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18.14.7 Pulmonary alveolar proteinosis 4259 FURTHER READING Cottin V (2014). Treatment of lymphangioleiomyomatosis: building evidence in orphan diseases. Eur Respir J, 43, 966–9. Cudzilo CJ, et al. (2013). Lymphangioleiomyomatosis screening in women with tuberous sclerosis. Chest, 144, 578–85. Gupta N, et al. (2015). Diffuse cystic lung disease. Am J Respir Crit Care Med, 191, 1354–66. Gupta N, et al. (2019). The NHLBI LAM Registry. Prognostic, physio- logic and radiologic biomarkers emerge from a 15-year prospective longitudinal analysis. Chest, 155, 288–96. Johnson SR, et al. (2010). European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J, 35, 14–26. Karbowniczek M, et al. (2003). Recurrent lymphangiomyomatosis after transplantation. Am J Respir Crit Care Med, 167, 976–82. Maisel K, et al. (2018). Immune checkpoint ligand PD-L1 is upregulated in pulmonary lymphangioleiomyomatosis. Am J Respir Cell Mol Biol, 59, 723–32. McCormack FX, et al. (2011). Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med, 364, 1595–606. Taveira-DaSilva A, et al. (2015). Severity and outcome of cystic lung dis- ease in women with tuberous sclerosis complex. Eur Resp J, 45, 171–80. Yao J, et al. (2014). Sustained effects of sirolimus on lung function and cystic lung lesions in lymphangioleiomyomatosis. Am J Respir Crit Care Med, 190, 1273–82. 18.14.7 Pulmonary alveolar proteinosis S. J. Bourke ESSENTIALS In 90% of cases pulmonary alveolar proteinosis is caused by auto- immune antibodies to GM-CSF which impair the function of al- veolar macrophages in clearing surfactant from the alveoli, giving rise to impaired gas exchange, breathlessness, and respiratory failure. Chest radiography shows extensive alveolar shadowing simulating pulmonary oedema, and CT scanning shows a characteristic ‘crazy paving’ pattern. The presence of GM-CSF antibodies in the serum is useful in diagnosis. Bronchoalveolar lavage or lung biopsy demon- strates alveolar secretions that are strongly PAS-positive. Treatment is by physical removal of the lipoproteinaceous material from the alveoli by whole-lung lavage. Massive inhalation of dust and fumes may overwhelm macrophage function, giving rise to secondary pulmonary alveolar proteinosis. Introduction Pulmonary alveolar proteinosis was first described by Rosen et al.
in 1958. It is a rare disease, characterized by the accumulation of surfactant lipids and proteins in the alveoli, giving rise to impaired gas exchange, breathlessness, and respiratory failure. Detailed

registry studies in Japan showed an incidence of 0.5 per million and a preva- lence of 6.2 per million, with a median age of onset of 51 years and a male:female ratio of 2:1, but the disease seems to be less common in other countries. Whole-lung lavage is effective in removing the lipoproteinaceous material from the alveoli. Aetiology and pathogenesis Surfactant is secreted by type 2 pneumocytes in the alveolar wall. It is a lipoproteinaceous material consisting of the phospholipid dipalmitoyl phosphatidylcholine which has an important role in reducing the surface tension of the alveoli, maintaining patency and preventing collapse. In pulmonary alveolar proteinosis there is defective clearance of surfactant, and this may arise by different mechanisms such that the disease is classified into three distinct forms: autoimmune, secondary, and hereditary. Autoimmune Autoimmune pulmonary alveolar proteinosis is the commonest form of the disease, accounting for 90% of cases. It is due to the development of systemic neutralizing antibodies to granulocyte macrophage-colony stimulating factor (GM-CSF). The mechan- isms giving rise to GM-CSF autoantibodies are unclear, and these patients do not usually have any other autoimmune diseases. The alveolar macrophage has an essential role in clearing surfactant, and in the presence of GM-CSF antibodies their function is impaired, clearance of surfactant is reduced, and the alveoli become filled with this lipoproteinaceous material. Inflammation and/or fibrosis are not usually found, and alveolar architecture is well preserved. Secondary infection can, however, give rise to additional problems. Secondary Secondary pulmonary alveolar proteinosis accounts for about 9% of cases and arises as a complication of other diseases. Acute inhal- ation of dust and fumes may cause the condition, presumably by overwhelming macrophage function, much as silica is known to impair macrophage handling of tubercle bacilli. This has been best described in acute silicosis (silicoproteinosis), which arises within months of massive exposure to respirable crystalline silica. It has also occurred after inhalation of aluminium, titanium, insecticides, or petrol fumes. Secondary pulmonary alveolar proteinosis may also occur as a complication of haematological disorders such as myelodysplasia, leukaemia, or lymphoma, and may also occur in association with im- munodeficiency states and chronic infections such as histoplasmosis, Pneumocystis jirovecii, and mycobacterial infections. The mechanisms underlying pulmonary alveolar proteinosis in these disorders are un- clear, but are thought to involve a reduction in the number or function of alveolar macrophages. These patients do not have GM-CSF antibodies. Hereditary Hereditary pulmonary alveolar proteinosis is a very rare form of the disease caused by mutations of the genes involved in GM-CSF signalling, particularly mutations in the CSF2RA and CSF2RB genes encoding for the GM-CSF receptor α- and β-chains. It presents as pro- gressive breathlessness in young children. These patients do not have GM-CSF autoantibodies, but have increased serum GM-CSF levels which can be a useful pointer in identifying the diagnosis.

section 18 Respiratory disorders 4260 Clinical features and diagnosis The clinical features depend on the stage and context of the disease. Typically the patient presents with progressive shortness of breath. Cough is common but is usually nonproductive. Some patients are seen at a time when they have developed a superadded infection, when they may then present with acute symptoms of fever, cough, and breathlessness, but they may well have had more prolonged insidious symptoms. Some patients are found to have extensive shadowing on an incidental chest radiograph before they have no- ticed symptoms. Physical examination is often normal despite extensive alveolar shadowing on the radiograph, but crackles may be present and some patients have clubbing. In advanced disease patients develop severe breathlessness, cyanosis, and respiratory failure. Investigation The predominant abnormality in pulmonary function tests is a re- strictive ventilatory defect with a reduction in lung volumes and gas diffusion. As the disease progresses the patients

become hypoxic, initially on exercise and then even at rest. The chest radiograph typically shows an extensive bilateral alveolar filling pattern, which often initially suggests pulmonary oedema or pneumonia. CT scanning shows a very characteristic pattern of widespread air space consolidation with thickened interlobular septa, producing a so-called ‘crazy paving’ pattern (Fig. 18.14.7.1). Some other conditions can give a similar appearance, including lipoid pneumonia, diffuse lepidic adenocarcinoma (bronchoalveolar cell carcinoma) and pneumocystis pneumonia. Bronchoalveolar lavage characteristically yields ‘milky fluid’ which consists of lipoproteinaceous material that stains a deep pink with periodic acid Schiff (PAS) stains. The material is negative on alcan blue stain, which differentiates it from mucins. There is a not- able absence of inflammatory cells, but the macrophages are en- larged and contain abundant phospholipoprotein inclusions giving the appearance of ‘foamy macrophages’. Lung biopsy is not often necessary, but pathological findings confirm a similar appearance to bronchoalveolar lavage fluid (Fig. 18.14.7.2). The alveolar architecture is usually well preserved, although there is septal thickening from oedema. Electron micros- copy shows lamellar bodies within the alveolar lumen representing phospholipids. In autoimmune pulmonary alveolar proteinosis the demonstra- tion of serum GM-CSF autoantibodies is both sensitive and specific in the diagnosis. These are not found in patients with secondary causes of pulmonary alveolar proteinosis, and it is important to obtain a detailed occupational and environmental history to assess for any inhalation of dust or fumes, and to identify any associated haematological conditions. In the very rare form of hereditary pul- monary alveolar proteinosis in children, GM-CSF antibodies are also absent, but these children often have high serum GM-CSF levels which may be a useful pointer to the diagnosis. Bronchoalveolar lavage is also useful in identifying any infections which may complicate pulmonary alveolar proteinosis. Because of impaired macrophage function these patients are vulnerable to opportunistic infections with nocardia, cryptococcus, cytomegalo- virus, histoplasmosis, and mycobacteria. Management and prognosis Whole-lung lavage The standard treatment of pulmonary alveolar proteinosis is whole-lung lavage, which is effective in physically removing the lipoproteinaceous material from the alveoli, thereby restoring gas Fig. 18.14.7.1 Computed tomography of a patient with pulmonary alveolar proteinosis, showing diffuse alveolar filling with septal thickening from oedema, giving a ‘crazy pavement’ pattern. Fig. 18.14.7.2 Pulmonary alveolar proteinosis arising acutely following massive exposure to silica. Some alveoli are filled with a noninflammatory proteinaceous exudate, characteristic of pulmonary alveolar proteinosis. The lung interstitium shows fibrosis and inflammation, which can be attributed to acute silicosis (haematoxylin and eosin, medium magnification). Courtesy of Dr D. E. Banks.

 exchange, improving macrophage function and reducing the occur- rence of secondary infections. This is a complex procedure, best per- formed in specialist centres with experience in the technique. Under general anaesthesia patients are intubated with a double-lumen endotracheal tube. The appropriate placement of the tube with iso- lation of each lung is crucial. Ventilation is then given to one lung while the other lung is lavaged with warmed normal (0.9%) saline, in aliquots of 250–500 ml, with total volumes of up to 60 litres. Effective removal of the lipoproteinaceous material may be enhanced by pos- itional changes, assisted clearance and percussion physiotherapy during the procedure. The fluid removed is initially milky but clears as the procedure progresses. The procedure is then reversed so that the other lung is treated. Most patients show substantial clinical improvement after whole- lung lavage, with immediate improvement in oxygenation. Lung function tests show that the vital capacity improves within one week and continues to improve over the subsequent year. The transfer factor for carbon

monoxide tends to improve more slowly, with no increase at one week but substantial improvement over the next six months. The longer-term outcome after whole-lung lavage is variable: about 50% of patients go into prolonged remission after one lavage, but some need repeat lavage as the lipoproteinaceous ma- terial reaccumulates. GM-CSF Autoimmune pulmonary alveolar proteinosis may also be treated by GM-CSF, which can be administered subcutaneously or by aerosol. A meta-analysis of GM-CSF treatment showed a response rate of about 60%, varying between 40 and 90% in different studies, with a relapse rate of about 30%. GM-CSF therapy is associated with minor systemic complications such as fever, and local complications at the site of injection. The optimal indication, dose and duration of therapy, and the sfactors predicting response and relapse, all need further clarification, but this treatment may be particularly useful in those with a poor response to whole-lung lavage or in those requiring repeated lavages. Other treatments Plasmapheresis has been used to reduce levels of GM-CSF autoanti- bodies, but this did not result in clinical improvement in the severity of the lung disease. Rituximab, a monoclonal antibody directed against the B-lymphocyte antigen CD20, has also been used, and resulted in a reduction in GM-CSF antibody levels and improve- ment in some patients, but whole-lung lavage remains the standard treatment. Recurrence of alveolar proteinosis has been reported in a patient who underwent lung transplantation for this condition. Secondary infections can occur and need to be promptly identified and treated. The occurrence of infection is reduced by effective whole-lung lavage, which restores macrophage function. Prognosis Seymour and Presneill reviewed 343 published cases and found survival rates of 79% (2 years), 75% (5 years), and 68% (10 years). Of the 69 deaths, 60 were attributed to pulmonary alveolar proteinosis—47 (72%) from respiratory failure, 12 (18%) from complicating infection, and one (2%) from cardiac arrest during lavage. The actuarial 5-year disease-specific survival was 88%. Of those dying within 5 years, more than 80% did so during the first year after diagnosis: thereafter there was a significantly reduced risk of mortality. FURTHER READING Bonella F, Theegarten D, Guzman J, Costabel U (2011). Alveolar lipoproteinosis syndromes. Eur Respir Mon, 54, 171–86. Borie R, et al. (2011). Pulmonary alveolar proteinosis. Eur Respir Rev, 20, 98–107. Inoue Y et al. (2008). Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med, 177, 752–62. Ishii H, et al. (2011). Clinical features of secondary pulmonary alveolar proteinosis: pre-mortem cases in Japan. Eur Respir J, 37, 465–8. Kavuru MS, et al. (2011). An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. Eur Respir J, 38, 1361–7. Khan A, Agarwal R, Aggarwal AN (2012). Effectiveness of granulocyte- macrophage colony stimulating factor therapy in autoimmune pul- monary alveolar proteinosis. Chest, 141, 1273–83. Kumar A, Abdelmalal B, Inoue Y, Culver DA (2018). Lancet Respir Med, 6, 554–65. Luisetti M, et al. (2009). Plasmapheresis for treatment of pulmonary alveolar proteinosis. Eur Respir J, 33, 1220–2. Rosen SH, et al. (1958). Pulmonary alveolar proteinosis. N Engl J Med, 258, 1123–42. Suzuki T, et al. (2010). Hereditary pulmonary alveolar proteinosis. Am J Respir Crit Care Med, 182, 1292–304. Tazawa R, et al. (2014). Duration of benefit in patients with auto- immune pulmonary alveolar proteinosis after inhaled GM-CSF therapy. Chest, 145, 729–37. Trapnell BC, et al. (2019). Pulmonary alveolar proteinosis. Nat Rev Dis Primers, 5(1), 16. doi: 10.1038/s41572-019-0066-3. 18.14.8 Pulmonary amyloidosis S. J. Bourke ESSENTIALS Pulmonary amyloidosis is characterized by the deposition of mono- clonal immunoglobulin light chain amyloid protein locally or dif- fusely in lung tissue. Local amyloid deposits in the airways, produced by B-cell clones within local tissues, may cause stridor, wheeze, cough, and haemoptysis. Diffuse alveolar deposition can occur as a complication of systemic amyloidosis when the AL protein is de- rived from immunoglobulins produced from bone marrow B cells in diseases such as multiple myeloma,

lymphoma, and monoclonal gammopathy.

section 18 Respiratory disorders 4262 Introduction Amyloidosis is a diverse disease characterized by the deposition of amyloid proteins in extracellular tissues (see Chapter 12.12.3). The aetiology and manifestations vary depending on the different pre- cursor amyloid protein and whether deposition is local or systemic. Several different amyloid proteins have been described, but the two main types relevant to lung disease are reactive systemic (AA) amyloidosis, in which the amyloid protein is derived from the acute phase protein serum amyloid A, and monoclonal immunoglobulin light chain (AL) amyloidosis, in which the amyloid protein is derived from monoclonal immunoglobulin light chains. In amyloidosis these proteins are deposited in extracellular tissue in an abnormal fibrillar form as aggregates of misfolded protein with an abnormal β-sheet conformation that is insoluble and resistant to proteolysis. Amyloid deposits are demonstrated in biopsies of affected tissues by Congo red dye producing green birefringence when viewed in po- larized light. The protein type can be identified by immunostaining or proteomic analysis. Amyloid deposits also contain some normal nonfibrillar plasma glycoprotein, serum amyloid P (SAP), and radiolabelled SAP scintigraphic imaging is available in some spe- cialist centres and is useful in defining the extent and burden of dis- ease in patients. AA systemic amyloidosis This form of amyloidosis does not cause pulmonary disease al- though amyloid may be present in the pulmonary vessels at post- mortem examination. In a large series of 374 patients with systemic AA amyloidosis, Lachmann et al. found that bronchiectasis was the underlying cause in 5%, and tuberculosis in 1% of patients, but in no case did AA amyloidosis cause clinically significant lung disease. Treatment is aimed at controlling the underlying inflammatory dis- ease to reduce the overproduction of serum amyloid proteins. AL amyloidosis In systemic AL amyloidosis the lungs show evidence of amyloid deposition in about 50% of patients, but only rarely does this give rise to symptoms. However, diffuse alveolar–interstitial deposition causes progressive impairment of gas diffusion in some cases. In local AL amyloidosis, isolated nodules of amyloid are deposited in the larynx, trachea, bronchial tree, or lung parenchyma. These nodules arise from B-cell clonal expansion in the tissues close to the amyloid deposits, such that the disease is localized without systemic involvement. The factors provoking local B-cell clonal expansion and local amyloid nodules are not understood. Clinical features The clinical features of pulmonary amyloidosis are diverse and de- pend on the location and pattern of amyloid deposits. Localized laryngotracheobronchial disease Amyloid deposits may produce nodules or more extensive plaques in the walls of the airways or the peribronchial tissues. In laryngeal amyloidosis the key features are hoarseness, stridor, and cough. In the bronchial tree symptoms depend on the anatomical location, but amyloid deposits may cause cough, obstruction, and haemoptysis. Obstruction of airways may lead to atelectasis of a lobe or segment with distal infection. Central lesions may pose particular difficulty for intubation and the administration of anaesthesia. When a single lesion is involved it may simulate the effects of a bronchial adenoma, appearing as a polypoid mass on endoscopic inspection. CT scans and bronchoscopy give anatomical definition of the disease, but bi- opsy is necessary to demonstrate amyloid. Localized parenchymal nodules Discrete nodules or masses, which may be single or multiple, are seen within the lung parenchyma on the chest radiograph and CT. They rarely cause symptoms or disrupt lung function and may eventually calcify, cavitate, or even ossify. They are likely to simu- late bronchial neoplasms if single and hence biopsy and surgical resection are often performed. Caution in conducting a biopsy on lesions is required because amyloid deposits may disrupt blood ves- sels, preventing vasoconstriction and contributing to an increased risk of bleeding. Diffuse alveolar–interstitial disease Amyloid deposited diffusely throughout the alveolar walls and interstitium of the lung is a rare manifestation of AL

amyloidosis (Figs. 18.14.8.1 and 18.14.8.2). Here the lung disease is part of more widespread systemic amyloidosis and these patients often also have cardiac and renal amyloidosis. There have been a few reports of AA amyloid affecting the lungs, but the fibril type may have been misidentified and all studies in which the fibril protein has been sequenced show AL type amyloid. Systemic symptoms of tiredness, malaise, and weight loss are common. There is progressive breathlessness and a dry cough, with prominent crackles on examination. Lung function testing shows impairment of gas diffusion and restriction of lung volumes. The prognosis is poor, with progressive hypoxia and respiratory failure, although death more commonly results from cardiac or renal involvement. Fig. 18.14.8.1 Alveolar–interstitial-type amyloidosis of the lung. Staining with haematoxylin and eosin (medium magnification) reveals interstitial deposits of hyaline eosinophilic material with a foreign body type giant cell response in adjacent tissue. This is an almost unique feature of amyloidosis affecting the lung. By courtesy of Dr T. Ashcroft.

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