18.14.6 Lymphangioleiomyomatosis 4257 S.J. Bourke

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18.14.6 Lymphangioleiomyomatosis 4257 Investigation and diagnosis The chest radiograph typically shows nodules, reticulation, and cysts in the mid and upper zones symmetrically, with sparing of the costophrenic angles; the lung volumes are often normal or increased, in contrast with many other fibrotic lung diseases. High-resolution CT (Fig. 18.14.5.1) characteristically shows multiple centrilobular nodules with cavitation, progressing to cyst formation and fibrosis in later stage disease. Pulmonary function tests often show a mixture of airways ob- struction, air trapping with elevated residual volume, and impaired diffusing capacity for carbon monoxide. Typical clinical and CT features may be sufficient for diagnosis, but video-assisted thoracoscopic lung biopsy is sometimes required. The characteristic histopathological features are mitotically active Langerhans' cells forming nodules and granulomas with a sur- rounding inflammatory cell infiltrate of lymphocytes, macrophages, and eosinophils (hence the previous diagnostic labels of eosinophilic granuloma and Langerhans' cell granulomatosis). Langerhans' cells are identified by immunostaining of the CD1a membrane antigens or the S100 intracellular protein, and by electron microscopy showing Birbeck granules—rods of tennis racket-shaped structures unfolding from the cell membrane. In advanced disease, fibrosis and honeycombing predominate. Biopsies often show features of other smoking-related diseases such as desquamative interstitial pneu- monia, obstructive bronchiolitis, and emphysema. Langerhans' cells can also be identified in bronchoalveolar lavage fluid, but this is nei- ther sensitive nor specific in diagnosing the disease. Management Because pulmonary LCH varies greatly in its clinical course, man- agement has to be individualized for the particular patient. Smoking cessation is crucial. About 25% of cases resolve, 50% stabilize, and 25% progress with loss of lung function. Corticosteroid therapy is usually given

for progressive disease, but the benefits are unclear. Cytotoxic drugs such as vinblastine, cyclophosphamide, and cladri bine show benefit in some reported cases. Treatment with inhibitors of mutated BRAF has resulted in stabilization or improvement in some patients. Pleurodesis or pleurectomy may be needed for recurrent pneumothoraces and, in view of the risk of bilateral pneumothorax, is best considered sooner rather than later. Lung transplantation is the main option for patients with advanced disease, although recurrence in the transplanted lungs has been described. FURTHER READING Caminati A, Harari S (2006). Smoking-related interstitial pneumonias and pulmonary Langerhans' cell histiocytosis. Proc Am Thorac Soc, 3, 299–306. Gaelle D, et al. (2006). Lung transplantation for pulmonary Langerhans' cell histiocytosis: a multicentre analysis. Transplantation, 81, 746–50. Hyman D, et al. (2015). Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med, 373, 726–36. Lorillon G, et al. (2012). Cladribine is effective against cystic pul- monary Langerhans' cell histiocytosis. Am J Respir Crit Care Med, 186, 930–2. Tazi A, et al. (2012). Serial computed tomography and lung function testing in pulmonary Langerhans' cell histiocytosis. Eur Respir J, 40, 905–12. Vassallo R, Harari S, Tazi A (2017). Current understanding and manage- ment of pulmonary Langerhans cell histiocytosis. Thorax, 72, 937–45. Websites Histiocytosis Association of America. http://www.histio.org Histiocytosis Research Trust (UK). http://www.hrtrust.org/web/guest/ about 18.14.6 Lymphangioleiomyomatosis S. J. Bourke ESSENTIALS Lymphangioleiomyomatosis is characterized by cystic destruc- tion of the lungs due to abnormal proliferation of smooth muscle cells. It is caused by mutations of the genes encoding hamartin and tuberin, sometimes in association with tuberous sclerosis. CT imaging shows characteristic multiple thin-walled cysts. There is usually progressive airways obstruction and impaired gas diffusion, and two-thirds of patients suffer pneumothoraces. Sirolimus can stabilize lung function and improve symptoms. Lung transplantation is the main option for advanced disease. Introduction Lymphangioleiomyomatosis (LAM) is a rare disease in which lymphatics ('lymph'), blood vessels ('angio'), and airways are infil- trated by proliferating abnormal smooth muscle cells ('leiomyo'), Fig. 18.14.5.1 High-resolution CT of a 45-year-old smoking man with biopsy-proven Langerhans' cell histiocytosis, showing centrilobular nodules, cysts, and reticulation.

 resulting in cystic destruction of the lungs, pneumothoraces, chylous effusions, and haemorrhage. LAM cells have low-grade neoplastic properties with enhanced proliferation and invasiveness. LAM can occur as a sporadic disorder or in association with tuberous sclerosis. Pathogenesis Both sporadic and tuberous sclerosis-associated LAM result from mutations of the tumour suppressor genes TSC1 and TSC2, which encode hamartin and tuberin that form a cytoplasmic com- plex that inhibits the protein mTOR. Loss of suppressor function upregulates mTOR, resulting in proliferation of LAM cells. Sporadic LAM occurs exclusively in women, predominantly between the menarche and the menopause. Exceptionally rare cases of LAM have been reported in men with tuberous scler- osis, but the disease is almost confined to women. The origin of LAM cells is unknown but they might arise from the uterus, and oestrogen and progesterone receptors have been found in some LAM cells. Sporadic LAM is due to somatic (noninherited) mutations in the TSC1 and TSC2 genes and occurs in about 2 in a million women. Tuberous sclerosis results from a germ-line mutation of the TSC1 and TSC2 genes and is an autosomal dominant inherited dis- order (OMIM 191 100) whose manifestations include epilepsy, learning difficulties, skin lesions (angiofibromas, shagreen patches), and hamartomas in the brain, kidneys, and other organs (see Chapter 24.17). Most women with tuberous sclerosis ultimately develop evidence of LAM on CT as they get older, with 63% developing symptoms and 12.5% dying of LAM. Clinical features and diagnosis Pneumothorax occurs in about two-thirds of patients with

LAM and is a common mode of presentation. Other manifestations include breathlessness from progressive parenchymal involvement, cough, haemoptysis, and chest pain. Involvement of the thoracic duct may result in chylous pleural effusions and ascites. Other ab- dominal features include renal angiomyolipomas, cystic lymphatic masses, and lymphadenopathy. Renal angiomyolipomas are present in about 50% of patients: they rarely cause symptoms, but bleeding may require treatment by embolization or surgical resection. The chest radiograph typically shows diffuse small cysts with re- ticular shadowing, but normal or increased lung volumes. Lung function tests usually show progressive airways obstruction and reduced gas transfer. The CT features are sufficiently character- istic to establish the diagnosis in many cases, with well-defined cystic airspaces with thin walls distributed throughout both lungs (Fig. 18.14.6.1), and more widespread use of CT imaging is detecting milder cases in an extended spectrum of patients including some postmenopausal women. Lung biopsy may be needed where there is doubt about the diag- nosis: this shows abnormal infiltration by smooth muscle cells, which can be identified by immunohistochemical staining for the HMB45 (human melanoma black) antigen. Aspirated pleural fluid may show diagnostic clusters of immature muscle cells. The serum levels of vascular endothelial growth factor, VEGF-D, are elevated, and this may be a useful biomarker of the disease. Management and prognosis Sirolimus inhibits the protein mTOR and has been shown to sta- bilize lung function, reduce symptoms, and improve quality of life and functional performance, such that it is now the recommended treatment for patients with progressive disease. Treatment has to be continued indefinitely, with the risk of adverse effects, and there is some evidence that low-dose therapy may sufficient. Patients should avoid exogenous oestrogens, including oestrogen contraceptives or hormonal replacement therapy. Pregnancy may be associated with an increased risk of pneumothorax and loss of lung function. Hormonal therapy with progesterone or tamoxifen appears to be ineffective; other antioestrogen therapies, such as letrozole, are being studied. Recent research shows that human LAM lungs express the immune checkpoint ligand PD-L1 and that treatment of a mouse LAM model with anti-PD-1 antibody improved survival. Pneumothorax is common and likely to recur such that med- ical or surgical pleurodesis is advisable. Lung transplantation is the main option for patients with advanced LAM, but recurrence of the disease due to migration of LAM cells to the donor lung has been reported. The clinical course of LAM is variable, but by 10 years after diag- nosis, 55% of patients are breathless on daily activities, 20% require supplemental oxygen, and 10% have died. Fig. 18.14.6.1 CT scan of a 37-year-old woman with pulmonary lymphangioleiomyomatosis and tuberous sclerosis. She had experienced sequential spontaneous pneumothoraces affecting each side. The scan shows multiple thin-walled cysts throughout the lung.

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