An unusual case of an anterior mediastinal mass in a child with cystic lung disease

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Introduction

A seven-month-old, HIV-unexposed male, of a mixed race ethnicity, presented to a district hospital with a six-day history of progressive shortness of breath and increased work of breathing, associated with a two-day history of fever, vomiting, and pyrexia. He was also noted to have a diffuse vesicular rash thought to be varicella zoster. There was no history of night sweats; however, a poor appetite and weight loss was noted by the mother. The birth history was uneventful and all immunisations were up to date. He was exclusively breastfed for six months with solids introduced at seven months. Development was age appropriate and he was thriving prior to presentation. The chest radiograph showed a pneumothorax on the left (see Figure 1) and an intercostal drain was inserted.

He was transferred to a secondary level hospital where a differential diagnosis of varicella pneumonia or pneumonia secondary to Stahphylococcus aureus with pneumatoceles was made. Examination revealed a hyperpigmented papular vesicular rash with a symmetrical distribution mainly in the trunk, groin, neck, scalp, and both the hands and feet (Figure 2). The chest radiograph showed multiple cystic lesions with a possible mediastinal mass that filled the right hemithorax on the frontal projection. The computed tomography (CT) scan showed a heterogeneous enhancing large anterior mediastinal mass. No calcifications or cysts were noted (Figure 3). The mass extended from the thoracic inlet and was abutting the right hemidiaphgram. No compression of the vessels or airways was noted. There was also no mediastinal lymphadenopathy. Scattered throughout the lungs were multiple small and large walled cysts (Figure 4). The largest cysts were present in the lingula and caused mediastinal shift to the right. The child completed seven days of intravenous cloxacillin and acyclovir and was transferred to a tertiary centre for further diagnostic workup and management.

On arrival at the tertiary centre, he was found to be severely underweight. He was moderately distressed with respiratory rate of 55, ala flaring and subcostal recessions with an oxygen saturation of 95% on one litre of nasal prong oxygen. He had no lymphadenopathy and his skin had a disseminated healing rash with punched out lesions. The chest examination revealed a central trachea with dullness and decreased air entry on the right compared with the left. There was no hepatomegaly or splenomegaly. Investigations showed a raised white cell count with a microcytic anaemia and a normal erythrocyte sedimentation rate (ESR). Beta-human chorionic gonadotropin, alfa-feto protein, uric acid, and lactate dehydrogenase were normal (see Table 1).

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Investigations

Punch biopsies of skin from the left groin and upper back were submitted for histology. Microscopic sections showed fragments of intact skin with spongiotic, hyperkeratotic epidermis demonstrating an infiltrate of Langerhans cells within the superficial dermis (Figure 5). These cells had lobulated, folded vesicular nuclei and abundant eosinophilic cytoplasm. Occasional eosinophils were also seen (Figure 6). The Langerhans cells were positive with the immunohistochemical markers, S100 and CD1a. The overlying epidermis was spongiotic and the stratum corneum demonstrated

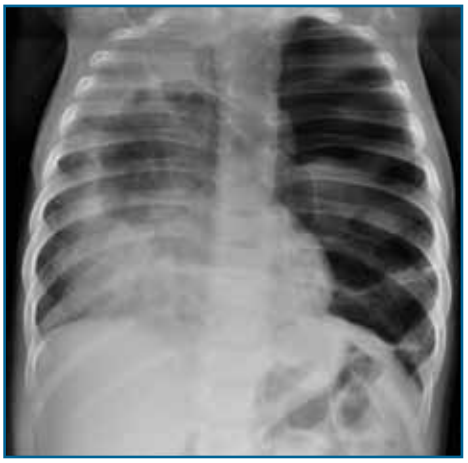

Figure 1: The initial chest X-Ray which demonstrates a pneumothorax on the left, with a diffuse opacity on the right side of the lung field

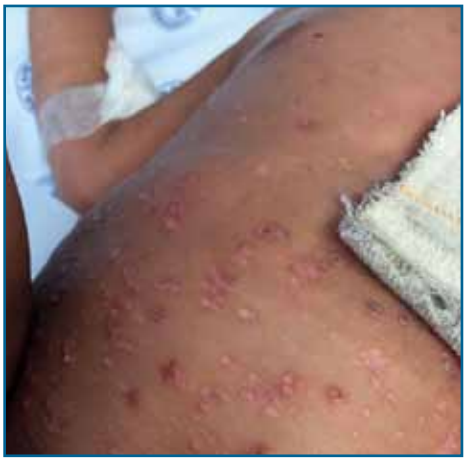

Figure 2: The diffuse rash that was initially treated as varicella zoster

hyperkeratosis, but ulceration was not seen.

A bone marrow trephine biopsy was very cellular and demonstrated morphological and immunohistochemical features suggestive of involvement by Langerhans cells/ Langerhans cell histiocytosis. The patient was commenced on chemotherapy which included prednisone and weekly vinblastine to which he showed a good initial response with regression of some of the skin lesions (Figure7). His clinical course, however, was complicated by recurrent pneumothorax on the left which required repeated intercostal drainage.

Full blood count (FBC)	White cell count: 19.56 x 109/L (n=6.00–18.00 x 10^9/L) Haemoglobin: 9.1 g/dL (n=10.1–12.9 g/dL) Mean corpuscular volume (MCV): 61.9 fL (n=70.0–86.0 fL) Platelet count: 521 x 109/L (n=140–35010^9/L) **Differential count** Neutrophils: 63.90 %; 12.50 x 109/L (n=2.00–5.50 x 10^9/L) Lymphocytes: 18.00 L%; 3.52 x 109/L (n=3.60–12.00 x 10^9/L) Monocytes: 17.90 %; 3.50 x 109/L (n=0.00–0.90 x 10^9/L) Eosinophils: 0.00 L%; 0.00 x 109/L (n=0.00–0.50 x 10^9/L) Basophils: 0.20 %; 0.04 x 109/L (n=0.00–0.20 x 10^9/L)
C-reactive protein (CRP)	5 mg/L (n=<10 mg/L)
TB gene Xpert	Negative
TB culture	Negative
Liver test (LFT)	Total protein=68 g/L (n=55–70 g/l) Albumin=35 g/L (n=28–48 g/L) Total bilirubin=5 µmol/L (n=5–21 µmol/L) Alanine transaminase=9 U/L (n=4–35 U/L) Alkaline phosphatase=179 U/L (n=82–383 U/L) Gamma-glutamyl transferase=15 U/L (n=1–39U/L)
Lactate dehydrogenase (LDH)	445 U/L (n=180–430 U/L)
Erythrocyte sedimentation rate (ESR)	7 mm/hr (n=0–10 mm/hr)
B-HCG (beta-human chorionic gonadotropin)	0 IU/L
Alfa-feto-protein	8.2 µg/L (n=0.6–28.3 µg/L)
Uric acid	0.33 mmol/L (n=0.09–0.39 mmol/L)
Blood culture	Negative
HIV Elisa	Negative

*Table 1: Relevant blood investigations (*n=normal value)*

Langerhans cell histiocytosis (LCH)

The presence of an anterior mediastinal mass with cystic lung disease, as in this child, is a rare presentation, however highly suggestive of Langerhans cell histiocytosis (LCH). LCH is a rare disease that results in monoclonal proliferation of the dendritic cell-related histiocytes.[1] The term eosinophilic granuloma has been used previously to describe local disease, whereas histiocytosis X, Letterer–Siwe disease, and Hand–Schüller–Christian disease have been used to describe the systemic form.[2]

LCH is part of a spectrum of histiocytic disorders that is classified into three classes.[3] Class 1, the dendritic cell disorders, includes LCH, secondary dendritic cell processes, juvenile xanthogranuloma, and solitary histiocytomas with a dendritic phenotype. Class 2 includes macrophage -related disorders and class 3 the malignant histiocytic disorders.[4]

Epidemiology

LCH is most common in children between one and four years of age with a peak incidence of about 0.1–1 per 100 000 children.[1] Males and females are equally affected with a higher frequency among Caucasians.[2,5] There are no genetic factors that affect the development of LCH and it is usually a sporadic illness.[2,5] A strong association between cigarette smoking and the development of pulmonary LCH has been described in adults; however, this association is not clear in children, neither is the effect of second-hand smoke exposure.[5,6]

Pathogenesis

In LCH, the histiocytes are morphologically and phenotypically similar to those of the Langerhans cells found in the skin as it expresses the same CD1a and CD207.[7-9] There is still a debate as to whether the clonal proliferation is due to a malignant transformation or is a result of an immunologic stimulus.[8,9]

Clinical features

LCH can be classified as single-system LCH (single organ involved) or multisystem LCH (two or more organs involved). In a retrospective analysis involving 1741 patients the following organs were involved: bone (77%), skin (39%), lymph nodes (19%), liver

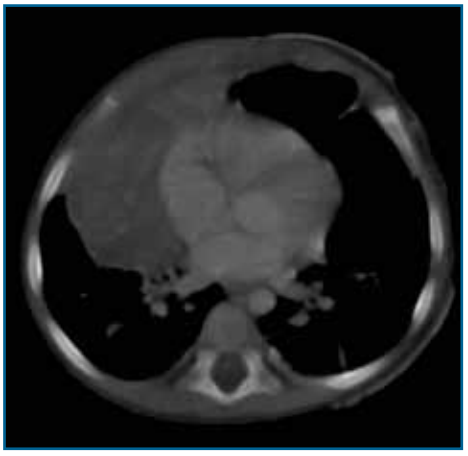

Figure 3: CT scan of the chest showing an anterior mediastinal mass

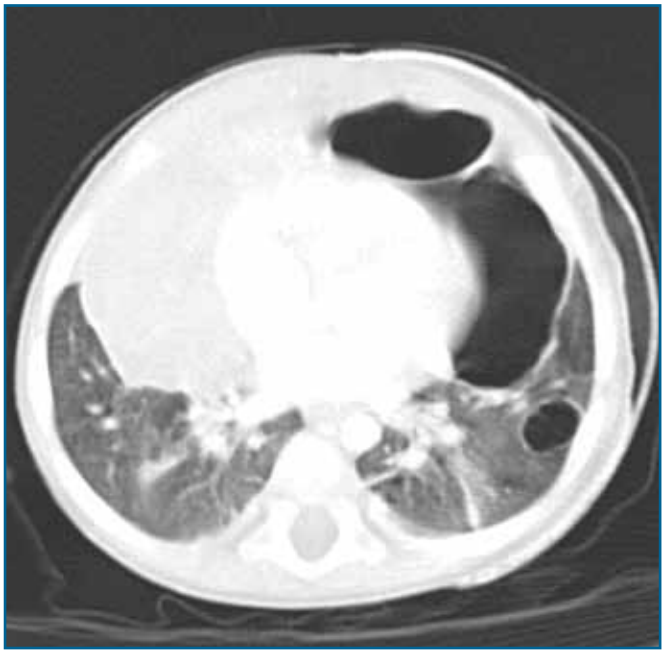

Figure 4: CT scan of the chest showing multiple cystic lesions of different sizes in the lung and a large anterior mediastinal mass

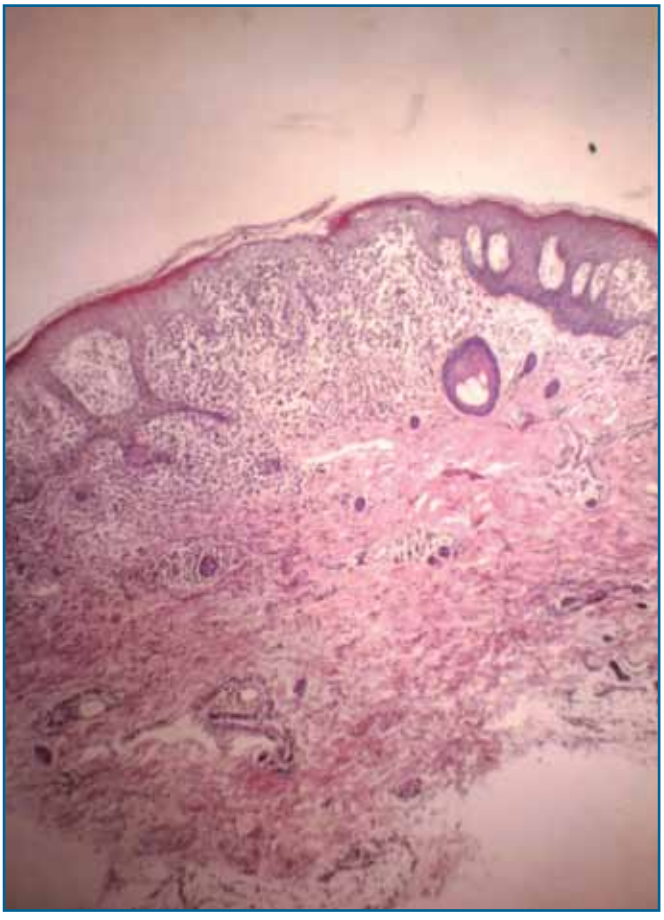

Figure 5: Low power of the punch biopsy showing a cellular infiltrate within the superficial dermis (Haematoxylin and eosin stain)

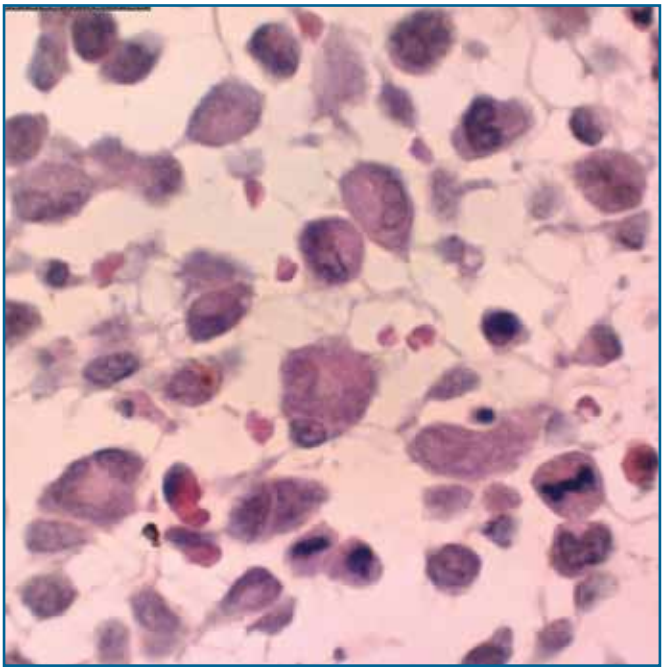

Figure 6: High power showing Langerhans cells associated with eosinophils (Haematoxylin and eosin stain)

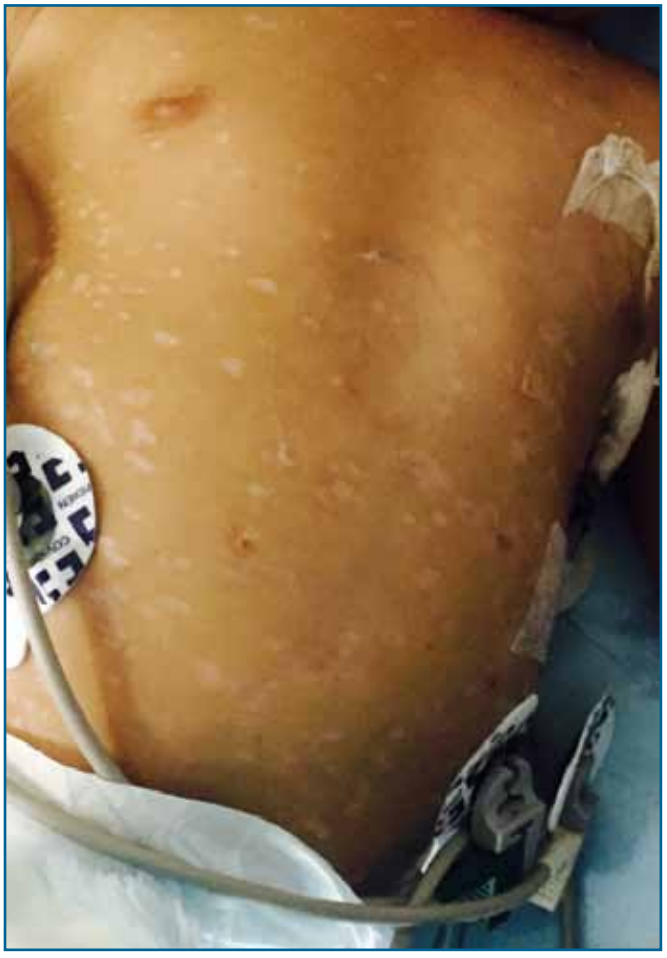

Figure 7: Skin lesions showing a substantial improvement on treatment (compared to Figure 2)

(16%), spleen (13%), oral mucosa (13%), lung (10%), and central nervous system (6%).[10]

Skin

In children under two years of age, cutaneous involvement is the most common presentation.[11] Cutaneous lesions can be extensive and can resemble seborrheic dermatitis and involve the face, trunk, and perineum. It may also present as papules, pustules, vesicles, petechiae, or purpura.[12] This was noted in our patient where this vesicular rash was initially thought to be varicella zoster and later a possible S aureus skin infection.

Lung involvement

Symptoms range from asymptomatic (with infiltrations noted on chest x-ray) to severe symptomatic respiratory disease.[6] These may be non-specific and include dyspnoea, cough, chest pain, wheezing, fatigue, wheezing, or tachypnoea. Chest pain may be associated with a pneumothorax.[1]

Mediastinal involvement

LCH with thymic and or mediastinal involvement is rarely reported. In a study with a large cohort of paediatric patients the frequency of mediastinal involvement was about 2.6% and the median age was 0.7 years.[13]

Diagnosis

The chest x-ray is usually abnormal and demonstrates a diffuse micro-nodular infiltrate or cytic changes (which are not common in children).[1,5] CT scan cysts may have a thick or thin wall and vary in size between a few millimetres up to 20cm. Involvement of the lower lung zones and costophrenic angles is noted in the paediatric population.[5] This was also noted in our child with the cysts involving the lingular of the left lung as well as the right lung.

Morphologic confirmation of pulmonary involvement can be obtained by bronchoalveolar lavage (BAL) or lung biopsy. The presence of Langerhans cells in BAL is identified by staining with antibodies against CD1a, and a proportion of CD1a-stained cells of more than 5% makes the diagnosis of pulmonary LCH likely.[2]

A skin biopsy can provide a quick and accessible way to make a diagnosis, and lung biopsy remains the gold standard to diagnose pulmonary LCH.[4] The CT scan is used to direct the area of the biopsy. This may be associated with sampling errors since the lesions of pulmonary Langerhans histiocytosis are focal.[2,5] A definitive diagnosis requires a positive staining with S-100 and CD1a antibodies and the presence of Birbeck granules on electron microscopy.[4] Electron microscopy however is not routinely used as immunohistochemistry is cheaper and more efficient.[3]

Treatment

Treatment protocols are based on whether there is single- or multi-organ involvement, as well as on the involvement of a high-risk (liver, spleen, hematopoietic organs) or low-risk organ (skin, bone, lymph node, pituitary gland, lung).[1,4]

No therapy is required in patients with limited cutaneous disease, however topical steroids are often used. Treatment for multi-organ disease is controversial, prednisone is sometimes used as a first line treatment, while others centres prefer the use of a single chemotherapy agent. Currently the protocol for the initial management of multi-system LCH include a six- week course of vinblastine and prednisone.[14] Newer therapies being investigated include monoclonal antibodies (targets CD1a or CD207), specific cytokine inhibitors, and 2-chlorodeoxyadenosine.[4]

Prognosis

Prognosis depends on the presence of high-risk organ involvement and a poor response to initial treatment. If both are present there is a 75% mortality rate, whereas those who respond to initial chemotherapy have a good survival rate.[1] Children who present at a younger age with multisystemic disease have a high mortality. Young age alone is not a risk factor for high mortality.[1]

Summary

The above patient provides a rare example of multi-organ (lungs, skin, and bone marrow) LCH presenting with an anterior mediastinal mass, cystic lung disease and typical skin features. In this case we illustrate the pulmonary features and complications caused by LCH in a young child. It also demonstrates the skin abnormality as one of the presenting signs, which may be misdiagnosed as eczema or cutaneous infections.

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