Isolated pulmonary histiocytosis

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SUMMARY Pulmonary disease in the 'histiocytosis syndromes' is not uncommon. Isolated pulmonary histiocytosis, however, is rarely diagnosed. We describe three patients with this condition, with ages ranging from 3 weeks to 9½ years, in whom there was no evidence of disease in any other organ. Their presentation, treatment, and clinical progress over three years of follow up are discussed.

Pulmonary histiocytosis most commonly occurs as part of multisystem disease by histiocytosis X. Disease limited to the lung is recognised as a cause of interstitial lung disease in adults¹ but has not been extensively reported in children.

We report here three cases of isolated pulmonary histiocytosis and describe their clinical course in the three years since diagnosis.

Case reports

Case 1. A 2 month old boy presented with a clinically diagnosed bronchopneumonia. Persistent cough and breathlessness were accompanied by poor feeding, vomiting, and weight loss. On examination he was tachypnoeic, not cyanosed, but crepitations were audible over both lung fields. A chest radiograph showed soft hazy infiltrative changes in both lungs, which were more noticeable on the left (fig 1). He was treated with antibiotics and chest physiotherapy with some resolution in his symptoms. At 4 months of age he had a further exacerbation of breathlessness that was accompanied by wheezing and cyanosis. A further chest radiograph showed asymmetrical fine reticular infiltration of the left lung. Isotope lung scanning showed normal perfusion, but diminished ventilation in the right lung. Histological examination of a specimen from an open lung biopsy of the left lower lobe showed diffuse proliferation of histiocytes between alveoli and around terminal bronchioles; this was compatible with a diagnosis of pulmonary histiocytosis X.

After a course of treatment with vinblastine, prednisolone, and etoposide (VP16) there was a definite improvement. Steroids were continued until the age of 15 months. At 3 years of age he remains free of symptoms and is on no treatment. Clinically

he has some chest overinflation with sternal prominence, and his height and weight are following the 50th and 10th centiles, respectively. The most recent chest radiograph showed reticular shadowing in both lung fields in the upper and mid zones. Histiocytosis has not developed at any other organ site.

Case 2. A 3 week old girl first presented with a two day history of cough, breathlessness, and slow feeding. She was feverish and had signs of respiratory distress with widespread crepitations and wheezes over both lungs. The rest of the examination was normal. A chest radiograph showed patchy shadowing in the right upper zone and antibiotics

Fig 1 Chest radiograph of case 1, aged 2 months at the time of presentation, showing soft hazy infiltrative changes, most noticeable in the left lung.

were prescribed for what was thought to be bronchopneumonia. Her condition improved but she was readmitted two weeks later with a similar illness and this was followed by a further six episodes warranting admissions during the first 13 months of life. There was severe failure to thrive with an appreciable fall off in weight. Medication including inhaled β_2 agonist bronchodilators, anticholinergic agents, antibiotics, and corticosteroids failed to show any improvement in her condition. Extensive investigations were performed; sweat chloride analysis and serum immunoglobulins gave normal results as did bronchography and a contrast oesophagogram. Serial chest radiographs showed widespread infiltrative changes and fine nodular shadows mainly in the upper and midzones of the left lung (fig 2). Isotope lung scanning showed mismatching with a greater diminution in ventilation than perfusion to these areas. At 11 months of age an open lung biopsy specimen showed infiltration of peribronchiolar and interalveolar walls by proliferating histiocytes. Full evaluation including bone marrow aspirate examination, plain radiograph skeletal survey, and isotope bone scan did not show evidence of histiocytosis at any other site. Treatment with prednisolone and vinblastine was given, but no improvement occurred until etoposide was substituted for vinblastine. There was then a noticeable improvement of respiratory symptoms and growth.

At 3 years 7 months of age, when clinically her symptoms were well controlled, a respiratory arrest occurred at home and the child was brought into

Fig 2 Chest radiograph of case 2, showing widespread infiltrative changes and nodular shadows in the left lung.

hospital dead. At postmortem examination the findings showed pulmonary histiocytosis. Both upper lobes contained small emphysematous cysts beneath the pleural surface and numerous small yellow nodules. These nodules showed the histological features of histiocytosis X.

Case 3. A boy, aged 9½ years, was referred because he had had a recurrent cough for four months that had been unresponsive to inhaled β_2 agonist bronchodilator treatment. Physical examination was normal and initial chest radiograph showed only minimal perihilar streaking. Symptoms persisted and after a further three months the radiological

Fig 3 Chest radiographs of case 3: (a) at presentation showing perihilar streaking and (b) three years later: this shows the progression to fibrotic changes with partial lobar collapse and granularity in the right midzone.

features had progressed to extensive perihilar and paratracheal streaky infiltrative changes accompanied by loss of lung volume (fig 3a). On chest auscultation crepitations were present over both lungs, but there was no wheezing. Peak expiratory flow rate was 67% predicted for height, and did not improve significantly after inhaled bronchodilators. Further pulmonary function tests showed a reduction in vital capacity (45% predicted), more so than functional residual capacity (78% predicted, measured by helium dilution). This reduction occurred at the expense of increased residual volume so that the ratio of residual volume to total lung capacity was increased (38%). The ratio of forced expiratory volume in one second to forced vital capacity was normal (85%). This reflects a restrictive defect with evidence of gas trapping. Isotope lung scanning showed patchy decreased ventilation to the left base but normal perfusion. As a consequence of this mismatching he was hypoxaemic at rest (PaO_2 7.9 kPa). An open lung biopsy specimen showed infiltration of peribronchiolar tissue and alveolar walls by histiocytes and plasma cells. He has remained well with minimal respiratory symptoms, and there is no disease in any other organ system in the three years since diagnosis. Despite absence of symptoms and physical signs his pulmonary histiocytosis has progressed radiologically with more noticeable perihilar streaking and fibrotic changes leading to partial right lower lobe collapse (fig 3b). There are no clinical or electrocardiographic signs of pulmonary hypertension.

Discussion

Histiocytosis limited to the lung as described in these three cases is a rare cause of interstitial lung disease in childhood. The entity, histiocytosis X, encompasses an overlapping group of disorders that share the common histological features of proliferation of atypical histiocytes, but each disorder has widely different patterns of organ disease and a variable prognosis ranging from excellent to lethal.² The lungs are affected in 50% of children who have multisystem disease³ but much of what is known about isolated lung histiocytosis is based on the experience in adult practice of a relatively benign, frequently self limiting cause of interstitial pneumonitis in the young or middle aged.¹ Reports of 'primary pulmonary histiocytosis' in children⁴ and adults⁵ have included patients with histiocytosis disease at other organ sites outside the lung. To our knowledge there have been only three previous reports in children of lung histiocytosis X as the sole organ to be affected.⁶⁻⁸

Two of the children reported here presented early

in infancy with failure to thrive and persistent breathlessness. Both infants had presentations suggestive of alternative diagnoses and their initial chest radiographs were not typical of interstitial lung disease. Only later in the clinical course did nodular or reticular shadows become apparent, and these were accompanied by prominent perihilar streaking.

The usual radiographic features of primary pulmonary histiocytosis in adult patients are fine or coarse reticular or nodular infiltrates in the upper and midzones with notable sparing of the costophrenic angles.⁹ If the disease progresses small cysts or bullae appear and eventually there is fibrosis and 'honeycombing'.¹ Hilar lymphadenopathy is unusual. The radiological features of primary pulmonary histiocytosis are not specific enough to make the diagnosis in adult practice, and our experience in children would support this. Investigations, other than lung biopsy, were not of diagnostic value but are necessary to exclude important alternative diagnoses. Pulmonary function testing in adults has shown variable patterns but the most consistent abnormality has been depression of diffusion capacity reflecting disease of the alveolar capillary vasculature.¹ Isotope ventilation/perfusion scanning in two of our patients gave considerably abnormal results though certainly not specifically diagnostic for histiocytosis. In general ventilation was more impaired than perfusion, and the areas affected were more extensive than shown radiologically. Isotope scanning of this type may be of value in serially following affected children as it is apparent that clinical symptoms, signs, and radiological appearances do not necessarily parallel one another. Gallium 67 isotope scanning has been unhelpful in adult patients.¹⁰

The histology of histiocytosis in the lung is not essentially different between primary pulmonary histiocytosis and the disseminated disease. The lungs contain yellow or grey nodules and subpleural cysts, which are predominantly in the upper lobes and vary in size from 1 mm to 1.5 cm. The nodules contain mainly atypical histiocytes (Langerhans cells) and eosinophils with few lymphocytes. This infiltrate is mainly peribronchiolar but is also present in the alveolar wall and around small vessels and capillaries. Langerhans cells are not normally present in the alveolar wall and rarely present in the bronchial wall of the adult lung.⁹ Electron microscopy of Langerhans cells shows characteristic cytoplasmic organelles (Birbeck granules). On disease progression affected areas are replaced by fibrous tissue leaving characteristic stellate shaped scars.

It is now thought that histiocytosis X is a non-malignant proliferative disorder of the Langerhans cell system, and that histiocytes share numerous

morphological and biological features with macrophages. The Langerhans cell system can be regarded as a subpopulation of the mononuclear cell system and is closely allied to T cell populations and the lymphocytic immune system.^{11 12} Identification of Langerhan cells containing Birbeck granules can now be performed using the monoclonal antibody OKT6 and antibody to S100 protein.^{4 13}

Such is the apparent rarity of isolated pulmonary histiocytosis in children that it is likely that only the most severe or fatal cases will be reported, therefore conclusions about clinical features, treatment response, and natural history must be viewed with caution. In our experience there is an initial phase of prominent respiratory symptoms (and growth failure in infants) but radiological features are not typically nodular or reticular until later. After a variable period the symptoms improve considerably but radiological signs of the disease do not show any resolution and may even show a progression.

The cause of death in case 2 at the age of 3 years 7 months is unexplained by postmortem findings. Despite extensive pulmonary disease with cyst formation she appeared to have been symptom free for some while. We speculate that she suffered catastrophic pneumothoraces from rupture of a subpleural cyst; this is a complication of pulmonary histiocytosis occurring in up to 10% of adult cases.⁵

Unlike histiocytosis limited to other single organ sites where the prognosis is usually good, the prognosis for primary pulmonary histiocytosis in childhood is, at best, unpredictable. Based on current available information no strong recommendations can be made for the treatment of primary pulmonary histiocytosis, although a ther-

apeutic trial of steroids in symptomatic patients is justified.

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