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identification of the underlying cause is important in directing specific treatments. Goodpasture’s syndrome is an autoimmune disorder charac- terized by alveolar haemorrhage and glomerulonephritis due to antibasement membrane antibodies. Renal failure is usually the dominant feature, but alveolar haemorrhage can precede renal involvement. Idiopathic pulmonary haemosiderosis is a rare disorder of un- known cause with recurrent alveolar bleeding, which may provoke pulmonary fibrosis, and anaemia. Introduction Diffuse alveolar haemorrhage typically presents as a combination of acute respiratory failure, bilateral infiltrates on a chest radiograph, haemoptysis, and anaemia. It is not a distinct disease entity but a clinical pattern with many different causes. Management is cru- cially dependent on recognizing that the lung infiltrates are due to alveolar haemorrhage rather than pulmonary oedema, infection, or inflammation. Bronchoscopy with bronchoalveolar lavage is often important in demonstrating acute bleeding at the alveolar level, or haemosiderin- laden macrophages in chronic cases, and in excluding infection or a bronchial cause of haemorrhage. Some patents presenting in respira- tory failure may need endotracheal intubation and ventilation before bronchoscopy can be performed. Considerable amounts of blood can accumulate in the alveoli before giving rise to haemoptysis, which is therefore not always apparent at presentation. Characteristically blood in the alveoli causes an elevation of the carbon monoxide transfer factor (TLco) and transfer coefficient (Kco) as red blood cells in the alveoli bind carbon monoxide, but often patients are not suffi- ciently stable to undertake lung function tests. The causes of diffuse alveolar haemorrhage are diverse but can be broadly classified into immune-mediated and nonimmune- mediated causes (Box 18.14.1.1). The clinical context is crucial in identifying the aetiology and a careful assessment is needed to iden- tify any provoking factors (drugs, tobacco smoke, inhaled toxins) 18.14 Miscellaneous conditions

 or any systemic diseases (cardiac, renal, connective tissue diseases). As can be seen in Box 18.14.1.1, diffuse alveolar haemorrhage (Fig. 18.14.1.1) may be a manifestation of many diseases, but is a defining characteristic of two, Goodpasture’s syndrome and idio- pathic pulmonary haemosiderosis. Immune-mediated alveolar haemorrhage Immune-mediated diseases account for about 35% of cases of diffuse alveolar haemorrhage and include primary pulmonary vasculitis, vasculitis secondary to connective tissue diseases, and antibasement membrane antibody disease (Goodpasture’s syndrome). In some of these diseases both the lungs and kidneys are involved such that they present as a pulmonary-renal syndrome. Pulmonary vasculitis Granulomatosis with polyangiitis (Wegener’s disease), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), and microscopic polyangiitis are usually associated with antineutro phil anticytoplasmic antibodies (ANCA). Granulomatosis with polyangiitis commonly causes a necrotizing glomerulonephritis and is associated with necrotizing inflammation of the nasopharynx, the central airways, the lung parenchyma, and the pulmonary ves- sels. Biopsy of the kidneys or nasopharynx is usually more appro- priate than lung biopsy, and the ANCA antibodies are usually of the cytoplasmic type (C-ANCA) and are directed against proteinase- 3. By contrast, microscopic polyangiitis does not typically involve the upper respiratory tract and is not granulomatous, and the ANCA antibodies are perinuclear (P-ANCA), directed against the myeloperoxidase of neutrophil cytoplasmic granules. In eosinophilic granulomatosis with polyangiitis there is an allergic granulomatous angiitis associated with high IgE levels and hypereosinophilia in a patient with asthma. Other vasculitic disorders rarely cause diffuse alveolar haemor- rhage, but include polyarteritis nodosa, Henoch–Schönlein pur- pura, and Takayasu’s arteritis. Pulmonary vasculitis with alveolar haemorrhage may also rarely be secondary to connective tissue dis- eases such as systemic lupus erythematosus, rheumatoid disease, mixed

connective tissue disease, IgA nephropathy, systemic scler- osis, and primary antiphospholipid syndrome. Goodpasture's syndrome Goodpasture's syndrome is a rare autoimmune disorder character- ized by diffuse alveolar haemorrhage and glomerulonephritis due to antibasement membrane antibodies. These antibodies are mainly directed against the α-3 chain of type IV collagen in the alveolar and glomerular basement membranes. Damage to this domain of col- lagen may elicit an autoimmune response. Increased susceptibility is Box 18.14.1.1 Causes of diffuse alveolar haemorrhage Immune-mediated diseases Vasculitis • Granulomatosis with polyangiitis (previously known as Wegener's disease) • Eosinophilic granulomatosis with polyangiitis (previously known as Churg–Strauss syndrome) • Microscopic polyangiitis • Polyarteritis nodosa • Takayasu's arteritis • Pauci-immune pulmonary capillaritis Connective tissue disease • Systemic lupus erythematosus • Rheumatoid disease • Mixed connective tissue disease • Systemic sclerosis • Goodpasture's syndrome (antibasement membrane antibody disease) Nonimmune-mediated diseases Cardiac • Left ventricular dysfunction • Valvular heart disease • Congenital cardiac anomalies • Pulmonary veno-occlusive disease Infection • Staphylococcal pneumonia • Leptospirosis Coagulation disorders • Thrombocytopaenia • Thrombolytic therapy • Disseminated intravascular coagulation Toxic • Cannabis, cocaine, tobacco • Volatile hydrocarbon glue solvents • Drugs (penicillamine, mitomycin C, amiodarone) Idiopathic • No cause identified • Idiopathic pulmonary haemosiderosis Fig. 18.14.1.1 Radiograph showing gross alveolar shadowing following severe pulmonary haemorrhage in a 60-year-old man with systemic vasculitis.

 associated with HLA DRB11 501 and DRB11 502 alleles, while pro- tection is associated with HLA DR1 and DR7. Acute glomerulonephritis with renal failure is usually the dom- inant feature of antibasement membrane antibody disease, but this is sometimes associated with alveolar haemorrhage, which can rarely precede renal involvement. Alveolar haemorrhage is strongly associated with cigarette smoking, or sometimes with inhalation of other toxins such as cocaine or volatile hydrocarbon glue solvents. This suggests that inhaled toxins enhance pulmonary endothelial damage and thus allow the initiation of autoimmunity or the access of existing autoantibodies to the basement membrane. The usual respiratory presentation is with cough, breathlessness, and haemoptysis, with diffuse shadowing on the chest radiograph. Renal function may be normal initially but can deteriorate rap- idly. The diagnosis is established by the detection of antibasement membrane antibodies in the serum or as linear deposits along the basement membrane by immunofluorescence of glomeruli on renal biopsy, or rarely on lung biopsy in cases without renal involvement at presentation. Prognosis generally depends more on the renal effects than the pulmonary effects. See Chapter 21.8.7 for further discussion. Nonimmune-mediated alveolar haemorrhage Diffuse alveolar haemorrhage can occur due to many diverse non-immune diseases which need to be sought and considered in the differential diagnosis. In a series of 112 consecutive patients with diffuse alveolar haemorrhage, nonimmune causes accounted for 65% of cases. These included cardiac disease in 29%, a diverse range of conditions in 23% (infection, toxins, drugs, coagulation disorders, barotrauma), and in 12% the cause was classified as idiopathic. Chronic pulmonary venous congestion is a mechanism of al- veolar haemorrhage in many cardiac diseases such as left ventricular dysfunction, valvular heart disease, pulmonary veno-occlusive disease, and in congenital cardiac anomalies. Alveolar haemor- rhage may occur as part of severe infections, notably in patients with Staphylococcal pneumonia, but also in other infections such as leptospirosis, invasive aspergillosis, and HIV. Bleeding disorders such as thrombocytopaenia, coagulopathies, disseminated intravas- cular coagulation, and thrombolytic therapy can precipitate alveolar haemorrhage. Drugs (amiodarone, methotrexate, mitomycin C, penicillamine) or inhaled toxins (cannabis, cocaine, volatile hydro- carbon glue solvents,

mycotoxins from moulds) have all been as- sociated with alveolar haemorrhage. Barotrauma with haemorrhage can occur in scuba diving or as a complication of mechanical venti- lation and general anaesthesia. A careful search for provoking fac- tors and underlying diseases is important in deciding on the best management. Idiopathic pulmonary haemosiderosis This is a rare cause of alveolar haemorrhage of unknown aetiology which particularly affects children and young adults, with recurrent episodes of haemoptysis resulting in iron-deficiency anaemia. Recurrent alveolar haemorrhage results in cough with haemop- tysis and breathlessness, sometimes associated with fever and (in children) failure to thrive. During acute bleeds, the chest radio- graph and CT scan show a nonspecific appearance of intra-alveolar blood. The alveolar blood may act as a fibrogenic stimulus resulting in diffuse pulmonary fibrosis, with a restrictive ventilatory defect and impaired gas transfer. Characteristically lung biopsy shows haemosiderin-laden macrophages with varying degrees of fibrosis, but does not show vasculitis or features of any other cause of alveolar haemorrhage. Antibasement membrane antibodies are not present, and the electron microscopic appearance of the basement mem- brane shows no consistent abnormality. Some cases previously classified as idiopathic pulmonary haemosiderosis may have been a consequence of vasculitis at the pulmonary capillary level (pauci-immune pulmonary capillaritis). Some cases may result from inhalation of toxins from moulds such as the stachybotrys mould, which may contaminate wet or damp ac- commodation, and which releases a particularly potent toxin with haemorrhagic properties. Idiopathic pulmonary haemosiderosis is also associated with cow’s milk allergy and coeliac disease. The rarity of the disease means that treatment regimens and prognosis are poorly defined and based mainly on case reports. In children with associated cow’s milk allergy or coeliac disease, avoid- ance of milk or gluten usually results in improvement. In adults the prognosis is more variable and protracted, with some patients re- sponding to corticosteroids and other immunosuppressant drugs. In longstanding cases, interstitial lung fibrosis may develop. About a quarter of patients go on to develop some form of systemic auto- immune disease. Management Treatment of alveolar haemorrhage is initially mainly supportive, with stabilization of the patient’s respiratory and haemodynamic status, and attention to any coagulation abnormalities or renal dys- function. In a large case series of consecutive patients with alveolar haemorrhage, 77% required admission to an intensive care unit, 18% needed endotracheal intubation and ventilation, and 16% renal replacement therapy. In-hospital mortality was 24%. Prompt identi- fication of the underlying cause allows the initiation of appropriate specific treatment. For patients with vasculitis, induction of remission is usually achieved by a combination of corticosteroids (typically intravenous methylprednisolone 500–1000 mg daily for 3–5 days, followed by prednisolone 1 mg/kg/day orally) and cyclophosphamide (typically 2 mg/kg/day orally or 15 mg/kg intravenously in pulses at 3-weekly intervals). As clinical improvement occurs, the dose of immunosup- pressants is gradually reduced. Alternative immunosuppressants such as rituximab, azathioprine, or methotrexate may be used in pa- tients who are refractory to initial treatment or as steroid-sparing agents. Goodpasture’s syndrome with pulmonary haemorrhage is usu- ally treated by a combination of plasmapheresis, corticosteroids, and cyclophosphamide. Plasmapheresis gives rapid removal of antibodies from the circulation and immunosuppressants reduce antibody synthesis. Some patients with idiopathic pulmonary haemosiderosis also appear to respond to immunosuppressants.

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