more diffuse. Focally, the cells showed a more spindled morphology, having blunt-ended nuclei and moderate volumes of eosinophilic cytoplasm (fig. 1b), a characteristic of lymphangioleiomyomatosis (LAM). All cells were positive for smooth muscle actin (SMA) and desmin, with focal positivity for HMB45. They were also positive for progesterone and oestrogen receptors. A periodic acid–Schiff stain for glycogen was focally positive. Following clinicopathological review, it was felt that the lack of imaging features characteristic of LAM, the lack of S-100 positivity characteristic of a clear-cell sugar tumour (CCST) and the overall perivascular epithelioid cell (PEC)omatous phenotype meant the case was best described as diffuse PEComatosis.

Because of the overlap between LAM and PEComatous disorders, treatment with hydroxyprogesterone was started. Genotyping for tuberous sclerosis was undertaken and proved negative. After 18 months of treatment, the patient's exercise tolerance had deteriorated further, and she also reported development of swelling of her left leg extending up to the gluteal region. Her lung function had deteriorated, with an FEV_1 of 1.58 L (63% pred), FVC of 2.03 L (70% pred) and $T_{L,CO}$ of 3.43 L (43% pred). CT showed interlobular septal thickening, a widespread micronodular pattern and a right-sided pleural effusion, subsequently confirmed to be chylous, but again no cysts (fig. 1c). CT of the abdomen and pelvis showed large retroperitoneal paraortic lesions of fluid density that, on biopsy, were shown to be lymphatic in nature. Lymphangiography showed decreased inguinal lymph drainage with dilatation of the pelvic lymphatic system. Following biopsy, significant chylous ascites developed. Because of the rapid clinical deterioration, combined with the lymphatic abnormalities, chylous pleural and abdominal effusions, a multimodal approach to therapy was adopted. The patient was commenced on: sirolimus (Rapamune, Wyeth, NJ, USA), at an initial dose of 0.25 $mg \cdot m^{-2}$ body surface area, increased over a period of 4 months to achieve serum sirolimus levels of 10–15 $ng \cdot mL^{-1}$; subcutaneous octreotide (100 μg three times daily); and a medium-chain triglyceride (MCT) diet (aiming for a dietary fat content of <14 $g \cdot day^{-1}$).

At review, 3 months after the initiation of this therapy, there had been a dramatic improvement in symptoms with improved exercise tolerance and virtual resolution of lower limb oedema, chylous ascites and pleural effusion (fig. 1d). Lung function tests disclose a marked improvement in both spirometry (FEV_1 2.26 L, 91% pred; FVC 2.97 L, 102% pred) and $T_{L,CO}$ (51% pred). The patient remained clinically and radiographically stable 24 months after stopping octreotide and having relaxed the MCT diet. She continues on sirolimus with target serum levels of 5–10 $ng \cdot mL^{-1}$.

The clinical presentation in this case is suggestive of LAM. However, in typical cases, spirometry shows an obstructive defect with widespread pulmonary cysts [1], while this patient presented with restrictive disease and no cysts. The presence of multiple nodules and an interstitial proliferation of cells with striking epithelioid/clear cell morphology are more character-

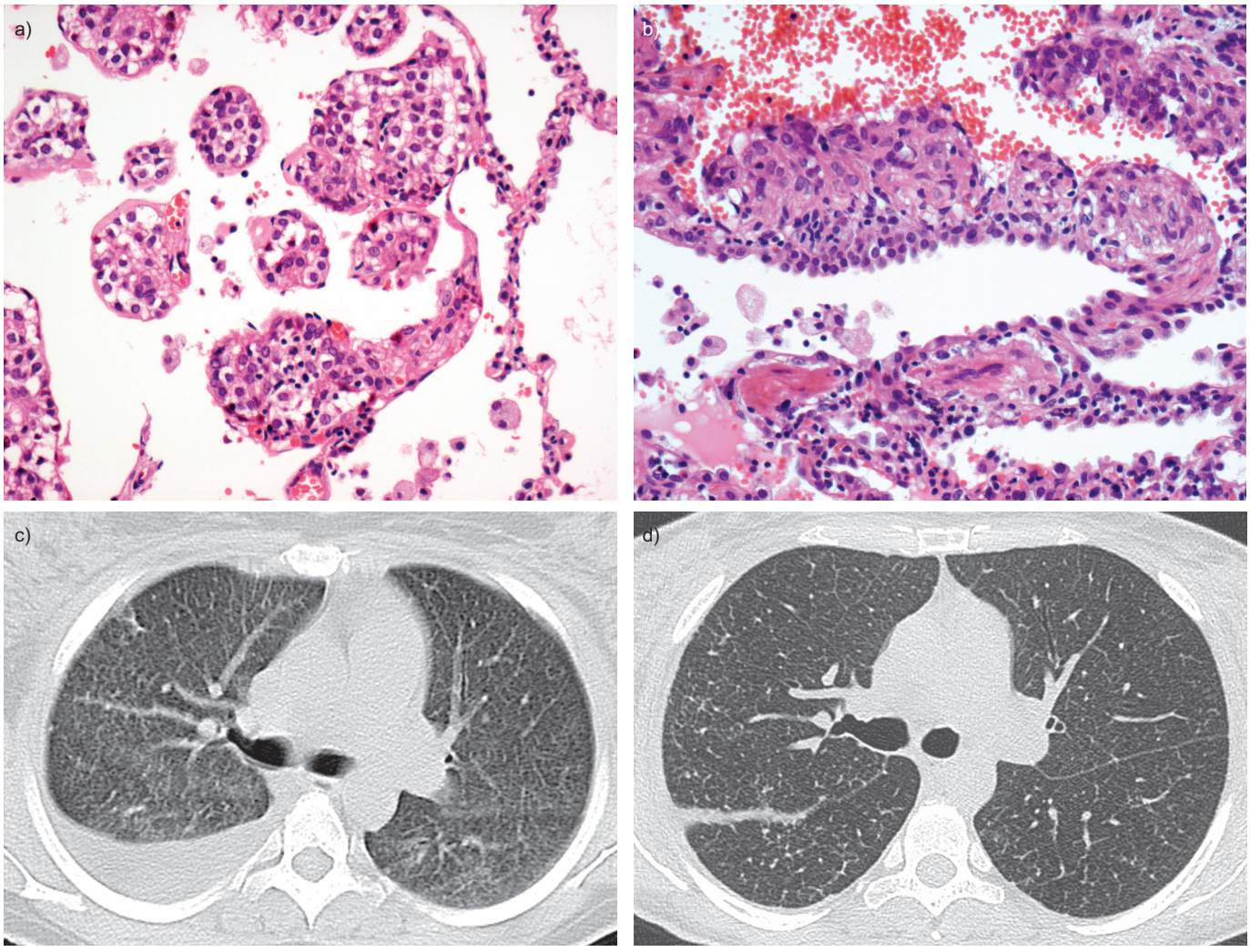

FIGURE 1. Diffuse PEComatosis. a) Many of the nodules comprise cytologically bland, clear cells, while b) focally, the cells show a more spindled morphology with the nuclei being blunt-ended and containing moderate volumes of eosinophilic cytoplasm characteristic of lymphangioleiomyomatosis. Haematoxylin and eosin. Magnification: ×200 c) Computed tomography (CT) 18 months after diagnosis showed marked interlobular septal thickening in the upper lobes, a probable micronodular pattern (on this thick CT section) and a right-sided pleural effusion, but no cystic air spaces. d) 3 months later there was an improvement with less thickening of the interlobular septa (a micronodular pattern persists) and almost complete resolution of the right pleural effusion.

istic of a CCST (or PEComa) involving the lung. However, PEComas of the lung are typically solitary and stain preferentially with S-100 rather than SMA and desmin. This case, therefore, lies within the spectrum of LAM and multiple PEComas within the lung, lesions viewed as clinically distinct but now known to be characterised by co-expression of myogenic and melanogenesis-related markers as well as genetic alterations related to the tuberous sclerosis complex [2, 3]. However, review of the literature shows no cases with this phenotype, although there are rare cases with overlapping features of LAM and CCST in females of reproductive age, one of whom also had multifocal micronodular pneumocyte hyperplasia and one of whom had tuberous sclerosis [4, 5]. A further two patients were found incidentally to have cystic changes, characteristic of LAM, and interstitial nodules on high-resolution CT, with histology showing a PEComatous proliferation, one patient again having tuberous sclerosis [6]. Finally, one case of localised cystic change with an associated nodule showed a CCST and coexistent LAM [7]. In three out of five patients, there was no progression outside the lung over 15 yrs [6, 7]. All published cases, therefore, contrast with this case in which there was no cystic disease and significant pulmonary and extrapulmonary progression over 18 months. Disease in this patient appeared to progress as a diffuse process rather than metastasise (as in the context of a malignant CCST), as there were no histologically malignant features and progression was continuous between anatomical compartments. Furthermore, the response to therapy was not that of a malignant condition.

The rationale for treatment in our patient was two-fold. Chylous ascites and pleural effusions were causing significant, debilitating symptoms that had necessitated prolonged hospitalisation. Furthermore, over serial visits, there was clinical, radiographic and physiological evidence of potentially fatal disease progression. The treatment approach chosen was intended to address both the PEComatous proliferation, and

the lymphatic leakage and chylous effusions. The exact aetiology of the chylous effusions is unclear, but is likely to have been a consequence of damage to dilated, tortuous intra-abdominal and intrathoracic lymphatics. MCT diet has been successfully used to treat a variety of disorders, including primary lymphangiectasia, traumatic chylous duct injury and recurrent chylous effusions in LAM [8]. Octreotide, a somatostatin analogue, has been used with variable success in a variety of chylous disorders [9]. Although the mechanism of action of octreotide is unclear, it is believed to prevent splanchnic vasoconstriction and inhibits absorption of triglycerides, thus reducing lymphatic flow. Sirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Aberrant activation of mTOR is central to the pathogenesis of LAM, with alterations in the mTOR pathways also seen in other PEComatous entities [3]. Clinical trials of sirolimus have demonstrated that, in females with LAM or tuberous sclerosis, sirolimus is effective in shrinking abdominal angiomyolipomas and in preventing progression of pulmonary disease [10]. In our patient, it is impossible to know, without repeat biopsy, whether the principal benefit of treatment has been to reduce lymphatic leakage or whether there has, in fact, been regression of the PEComatosis.

In conclusion, diffuse PEComatosis should be added to the spectrum of entities characterised by PEC differentiation. Furthermore, it should be appreciated that PEComatosis can be progressive both within and outside the lungs. Finally, this case highlights sirolimus and strategies that reduce lymphatic flow as therapies that are effective in the treatment of diffuse PEComatosis.

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