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CASE REPORT

Pulmonary alveolar microlithiasis and lymphocytic interstitial pneumonitis in a ten year old girl

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Pulmonary alveolar microlithiasis and lymphocytic interstitial pneumonitis in a ten year old girl. FA. Ratjen, B. Schoenfeld, H.G. Wiesemann.
ABSTRACT: Pulmonary alveolar microlithiasis (PAM) is a rare lung disease, characterized by progressive formation of intra-alveolar calculi in response to an unknown stimulus. We report an unusual presentation of PAM in a 10 year old girl with clinically significant interstitial lung disease and histological evidence of both PAM and lymphocytic interstitial pneumonitis. A rapid improvement of pulmonary function and exercise tolerance was seen in response to glucosteroid therapy.
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Pulmonary alveolar microlithiasis (PAM) is a rare disease of unknown cause that is usually diagnosed in adulthood [1]. The disease is characterized by calcium phosphate microliths filling the alveoli [2]. Changes in the interstitium surrounding the alveoli are not found until late in the disease, when fibrosis is a common feature [1]. The diagnosis is often made by chest X-ray at a time when the patient is still asymptomatic [2]. We report PAM in a 10 year old girl in whom clinical presentation and histological findings differed from those reported in the literature.

Case report

A 10 year old girl was referred to our cardiology department by her paediatrician, with a seven month history of dyspnoea on exertion and a dry unproductive cough. No diagnostic procedures had been undertaken prior to the referral. Previously, the patient had been in excellent health and her development in early childhood had been normal. She had had measles and scarlet fever but not Varicella. There was no evidence of allergy; no contact with birds or pets was reported. The patient had never travelled to a foreign country. There was no history of respiratory tract infection in the past 12 months. The family history was noncontributory. On physical examination the patient showed mild peripheral cyanosis and mild clubbing. Auscultation of the lung revealed end-inspiratory crackles. There was marked dyspnoea on exertion. On capillary blood gas analysis at rest, (Pao_2) was 57 mmHg (7.6 kPa) and arterial carbon dioxide tension ($Paco_2$) 38 mmHg (5.1 kPa) with a normal pH and bicarbonate; oxygen saturation was 90%. An exercise test had to be stopped at 25 W because the oxygen saturation measured by pulse oximetry fell to 65%. Spirometry revealed marked pulmonary restriction with a reduction of vital capacity to 0.3 *l* (24% predicted) and of total lung capacity to 0.79 *l* (47% predicted). Prominent features on chest X-ray were bilateral reticular pulmonary densities (fig. 1).

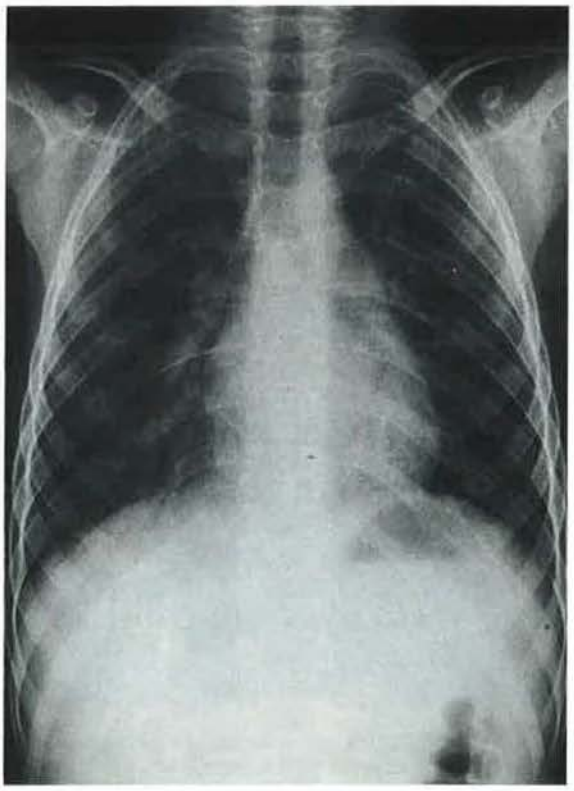

Fig. 1. – Chest X-ray at the time of diagnosis.

Bronchoalveolar lavage (BAL), performed in the medial segment of the middle lobe, showed a relative increase of both lymphocytes and granulocytes (table 1). In addition, activated T-lymphocytes and natural killer cells were above the normal range for adults. The CD4+/CD8+ ratio was normal. No microliths were seen in the BAL fluid.

Table 1. – Differential cytology and lymphocyte typing of bronchoalveolar lavage fluid

	Results	Normal
Differential cytology %		
Macrophages	26	>84
Lymphocytes	42	<13
Granulocytes	33	<3
neutrophils	19	<3
eosinophils	14	<0.5
mast cells	0.1	<0.5
Lymphocytic surface markers	**% of lymphocytes**	
B-cells	3	<4
T-total (CD3)	78	63–83
T-helper (CD4)	47	40–70
T-suppressor (CD8)	40	20–40
CD4+/CD8+	1.2	1.1–3.5
NK cells (Leu7)	20	2–14
Activated T-lymphocytes	26	<6
IL-2 receptor+	1.5	<6

NK: natural killer; IL-2: interleukin-2.

An open lung biopsy was performed by left lateral thoracotomy. The lung was poorly aerated and felt dense on palpation. No calcifications were observed macroscopically. A part of the lingula was resected for histological examination. Haematoxylin and eosin stained sections showed marked widening of the pulmonary interstitium caused by lymphocytic infiltrates (fig. 2). In addition, numerous alveoli were filled with small calcifications (fig. 2). Some of these calcifications were surrounded by foreign body giant cells.

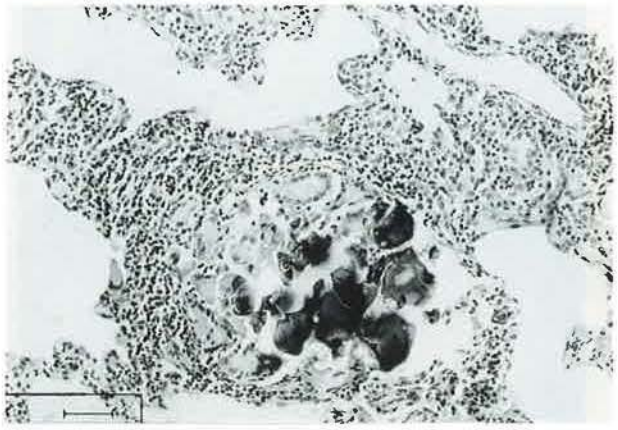

Fig. 2. – Haematoxylin and eosin stained histological slide of the lung. Marked widening of the interstitium with lymphocytic infiltration is seen, as well as multiple intra-alveolar calcifications. The internal scale marker equals 100 μm.

Staining of collagen material revealed a minor degree of interstitial fibrosis. The histological findings were compatible with pulmonary alveolar microlithiasis and lymphocytic interstitial pneumonitis.

Treatment with prednisone (2 mg·kg^{-1} body weight *q.d.*) for lymphocytic interstitial pneumonitis was initiated. The patient showed rapid improvement clinically and in spirometric values as illustrated in figure 3. After four months of treatment the patient reported a normal exercise tolerance. The chest X-ray was unchanged. Blood gases at rest were normal, whilst spirometry still revealed a restrictive pattern with a diminished vital capacity (fig. 3).

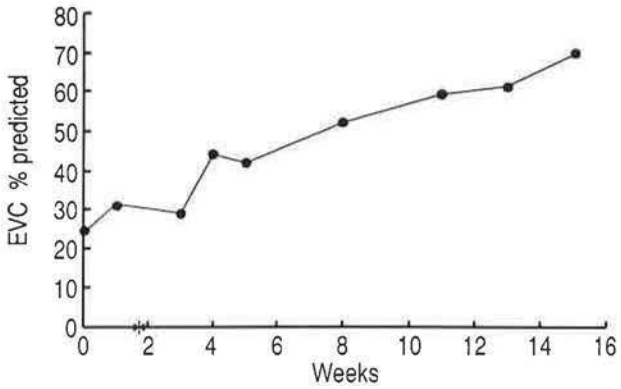

Fig. 3. – Expiratory vital capacity (EVC) as percentage predicted in the course of the illness. The asterisk on the time scale marks the date when steroid therapy was started.

Discussion

Pulmonary alveolar microlithiasis (PAM) is a rare disease of unknown origin; approximately 130 cases have so far been reported in the literature [2]. The disease has been found in all age groups, including premature infants, but the mean age of diagnosis in Western countries is 30–40 yrs [2, 3]. An increased frequency of the disease has been found in relatives of patients, but this appears to be limited to their siblings [4, 5]. PAM shows an equal distribution among both sexes [1]. Histology is usually not obtained in typical cases, where the diagnosis can be made by chest X-ray [2]. When obtained, calcium phosphate deposits ranging in size from 0.1–2.5 mm are seen in the alveoli. Patients are usually asymptomatic early in the disease or have only unspecific pulmonary symptoms [2]. The disease can be stable for decades but eventually leads to pulmonary insufficiency and death [2]. On progressive disease, pulmonary fibrosis becomes a common feature.

Intra-alveolar calculi are also seen as degenerative changes after Varicella pneumonia, which is the most important differential diagnosis. No treatment of PAM has been found to influence the progression of the disease; both steroids and therapeutic bronchoalveolar lavage have been tried unsuccessfully [6].

Our 10 year old patient showed a number of features that differ from those reported in previous

cases. Firstly, she was clinically ill at the time of presentation, with evidence of marked pulmonary restriction and exercise intolerance. Secondly, because of the small size of the calcifications, they were not seen on the chest X-ray, which rather suggested an interstitial pulmonary disease. Thirdly, the histological examination showed a lymphocytic interstitial pneumonitis (LIP) in addition to the changes of PAM. No similar case has yet been reported but Costabel (personal communication) found an increase in lymphocytes and granulocytes in BAL fluid in an adult female with PAM.

Whilst the basic defect causing PAM remains elusive, some theories regarding its pathogenesis have been proposed. Since calcium is less soluble at higher pH, it has been speculated that an undefined process leading to alkalization of the alveoli would trigger the deposition of calcium [7]. Although LIP, as an inflammatory disease of the interstitium, can be expected to damage the epithelial barrier, there are no data suggesting that it increases alveolar pH. Alternatively, secondary calcification of desquamated epithelial cells has been postulated to result in PAM [8]. Whilst this may have occurred earlier in the disease in our case, we did not find evidence of epithelial desquamation in the biopsy specimens. Calcifications have not been described in other cases of paediatric LIP. LIP itself is an uncommon disease in childhood, except for patients with the acquired immune deficiency syndrome (AIDS), when it has been linked to Epstein-Barr virus (EBV) infection [9]. The girl presented had neither AIDS nor EBV infection and no evidence of any other viral infection was found at the time of referral to our hospital. Unfortunately, no viral studies were performed at the time of initial complaints.

It therefore remains possible that the disease has been triggered by an infectious agent. Regardless of the underlying mechanism, one would expect that the calcifications are related to the inflammatory process in the interstitium. Whether the histological changes seen represent an earlier form of PAM, which eventually will evolve to its typical presentation, remains to be determined by the further course of the illness in this child.

In summary, we have reported a case of pulmonary alveolar microlithiasis, in association with lymphocytic interstitial pneumonitis, in a 10 year old girl. The patient was treated with steroids and showed rapid improvement in pulmonary function and exercise tolerance.

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