Diffuse pulmonary angiomatosis

G J Canny, E Cutz, I B MacLusky, H Levison

Abstract

A six year old girl with diffuse pulmonary angiomatosis presented with haemoptysis and diffuse interstitial changes with bilateral pleural effusions on the chest radiograph. The lung lesion as seen on biopsy specimens (and confirmed at necropsy) consisted of bloodless, thin walled, endothelium lined channels, affecting the interstitial septae, pleura, bronchi, and adventitia of large vessels. There was no response to oral corticosteroids or a trial of cyclophosphamide. This lesion may be an example of an angioendothelial diseases. Benign proliferation of the pulmonary vascular tissue is a rare lesion, which usually presents as a solitary nodule—that is, a benign haemangiomatosis. Diffuse pulmonary haemangiomatosis, characterised by proliferation of blood filled vascular spaces, is even less common. This entity has been described mainly in neonates as part of a generalised process affecting the skin, mucous membranes, and visceral organs ("miliary haemangiomatosis"). A variant of this condition, in which the endothelium lined spaces contain no blood, has been referred to as "angiomatosis" (hamartomatous haem-lymphangiomatosis) by Koblenzer et al. These authors used the term "angiomatosis" in view of the uncertain histological origin of the abnormal vascular channels.

There are only a few reported cases of haemangiomatosis affecting the lung tissue primarily. Rowen et al. described three cases of diffuse "cavernous" haemangiomatosis of the lung, and a 12 year old boy with mixed capillary and cavernous haemangiomatosis of the lung was reported by White et al. We describe a six year old girl who died of a diffuse vascular proliferative lesion, largely confined to the lungs and pleura and not associated with cutaneous lesions. Although in clinical presentation, radiological findings, and fatal outcome our case resembles those reported by Rowen et al., the histological appearance of our patient’s pulmonary lesion was that of angiomatosis as the abdominal vascular spaces appeared empty.

Case report

A six year old black girl presented with haemoptysis (100 ml) and a chronic, non-productive cough of two years’ duration. She had no other symptoms. The family history was non-contributory. Physical examination showed a well nourished patient in no acute distress. Her temperature was 38.5°C, pulse 84/min, blood pressure 120/80 mm Hg, and respiratory rate 24/min. She was not cyanosed, but had finger clubbing and crackles over the lower lung fields. A chest radiograph showed a diffuse interstitial infiltrate and blunting of the costophrenic angles (fig 1) but normal cardiac size and no hilar lymphadenopathy. A tentative diagnosis of pulmonary haemosiderosis (primary or secondary) was made.

Investigations

The haemoglobin concentration was 117 g/l, the white cell count 12 x 109/l with a normal differential, the platelet count 140 x 109/l, and the erythrocyte sedimentation 6 mm in one hour. Serum electrolyte, urea, and creatinine concentrations and a coagulation profile were normal and urine analysis gave normal results. Serological tests (for antinuclear factor, rheumatoid factor, and antiremuneum end membrane antibodies) gave negative results. An electrocardiogram and echocardiogram were normal. A sweat test and a tuberculin (purified protein derivative, 5 TU) skin test gave negative results. Cytological examination of sputum showed occasional haemosiderin laden macrophages, but no acid fast bacilli were identified. Pulmonary function studies showed a restrictive ventilatory defect (forced vital capacity (FVC) 56% predicted, forced expiratory volume in one second (FEV1) 59% predicted; FEV1/FVC ratio 88%). An open lung biopsy was performed in the hope of obtaining a definitive diagnosis. This showed pronounced thickening of the pleura and pulmonary septa by fibrous tissue with an abnormal proliferation of empty vascular channels throughout the lung. These channels, which were lined with a single layer of endothelial cells, had variable amounts of fibrous tissue and irregular bundles of smooth muscle in the walls. Areas of haemorrhage, intra-alveolar oedema, and aggregates of chronic inflammatory cells were noted within the pulmonary parenchyma, and pulmonary macrophages stained positively for iron. The pathological findings were thought to be consistent with a diagnosis of diffuse pulmonary lymphangiomatosis or haemangiomatosis.

Subsequent course

The patient was treated with oral corticosteroids (prednisone 3 mg/kg/ day) for 10 weeks. She developed a persistent cough, daily haemoptysis, and considerable
Microscopically, the abnormal vascular proliferation seen in lung biopsy specimens was present in all sections of both lungs. These thin walled, endothelium lined channels with empty lumina were most prominent in the subpleural regions and the pulmonary septa and particularly in the pulmonary hila, where they appeared in the adventitia of the pulmonary arteries and veins (fig 2). Focal clusters of loosely arranged spindle cells were observed in the perivascular tissue (fig 2, insert). Immunohistochemical studies on these cells showed staining for vimentin and actin (markers of mesenchymal cells), with only occasional cells positive for factor VIII (a marker for endothelial cells). These abnormal vascular channels were also seen in the walls of the bronchi, extending to the basement membrane of the respiratory epithelium. Areas of pulmonary oedema and haemorrhage were noted. Both pleural cavities contained blood, and extensive fibrous adhesions were present. Abnormal vascular proliferation was also found in the mediastinum, the pericardium, and the adventitia of the great arteries and in the peripancreatic adipose tissue.

Discussion
Our patient had diffuse angiomatosis of the lung, mediastinum, pericardium, great vessels, and peripancreatic adipose tissue. The non-committal term “angiomatosis” is used as it was not entirely clear whether this lesion originated from the haematogenous or the lymphatic system. Within the lungs the angiomatous lesions primarily affected the pleura, the interlobular septae, and the walls of the bronchi, pulmonary arteries, and veins. This distribution accounts for the substantial interstitial infiltrate and pleural thickening seen radiographically. The angiomatous process was non-malignant in nature, and there was no inherited basis for the condition. Several reports have described young infants with diffuse haemangiomatosis, affecting mucocutaneous surfaces as well as multiple internal organs. The prognosis for such infants is generally poor because of the development of complications—for example, congestive heart failure, consumptive coagulopathy, severe bleeding, and compression of vital organs. Rowen et al described three children (2.5–7 years of age) with diffuse haemangiomatosis of the lungs and pleura without concomitant skin lesions. In these patients the clinical and radiographic findings were virtually identical to those in our case and, despite systemic corticosteroid treatment, they died of their disease several years after diagnosis. The histopathological findings in our case, however, differed somewhat from those described by Rowen et al in that the abnormal channels contained no blood—that is, a haemangiomatous component was absent. Rowen et al suggested that, once a malignant process has been excluded, the combination of diffuse interstitial lung disease and bloody pleural effusions in a child is pathognomonic of pulmonary haemangiomatosis. Diffuse pulmonary haemangiomatosis and

exercise intolerance over this time. The pleural effusions increased in size, and severe restrictive lung disease developed (FVC 24% predicted). Corticosteroids were discontinued, and she was given a four day course of cyclophosphamide (1 mg/kg/day) intravenously. She developed severe respiratory distress after two weeks, however, with an increase in the right pleural effusion on the chest radiograph. She subsequently died of respiratory failure.

Necropsy findings A postmortem venogram was performed in an attempt to discover the origin of the abnormal vascular channels. This showed normal distribution of barium into the large pulmonary veins, and microscopically the injected barium was seen within veins, venules, and capillaries in the expected locations. The abnormal vascular spaces were devoid of barium, however, indicating that they were not connected to the venous system.

Figure 2 Low magnification view of an area of interlobular septum between alveolar tissue (Alv) and the pulmonary artery (PA) wall. The septum is expanded with irregularly shaped channels with empty lumina. A focal area of spindle cell proliferation is located near pulmonary artery (arrow). (Haematoxylin and eosin). Inset Close up of spindle cells around the adventitia of the pulmonary artery. (Haematoxylin and eosin).
Diffuse pulmonary angiomatosis need to be differentiated from pulmonary capillary haemangiomatosis, seen in older children and adults. The latter is characterised by proliferation of capillary sized channels that infiltrate the lung interstitium and the walls of vessels and airways and leads to death from progressive pulmonary hypertension. Although the exact cause of these pulmonary vascular disorders is not clear, it has been suggested that they may represent an angiogenic disease—that is, lesions arising from non-neoplastic microvascular proliferation. The concept of angiogenic disease is based on the discovery and characterisation of several angiogenic polypeptides that can stimulate or inhibit capillary growth and differentiation.

Several therapeutic strategies have been attempted in diffuse angiomatosis. Although corticosteroids have been reported to shrink haemangiomas, this approach was unsuccessful in our patient, as in the cases of pulmonary haemangiomatosis described by others. Radiotherapy may also cause regression of haemangiomas, but this approach was not considered feasible in our patient in view of severe restrictive lung disease. Similarly, diffuse pleural lesions precluded lung transplantation as a therapeutic option. A trial of cyclophosphamide treatment was embarked on, in view of a previous report attesting to its effectiveness in disseminated life threatening vascular tumours. Unfortunately, this approach was unsuccessful, possibly because the beneficial effects of cyclophosphamide in these circumstances do not materialise for several weeks and repeated courses of cyclophosphamide may be necessary. In recent reports a therapeutic response to interferon, an antiproliferative agent, was obtained in three children with pulmonary haemangiomatosis.

Whether more patients with pulmonary haemangiomatosis will benefit from such treatment remains to be seen.

In summary, diffuse pulmonary angiomatosis is a rare clinical entity with an extremely poor prognosis. The possibility of this condition should be considered in a child with diffuse interstitial lung disease associated with increasing bloody pleural effusions.

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Achilles tendon rupture: an underrated complication of corticosteroid treatment

D M Newnham, J G Douglas, J S Legge, J A R Friend

Abstract

Ten patients attending outpatient clinics who were taking oral corticosteroids ruptured their Achilles tendon in the course of 12 years. It is suggested that Achilles tendon rupture is a complication of corticosteroid treatment.

Oral corticosteroid treatment has many side effects but Achilles tendon rupture is not widely recognised as one of them. Several patients with chronic airflow obstruction attending our hospital clinics were noted to have non-traumatic Achilles tendon ruptures while having long term oral corticosteroid treatment. We have reviewed our clinic population and found that during 12 years 10 patients had an Achilles tendon rupture related to steroid treatment.

Details of the patients

Details of the 10 patients and their episodes of tendon rupture are given in the table. Their mean age was 68-5 years and in every case the rupture occurred while they were walking on level ground. Rupture was diagnosed in five patients immediately after the sudden onset of pain in the Achilles tendon with local tenderness, swelling, and a palpable discontinuity that was sometimes visible. Extensive subcutaneous bruising developed around the ankle and extended over the dorsum of the foot within hours. The remaining patients presented some weeks after the onset of