Rare diseases • 6

Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis

Pallav L Shah, David Hansell, Peter R Lawson, Kenneth B M Reid, Cliff Morgan

Pulmonary alveolar proteinosis was first described by Rosen et al in 1958. It is an unusual diffuse lung disease characterised by the accumulation of large amounts of phospholipoproteinaceous material in the alveoli. It has a variable clinical presentation and course. Most cases are primary but occasionally the condition is secondary to other conditions or inhalation of chemicals. Whole lung lavage remains the most effective treatment and the overall prognosis is good. Surfactant homeostasis is abnormal and animal experiments suggest that this may relate, in some instances at least, to defects in GM-CSF signalling. There are at least two congenital forms of the disease and several different animal models suggesting that pulmonary alveolar proteinosis is unlikely to be a single disease entity and more likely to represent a clinical syndrome.

Epidemiology
Pulmonary alveolar proteinosis is a rare lung disease and accurate estimates of incidence are not available. Current estimates suggest an incidence of one in two million people. The series reported in the literature suggest a male preponderance (male:female ratio 3:1). Peak onset is in the third or fourth decade of life with over 80% of reported cases occurring in this age group. However, there are reports of the disease occurring in neonates, children, and the elderly.

Clinical features
CLINICAL PRESENTATION
Dyspnoea is the most common presenting symptom. It usually occurs on moderate exertion but in a few patients occurs at rest. Cough is the other common symptom. These symptoms are often trivial and some patients do not present until they develop a supervening infection. This may explain the acute onset of symptoms and fever observed in some patients. A low grade fever may also occur as a consequence of pulmonary alveolar proteinosis in the absence of secondary infection. Physical examination is often normal and inspiratory crackles on auscultation is the commonest abnormality. Clubbing of the fingernails is present in about one third of cases. Patients with advanced disease may have central and peripheral cyanosis. Raised serum levels of lactate dehydrogenase (LDH), tumour markers, mucin like glycoprotein (KL-6), and the surfactant proteins A and D have been observed in pulmonary alveolar proteinosis.

PULMONARY FUNCTION TESTS
The predominant abnormality is a restrictive ventilatory defect with a reduction in lung volumes and diffusion capacity. Obstructive ventilatory changes are unusual but may be observed in smokers. Hypoxaemia is a prominent finding and patients with extensive disease have an increased alveolar/arterial oxygen pressure difference (P(A-a)O2) which widens further on exercise. This is thought to be due to shunting of blood from right to left through an intact pulmonary capillary bed perfusing large numbers of poorly ventilated alveoli filled with lipoproteinaceous material. Other contributory mechanisms may be septal oedema and, in rare cases, a degree of interstitial fibrosis has been reported.

Pulmonary function tests can be used to assess disease severity, progression, and response to treatment. Arterial blood gas tensions, alveolar-arterial oxygen gradients, and change in P(A-a)O2 gradient on exercise are better predictors of disease severity and functional impairment. Kariman et al suggested that patients with an arterial partial pressure of oxygen (Pao2) of greater than 9.3 kPa (70 mm Hg) or P(A-a)O2 gradient of less than 5.3 kPa (40 mm Hg) are more likely to improve spontaneously whilst those who do not meet these criteria are more likely to progress.

RADIOLOGY
Accumulation of phospholipoproteinaceous material in the alveoli results in a non-specific radiographic pattern of air space consolidation. There are no ancillary signs or specific features of the distribution of the consolidation to suggest the diagnosis of alveolar proteinosis on the basis of radiographic appearances alone. The consolidation is usually bilateral and patchy and in some patients is very extensive, despite relatively mild respiratory symptoms. In some series of alveolar proteinosis the patchy consolidation was peripheral (bat’s wing pattern; fig 1A) in up to 50% of cases. However, the distribution of consolidation is highly variable and may be predominantly peripheral or basal (fig 1B).
The abnormalities may be asymmetrical in up to 20% of cases \textsuperscript{11} and isolated lobar involvement has been reported. \textsuperscript{33,34} Other radiographic patterns that reflect air space filling include poorly defined acinar nodules and ground glass opacification, both of which usually occur in conjunction with more widespread dense consolidation. \textsuperscript{35} Air bronchograms within the consolidated lung are not usually a feature.

High resolution computed tomographic (HRCT) scans of the thorax demonstrate the expected appearance of widespread air space consolidation, but also thickened interlobular septa, clearly visible within the affected lung and producing the so called “crazy paving” pattern (figs 2A and B). \textsuperscript{35} The extent of lung involvement is more easily defined on CT scans (which sometimes reveal sharply demarcated geographical areas of lung involvement). As with plain chest radiography, air bronchograms are not a feature despite widespread pulmonary consolidation. None of the CT studies published to date has identified a specific lobar or zonal distribution in this disease. \textsuperscript{36–38} Chest radiographs and HRCT scans of the thorax are of similar value for assessing disease severity. \textsuperscript{35}

The appearances of alveolar proteinosis in children are not well characterised but a reticulonodular pattern, small nodules mimicking miliary disease, and a coalescence of various sized acinar nodules have been described. \textsuperscript{39}

It was initially suggested that the crazy paving pattern in geographical areas of pulmonary opacification were specific for alveolar proteinosis. However, other conditions, most notably lipoid pneumonia \textsuperscript{40} and bronchio-alveolar cell carcinoma, \textsuperscript{41} can sometimes mimic the CT features usually associated with alveolar proteinosis.

PATHOLOGY

The gross pathological findings in pulmonary alveolar proteinosis are patchy areas of yellow consolidation with an oily substance exuding from abraded surfaces. The classical finding on light microscopy is filling of the alveoli and terminal bronchioles with a granular lipoproteinaeous substance which stains a deep pink with periodic acid Schiff (PAS) stain. \textsuperscript{1} The alveolar architecture is usually well preserved although septal thickening from oedema \textsuperscript{37} or lymphocytic infiltration has been observed. \textsuperscript{42}

Ultrastructure analysis of lung specimens by transmission electron microscopy (TEM) shows abundant cellular debris and concentrically arranged laminated annular structures (lamellar bodies) within the alveolar lumen (fig 3). \textsuperscript{6,42–49} The structures range from uniformly spaced laminated structures (fig 4A) to irregular whorl-like structures with or without a dense osmiophilic core (fig 4B). \textsuperscript{50,51} These structures represent phospholipids and are identical to inclusions found in normal type II pneumocytes. \textsuperscript{52} In contrast, tubular myelin structures are sparse (aggregates with well formed lattice structures that are formed in the alveoli under normal circumstances). The few alveolar macrophages that are present in the alveoli are enlarged and contain numerous complex phospholipoprotein inclusions (fig 5). \textsuperscript{53} The inclusions are similar to the lamellar bodies and osmiophilic inclusions observed in the alveolar lumen and type II pneumocytes.

BRONCHOALVEOLAR LAVAGE

Milky fluid is usually obtained on bronchoalveolar lavage of an affected segment. \textsuperscript{54–56} Examination of the cytospin demonstrates a basophilic granular extracellular deposit with a few enlarged foamy macrophages and cellular debris on staining with May-Grünwald Giemsa. The extracellular substance is stained pink with PAS but negative with alcian blue, which allows the differentiation of the phospholipoprotein aggregates from mucins. The cellular content is usually sparse and differential cell counts of the lavage fluid is usually unhelpful in making the diagnosis; an inflammatory infiltrate may indicate a superimposed infection. \textsuperscript{57,58} The ultrastructural appearance on electron microscopy is characteristic with abundant lamellar bodies and cellular debris but only a few tubular myelin aggregates. \textsuperscript{50,54–56,59,60} The alveolar macrophages...
are usually enlarged with abundant lipid inclusions with the same ultrastructural characteristics as those found in the extracellular material. Numerous studies have characterised the intra-alveolar material obtained following bronchoalveolar lavage in patients with pulmonary alveolar proteinosis. The major constituent of the lavage fluid is phospholipid, mainly lecithin, the main component of surfactant.

The lavage material also contains serum proteins and surfactant specific proteins including increased concentration of surfactant protein A (SP-A) and surfactant protein D.

One of the SP-A oligomers in pulmonary alveolar proteinosis tends to form large aggregates which retain an ability to bind with phospholipids but fails to form the uniform lattice structure of tubular myelin.

Various tumour markers have been detected in the bronchoalveolar lavage fluid of patients with pulmonary alveolar proteinosis. However, their diagnostic value is limited as they are found in other pulmonary diseases.

**DIAGNOSIS**

The diagnosis of pulmonary alveolar proteinosis can be made with confidence on the basis of the appearance of the lung on the HRCT scan of the thorax in conjunction with an examination of lavage fluid obtained from segmental alveolar lavage. Examination by light microscopy is adequate but ultrastructural analysis by electron microscopy strengthens the diagnosis. Transbronchial biopsy specimens provide a tissue diagnosis but, in view of the patchy nature of the disease, may be inconclusive. The procedure also carries the risk of a pneumothorax or haemorrhage. Open lung biopsy specimens obtained by the video assisted thoracoscopic route have the same disadvantages, in addition to the potential for surgical complications. Bronchoalveolar lavage samples a larger distal lung field and is a much safer procedure.

**Treatment of pulmonary alveolar proteinosis**

Whole lung lavage is the safest and most effective form of treatment for alveolar proteinosis. Historically, treatment has included corticosteroids, potassium iodide, and streptokinase with variable success. Ambroxol stimulates the intracellular formation and secretion of surfactant and, although this would be expected to exacerbate the intra-alveolar accumulation of surfactant, there is a single report of improvement in one patient following treatment. Aerosolised trypsin has been used to treat pulmonary alveolar proteinosis on the grounds that trypsin would hydrolyse the proteinaceous material and hence improve clearance. Some of the patients treated with trypsin developed an allergic reaction and there is the potential for proteolytic damage. However, none of these studies was controlled and the response observed in some patients may represent the spontaneous improvement that is seen in up to...
WHOLE LUNG LAVAGE

Whole lung lavage is now considered the treatment of choice. The technique has evolved since the early instillation of heparinised saline via an intratracheal catheter. Although there are no randomised controlled studies, there is good evidence of efficacy with several studies showing improvement in exercise tolerance and symptoms following whole lung lavage whilst others have shown objective improvements in pulmonary function, arterial oxygenation, and shunt fraction. Some studies have shown improvement following the lavage followed by a gradual decline and subsequent improvement following a repeat lavage. Radiological clearing is less impressive immediately after lavage but occurs more gradually, the time period varying between individuals. Whole lung lavage is associated with improvements in macrophage function and a decreased incidence of opportunistic infections.

INDICATIONS FOR WHOLE LUNG LAVAGE

The main indication for whole lung lavage is limitation in daily activities due to dyspnoea. The threshold for lavage is therefore lower for a person who works as a heavy labourer than someone who has a sedentary lifestyle. Some authors have suggested that patients with a Pao₂ of less than 9.3 kPa (70 mm Hg) or a P(Å–a)O₂ of more than 5.3 kPa (40 mm Hg) are more likely to progress and hence require whole lung lavage.

TECHNICAL ASPECTS OF WHOLE LUNG LAVAGE

The technique used at the Royal Brompton Hospital is described in detail and is similar to that practised at other centres. Following induction of general anaesthesia, an experienced anaesthetist introduces a double lumen endobronchial tube. A careful check is made to ensure that the two lungs are isolated. Both lungs are ventilated with 100% oxygen for at least 20 minutes to eliminate nitrogen from the alveolar gas. The lung to be treated is then isolated at the end of expiration. The volume of that lung at the end of expiration is estimated to be equal to the functional residual capacity (FRC). The volume of oxygen is gradually absorbed from the non-ventilated lung at a rate of approximately 100 ml/min. Warm (36–37°C) neutral sterile saline (0.9% saline with 0.6 mmol sodium bicarbonate per litre saline) is instilled into the lung through a closed system at the same rate as oxygen is absorbed until the estimated FRC value has been reached. At this point the lung is completely de-gassed and full of saline. Tidal volume increments (500–1200 ml) of the saline are let into the lung under gentle gravitational force—that is, a saline column of not more than 50 cm—and then let out again via the closed system into a measuring cylinder. The temperature, volume of saline instilled, and fluid balance is carefully controlled. The initial returns are typically very milky or turbid and the process of filling and draining the lungs with saline is repeated until the effluent becomes clear. Total volumes of saline required can range from 20 to 40 l. At the end of the procedure the residual saline is drained and aspirated from the lung and ventilation with 100% oxygen is resumed. The double lumen tube is replaced by an endotracheal tube and the patient transferred to the recovery unit for approximately one hour of postoperative ventilation. The temperature, volume of saline instilled, and fluid balance is carefully controlled. The initial returns are typically very milky or turbid and the process of filling and draining the lungs with saline is repeated until the effluent becomes clear. Total volumes of saline required can range from 20 to 40 l. At the end of the procedure the residual saline is drained and aspirated from the lung and ventilation with 100% oxygen is resumed. The double lumen tube is replaced by an endotracheal tube and the patient transferred to the recovery unit for approximately one hour of postoperative ventilation. At the end of this recovery time any residual neuromuscular block is antagonised and the patient is awakened and extubated. Patients are transferred back to the ward within the following hour.

It has recently been possible to perform bilateral sequential whole lung lavage in the same treatment session. The principles are identical except that at the end of the lung lavage of the first lung a decision is made on the ability of the patient to tolerate one lung ventilation of the lung that has just been treated. The second lung is then isolated and treated as described above.

The process of whole lung lavage is slow (2–4 h) and requires an experienced theatre
Pulmonary alveolar proteinosis can occur with rapid instillation of large volumes of fluid. Other reported complications include pleural collections, hydropneumothoraces, and surgical emphysema. The risk of hypothermia is minimised by careful monitoring of the patient’s core temperature. The patient lies on a heated mattress and is covered with a convective heated blanket. The lavage fluid temperature is controlled using an in-line heat exchanger.

**SAFETY OF WHOLE LUNG LAVAGE**

The major adverse effect from whole lung lavage is hypoxaemia which can be improved by ventilation with a high inspired oxygen concentration. Arterial oxygenation improves during the filling phase due to the increase in airway pressure and shunting of blood to the contralateral ventilated lung. Emptying of the lung causes a decrease in airway pressure and perfusion of the surfactant due to its potential to exacerbate opportunistic infections. Corticosteroids should not be used as empirical treatment for alveolar proteinosis due to its potential to exacerbate opportunistic infections. The development of interstitial fibrosis in patients with pulmonary alveolar proteinosis has been reported in isolated cases, though whether this is a causal finding or coincidental occurrence is uncertain. One patient died from progressive pulmonary fibrosis. Other rare reports include the development of emphysematous bullae, pneumothorax, and asphyxia due to alveolar flooding in a patient during general anaesthesia.

The overall prognosis for alveolar proteinosis treated by whole lung lavage is excellent. There are also several reports of spontaneous resolution, and series prior to the introduction of whole lung lavage quote spontaneous improvement in up to 25% of patients.
Pathogenesis
NORMAL SURFACTANT HOMEOSTASIS
Surfactant homeostasis is a complex dynamic process involving alveolar type II cells and macrophages. The hydrophobic (surfactant proteins B and C) and hydrophilic (surfactant proteins A and D) proteins associated with the surfactant and the phospholipids are synthesized and secreted mainly by alveolar type II cells. The importance of surfactant proteins B and C (SP-B and SP-C) in surfactant homeostasis is well established from findings such as their ability to accelerate the adsorption of lipids to an air-liquid interface. The roles of SP-A and SP-D on lipid interactions is less clear.

The freshly synthesized surfactant complex is packaged in lamellar bodies within alveolar type II cells and then released from these intracellular storage granules into the liquid hypophase covering the alveolar epithelium. The material secreted from the lamellar bodies is transformed by an as yet ill-defined pathway into a lattice like structure known as tubular myelin. From this structure the phospholipids spread over the epithelial surface to form a monolayer film, rich in dipalmitoylphosphatidylcholine, which reduces the surface tension forces tending to collapse the lung. Alveolar type II cells and alveolar macrophages have an important role in uptake, degradation, and recycling of surfactant. Surfactant protein A may play a part in the re-uptake of phospholipids and regulate the secretion of surfactant but its precise role remains unclear. The lipid monolayer also regulates secretion of phospholipid, presumably by altering exocytosis. This process is influenced by the amount of saturated phospholipid in the lipid monolayer.

MACROPHAGE FUNCTION IN PULMONARY ALVEOLAR PROTEINOSIS
Alveolar macrophages in pulmonary alveolar proteinosis have defective chemotaxis, phagocytosis, and phagolysosomal fusion. These defects are thought to be acquired since normal macrophages develop impaired phagocytic activity following incubation with lavage fluid from patients with pulmonary alveolar proteinosis. The lipoproteinaceous material also acts as a scavenger for free radicals and hence impairs the oxidative burst that occurs in macrophages during phagocytosis. Binding of SP-A and SP-D to the collectin receptor on alveolar macrophages initiates the oxidative burst in macrophages and enhances phagocytosis. Surfactant proteins bind to various bacteria, influenza A virus, and Cryptococcus neoformans and this facilitates the uptake of these organisms by alveolar macrophages. The important role of surfactant proteins in host defence may explain the higher incidence of opportunistic infections associated with pulmonary alveolar proteinosis.

DISEASE ASSOCIATIONS
A number of cases of pulmonary alveolar proteinosis have been described in association with other diseases or a definite aetiological agent and have been termed secondary pulmonary alveolar proteinosis. Secondary pulmonary alveolar proteinosis can be distinguished from primary or idiopathic disease on the basis of the staining pattern of surfactant specific apoproteins in histological specimens. In primary cases a uniform staining pattern is seen while in the secondary form of the disease a patchy focal pattern occurs. Pulmonary alveolar proteinosis has been described in association with immunodeficiency states and haematological malignancies. It is more common in myeloid leukaemias but has also been reported in lymphomas, Fanconi’s anaemia, and IgG monoclonal gammopathy. The overall incidence of secondary pulmonary alveolar proteinosis in patients with haematological malignancies is 5.3%, though it is higher in neutropenic patients (8.8%) and in those with acute myeloid leukaemia (10%). However, most cases are mild and require no intervention. Treatment of the underlying condition may produce improvement but whole lung lavage may need to be considered in patients who are very symptomatic.

In a number of cases of pulmonary alveolar proteinosis following exposure to a variety of mineral dusts and drugs such as iprindole. One study reported greater amounts of birefringent particles in lung tissue in over three quarters of patients with pulmonary alveolar proteinosis in comparison with controls. Specific reports have included exposure to aluminium dust, titanium, and drugs such as busulfan and chlorambucil. Similar changes have been reported in sandblasters exposed to high levels of silica dust.

Animal experiments have reproduced the pathological features of pulmonary alveolar proteinosis following exposure to a variety of mineral dusts and drugs such as iprindole. However, extrapolating the experimental model to the human disease is difficult, especially as effects of agents are specific to species and dependent on dose and environmental conditions.

GENETIC PREDISPOSITION
Congenital alveolar proteinosis was identified as an autosomal recessive inherited deficiency and a deficiency in SP-B was subsequently identified as the cause of the disease. Further studies have revealed two mutations in the SP-B gene, a frameshift mutation consisting of a substitution of three bases (GAA) for the single nucleotide C in codon 121 (121ins2) and a deletion of one base pair at (122delT), resulting in a premature stop codon and the absence of SP-B in surfactant. Congenital alveolar proteinosis is a genetically heterogeneous disease exhibiting a wide range of phenotypic variations which implicates the involvement of other loci or novel SP-B mutations in its manifestations.

Studies on cells cultured from patients with congenital alveolar proteinosis with normal SP-B protein levels have found normal levels of granulocyte colony stimulating factor (GM-
Pulmonary alveolar proteinosis

includes pulmonary inflammation and alveolar growth and influence the regulation of haemopoietic cell the ubiquitin machinery which is thought to

GM-CSF signalling. The evidence also suggests that surfactant clearance is affected by defects in GM-CSF receptor signalling. Defective GM-CSF receptor expression has been observed on leukocytes in acute myeloid leukaemia and may account for the high incidence of pulmonary alveolar proteinosis in this condition. The fourth gene implicated in alveolar proteinosis is at the Ich locus; it encodes a gene product of the ubiquitin machinery which is thought to influence the regulation of haemopoietic cell growth and differentiation. Disruption of this locus leads to a complex fatal disease which includes pulmonary inflammation and alveolar proteinosis.

HYPOTHESIS OF DISEASE MECHANISMS IN PULMONARY ALVEOLAR PROTEINOSIS

The complex process of surfactant homeostasis, the occurrence of at least two different congenital forms, and the presence of different animal models suggest that pulmonary alveolar proteinosis represents a clinical syndrome rather than a single disease.

Deficiency or complete lack of SP-A is unlikely to be implicated in the pathogenesis of pulmonary alveolar proteinosis as illustrated by the murine models, but structural abnormalities of surfactant proteins may cause an imbalance in the surfactant life cycle. Surfactant proteins have a complex structure with distinct binding domains, and structural abnormalities that allow them to interact but not activate receptors may interfere with surfactant homeostasis. Abnormal oligomers of SP-A have been identified in patients with pulmonary alveolar proteinosis. Abnormal multi-merised SP-A isolated from patients with pulmonary alveolar proteinosis failed to form tubular myelin and had a lower affinity to bind to type II cells. The multi-merised oligomer was a less effective inhibitor of lipid secretion. It is unclear whether the abnormal proteins are a consequence of alveolar stasis or the primary defect. The complex protein structure may be susceptible to denaturation and may explain the association of some cases of pulmonary alveolar proteinosis with exposure to high levels of inhaled minerals and chemicals.

The presence of an antagonist for the surfactant protein receptors would be expected to have much the same effect. The removal of abnormal oligomers of surfactant proteins or receptor antagonists may explain the gradual improvements observed after lung lavage. Differential changes in surfactant composition leading to a greater decrease in SP-A following lung lavage also support this hypothesis. The various surfactant components have differing clearance rates and changes in composition following lavage suggests a restoration of normal surfactant homeostasis.

Evidence from the murine models and the occurrence of pulmonary alveolar proteinosis in haematological malignancy suggests that imbalances in cytokines, particularly IL-10 and GM-CSF, may lead to abnormal surfactant metabolism. Investigation of GM-CSF expression in one patient with pulmonary alveolar proteinosis suggested that expression of messenger RNA for GM-CSF was normal but there was a failure to secrete GM-CSF. This study demonstrated high basal levels of IL-10, a potent inhibitor of cytokine secretion at the transcription level and the addition of IL-10 antibody normalised secretion of GM-CSF. These results are beginning to illustrate the complex role of cytokines in surfactant homeostasis. Secretagogues also regulate the number of cellular receptors acting through protein kinase C or cyclic AMP pathways to raise cytosolic Ca²⁺ levels. Abnormalities in intracellular processing and expression of receptors may also lead to abnormal surfactant homeostasis.

In murine models bone marrow transplantation reverses the intra-alveolar accumulation of surfactant but the lymphocytic infiltrate persists. Lung transplantation has been considered for some individuals with alveolar proteinosis but there is a report of recurrence following double lung transplantation. This suggests that a systemic factor may be involved in some cases of the disease. It is possible that there is a defect in cellular mechanisms or receptor involving macrophages and type II pneumocytes. Correcting only one of these defects by lung transplantation or a bone marrow transplant may not lead to a complete cure. Furthermore, the spontaneous occurrence of alveolar proteinosis has been reported in patients following lung transplantation.

Future potential treatments

The murine models of GM-CSF deficiency emphasised the role of GM-CSF in surfactant homeostasis. One patient who failed to respond to lung lavage has been treated with recombinant GM-CSF with an improvement in exercise tolerance, partial clearing of alveolar infiltration on the chest radiograph, and an improvement in the P(A-a)O₂ gradient. There was reasonable evidence of efficacy in
this single case with a time course pattern of improvement in the P(A-a)O2 gradient following treatment with GM-CSF, deterioration on discontinuation of treatment, and improvement on resumption of treatment. The treatment of three further patients with GM-CSF has been recently reported in abstract form.111 Only one patient responded and the degree of improvement was similar to previous improvements seen with whole lung lavage in that individual. Potential side effects of GM-CSF are local reactions, fever, myalgia, headache, and flu-like reactions. More serious side effects include anaphylaxis, cardiac failure, and leaky capillary syndrome. Other disadvantages are the need for a daily subcutaneous injection and the high cost of GM-CSF.

Gene therapy may be a future treatment option in patients with specific genetic defects. This may include patients with a congenital abnormality of surfactant protein B118–119 and defect in the β chain of the common receptor for GM-CSF/IL-3/IL-5.120 Other genetic disorders are likely to exist as illustrated by the gene micrographs used in this publication. The authors thank Ann Dewar for providing the electron micrographs used in this publication.

Summary

Pulmonary alveolar proteinosis represents a syndrome with a number of possible aetiologies. The appearances on the HRCT scan of the thorax will often suggest the diagnosis and should be confirmed by examination of bronchoalveolar lavage fluid. Whole lung lavage appears to be the most effective form of treatment and is a safe technique in experienced hands. The overall prognosis is excellent with treatment. A few patients are resistant to whole lung lavage. It is important to investigate these non-responders further as they may respond to some of the more targeted treatments.

The authors thank Ann Dewar for providing the electron micrographs used in this publication.

Pulmonary alveolar proteinosis


140 Kuroda Y, Mason RJ, Voelker DR. Alveolar type II cells express a high affinity receptor for the pulmonary surfactant protein A. Proc Natl Acad Sci USA 1988;85:5566–70.


Pulmonary alveolar proteinosis


Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis

Pallav L Shah, David Hansell, Peter R Lawson, Kenneth B M Reid and Cliff Morgan

Thorax 2000 55: 67-77
doi: 10.1136/thorax.55.1.67

Updated information and services can be found at:
http://thorax.bmj.com/content/55/1/67

These include:

References
This article cites 185 articles, 36 of which you can access for free at:
http://thorax.bmj.com/content/55/1/67#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Collections
Articles on similar topics can be found in the following collections

Pulmonary alveolar proteinosis (12)
Child health (843)
Tobacco use (youth) (191)
Health effects of tobacco use (211)
Health education (1223)
Smoking (1037)
Tobacco use (1039)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/