Eur Respir J 2005; 26: 974–977
DOI: 10.1183/09031936.05.00018305

CASE FOR DIAGNOSIS

A 3-year-old child with abdominal pain and fever

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CASE HISTORY

A previously healthy 3-yr-old male was evaluated for fever and abdominal pain, and a chest radiograph was performed (fig. 1). A detailed history was collected and the parents reported the child having a ''distended abdomen'' from a few months old. They had the impression he was a calm child, less inclined to run and play than his peers. In the previous year, two episodes of bronchitis had prompted skin-prick tests, showing sensitisation to trees, dogs, cats, *Alternaria alternata* and *Aspergillus fumigatus*. The child's history was otherwise uneventful for respiratory symptoms, such as tachypnoea, persistent cough, wheezing or chest pain.

Clinical examination

On clinical examination, the child was eupnoeic with normal chest sounds and 98–99% saturation in room air. His liver and spleen were 3 cm and 2 cm below the costal arch, respectively; weight and height were at the 75th and 25th percentiles, respectively. Laboratory data are shown in table 1.

Pulmonary function test

Spirometry, performed with poor compliance, demonstrated a low forced vital capacity (FVC) and a low forced expiratory volume in one second (FEV_1; 66 and 72% predicted, respectively) and a FEV_1/FVC ratio of 98%, consistent with a restrictive pattern.

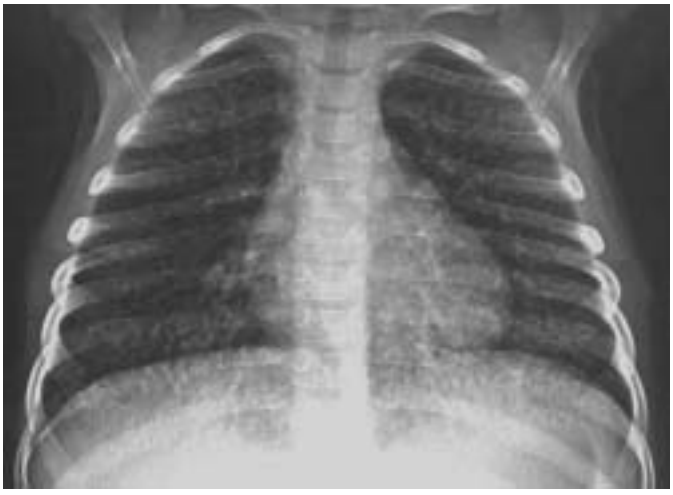

FIGURE 1. Posteroanterior radiograph of the chest.

Radiological, endoscopic, cytological and histological evaluation

A high-resolution computed tomography (HRCT) of the chest (fig. 2) and bronchoscopy with bronchoalveolar lavage (BAL) were performed. Bronchoscopy showed no macroscopic abnormalities. Cytological analysis of the BAL revealed a slight increase in the lymphocytes (24%). BAL culture for bacteria and fungi and stains for *Mycobacterium tuberculosis* were negative. Bone marrow aspirates and biopsies were also collected. A bone marrow specimen is shown in figure 3.

TABLE 1 Laboratory data

Test	Results	Normal values
Haemoglobin $g \cdot L^{-1}$	130	115–155
WBC 10^9 cells$\cdot L^{-1}$	13.05	5–14.5
Eosinophils 10^9 cells$\cdot L^{-1}$	0.85	0.1–0.6
Platelet count 10^9 cells$\cdot L^{-1}$	195	150–450
ESR $mm \cdot h^{-1}$	20	2–38
C reactive protein $mg \cdot L^{-1}$	3.16	<6
ALT $U \cdot L^{-1}$	72	5–40
AST $U \cdot L^{-1}$	82	15–40
Cholesterol $mmol \cdot L^{-1}$	240	<239
LDL $mmol \cdot L^{1}$	184	<158
HDL $mmol \cdot L^{-1}$	19	>38
Ferritin $\mu g \cdot L^{-1}$	50	31–300
Prothrombin time %	75	75–112
IgE $kU \cdot L^{-1}$	1227	0–80
Angiotensin-converting enzyme $U \cdot L^{-1}$	185	8–52
ANA/ANCA	Absent	Absent
Tuberculin skin test	Negative	Negative
Sweat chloride test	Negative	Negative
Serology for CMV, EBV, *Legionella*, *Mycoplasma pneumoniae*, *Chlamydia influenza*, adenovirus and *Aspergillus fumigatus*	Negative	Negative

WBC: white blood cells; ESR: erythrocyte sedimentation rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDL: low-density lipoprotein; HDL: high-density lipoprotein; Ig: immunoglobulin; ANA: anti-nuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; CMV: cytomegalovirus; EBV: Epstein-Barr virus.

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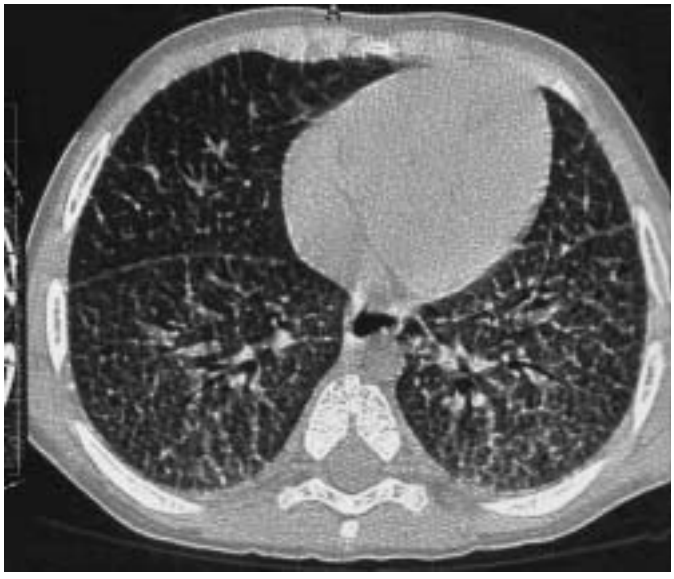

FIGURE 2. High-resolution computed tomography scan of the chest.

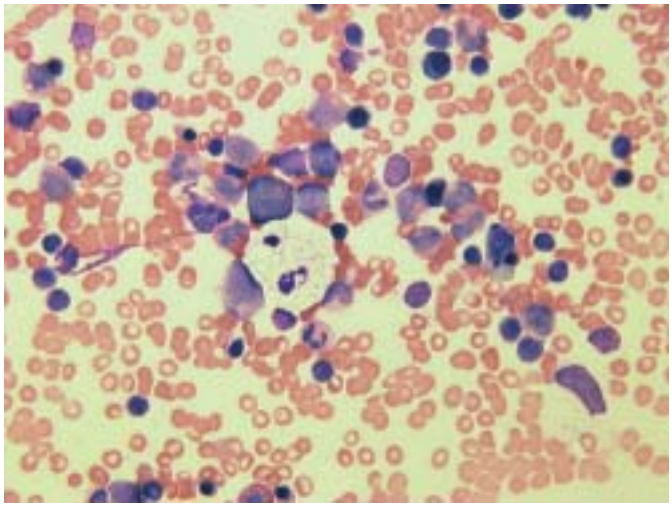

FIGURE 3. Bone marrow aspirate (Giemsa stained).

BEFORE TURNING THE PAGE, INTERPRET THE CHEST RADIOGRAPH, THE COMPUTED TOMOGRAPHY SCAN AND THE BONE MARROW SPECIMEN, AND SUGGEST A DIAGNOSIS.

INTERPRETATION

Chest radiograph

The chest radiograph showed diffuse interstitial lung infiltrates with a nodular pattern and diffuse increase in density (fig. 1).

High-resolution computed tomography

Diffuse bilateral interstitial opacities with a reticular pattern involving all the lobes, no hilar or mediastinal adenopathies were shown on the chest HRCT scan (fig. 2).

Bone marrow specimen

Presence of foamy cells (lipid-storing macrophages) on bone marrow smear (fig. 3). Analogous cells were found in the BAL fluid.

Diagnosis: Niemann-Pick disease type B.

The clinical representation supported a tentative diagnosis of a lysosomal storage disorder.

The disease most compatible with the clinical, laboratory and pathological findings was Niemann-Pick disease type B. This diagnosis was confirmed by the decreased sphingomyelin phosphodiesterase activity level in peripheral leukocytes (1.25 $nmol \cdot mg^{-1} \cdot h^{-1}$; normal values 3.4 ± 0.9) and in cultured fibroblasts. The analysis of lysosomal acid sphingomyelinase gene *SMPD1* identified two mutations (W32X/L225P).

CLINICAL COURSE

During a 1-yr follow-up, the child was always healthy and never suffered from respiratory symptoms or infections and no therapy was needed. He became more cooperative and pulmonary function tests were repeated. Airway resistance was measured with the RINT method (MicroRint®; Micro Medical Ltd, Rochester, UK), and was within normal values ($0.71\ kPa \cdot L^{-1} \cdot s^{-1}$). His functional residual capacity, measured using a multiple-breath technique and an ultrasonic flow meter (Spiroware®; ECO Medics AG, Durnten, Switzerland), was lower than normal for his height ($13.7\ mL \cdot kg^{-1}$). Spirometry, performed with a water-bell spirometer (Biomedin, Padova, Italy), showed values at the lower limit of the normal range: FVC 81% pred; FEV_1 84% pred; FEV_1/FVC ratio 89%; and forced mid-expiratory flow 86% pred. No hypoxaemia or significant bronchial obstruction were seen after an exercise challenge (maximal FEV_1 drop after exercise was 6%).

DISCUSSION

Children's interstitial lung disease comprises a large group of rare disorders in children. Its diagnosis requires a high index of suspicion as the onset of the disease is often insidious, but any delay can lead to significant lung remodelling. Presentation and outcome differ from adult patients and many cases are found to have an underlying cause, making it crucial to arrive at a correct aetiological diagnosis [1, 2].

Sarcoidosis was the first condition suspected in the case presented here. The insidious onset of the signs and symptoms, the hepatosplenomegaly, abnormal liver function test findings, high angiotensin-converting enzyme (ACE) levels and radiological signs were consistent with this diagnosis. However, sarcoidosis is rare in children, and, furthermore, up to the age of 4 yrs, skin, eyes and joints are the most often affected sites, while lungs are usually spared. Moreover, there was no hypercalcaemia, hypercalciuria or lymph node involvement making this diagnosis unlikely [3, 4].

Immunoglobulin E for *Aspergillus fumigatus* and hypereosinophilia might point to a fungal allergic alveolitis, but the chest radiograph, CT image and BAL were not consistent with such a diagnosis.

Pulmonary haemosiderosis was ruled out in the absence of anaemia and hyperferritinaemia. Pulmonary involvement in a collagen disease was considered improbable because there were no related clinical signs or circulating auto-antibodies.

The next diagnostic step would have logically been an open lung biopsy. However, the child's hepatosplenomegaly, high ACE levels and hypercholesterolaemia with a low high-density lipoprotein fraction were suggestive of a lysosomal storage disorder (supported by the presence of foamy cells in the BAL and bone marrow aspirate). Enzyme assay enabled the differential diagnosis between Gaucher type I and Niemann-Pick type B disease and led to the final diagnosis even without a biopsy being performed.

Niemann-Pick is a heterogeneous, lisosomal, storage disorder with six variants presenting distinct clinical and biochemical features. All of them are inherited as autosomal recessive and involve many tissues (liver, spleen, bone marrow, nervous system and lung) with a variable proportion. Type A, B, E and F are due to lysosomal sphingomyelinase deficiency, whereas type C and D are caused by an altered intracellular cholesterol processing. Type A is characterised by failure to thrive, visceromegaly, retinopathy and a progressive neurological degeneration leading to death in the first years of life. Type C and D present a subacute course with visceral and neurological involvement. Type B is characterised by hepatosplenomegaly, hyperlipidaemia and pulmonary involvement. It is also more slowly progressive with most of the patients surviving until adulthood and does not involve the central nervous system. Pulmonary involvement is due to the accumulation of lipid-storing foam histiocytes in the interlobular septa or alveolar spaces. Recent studies in animal models show that the deficient sphingomyelinase activity can also interfere with a normal surfactant composition and catabolism, contributing to lung function impairment [5, 6]. In this child, a pronounced reduction was found in FVC accompanied by a mild restrictive pattern, which did not get worse during the 1-yr follow-up. To the current authors' knowledge, this is the first description of pulmonary function in a pre-school child with Niemann-Pick interstitial lung disease.

Most cases of Niemann-Pick disease type B are diagnosed in infancy or childhood, when liver or spleen enlargement is detected during a routine medical check-up. At the time of diagnosis, there are usually only mild radiological signs of lung involvement. More severely affected individuals can develop dyspnoea on exertion and hypoxaemia in the second decade of life. The liver involvement seldom leads to cirrhosis, portal hypertension or ascites. However, spleen enlargement can cause pancytopenia. Some patients may have cherry red maculae [7].

Enzyme activity can be measured in leukocytes and cultured fibroblasts. This is useful for the differential diagnosis *vis-à-vis* other storage disorders, particularly Gaucher disease, with which it shares many clinical features. Family members can be tested for heterozygous status by DNA analysis and a pre-natal diagnosis can be made in cultured cells from the amniotic fluid.

In conclusion, there are a handful of reported paediatric cases of Niemann-Pick type B disease being diagnosed after the detection of interstitial lung disease [8–11]. The current authors presented a case of interstitial lung involvement in a pre-school child with no respiratory symptoms. The associated organ involvement and subtle biochemical alterations narrowed the diagnostic spectrum and led to a final diagnosis without the need to perform a lung biopsy.

REFERENCES

1 Clement A, ERS Task Force. Task force on chronic interstitial lung disease in immunocompetent children. *Eur Respir J* 2004; 24: 686–697.
2 Fan LL, Deterding RR, Langston C. Pediatric interstitial lung disease revisited. *Pediatr Pulmonol* 2004; 38: 369–378.
3 Hunninghake GW, Costabel U, Ando M, *et al.* Statement on sarcoidosis. *Am J Respir Crit Care Med* 1999; 160: 736–755.
4 Hetherington S. Sarcoidosis in young children. *Am J Dis Child* 1982; 136: 13–15.
5 Ikegami M, Dhami R, Schuchman EH. Alveolar lipoproteinosis in an acid sphingomyelinase-deficient mouse model of Niemann-Pick disease. *Am J Physiol Lung Cell Mol Physiol* 2003; 284: L518–L525.
6 Minai OA, Sullivan EJ, Stoller JK. Pulmonary involvement in Niemann-Pick disease: case report and literature review. *Respir Med* 2000; 94: 1241–1251.
7 Wasserstein MP, Desnick RJ, Schuchman EH, *et al.* The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. *Pediatrics* 2004; 114: 672–677.
8 Reich D, Kedar A, Kibansky C. Clinical and biochemical study of a child with the non-neuropatic-type B form of Niemann-Pick disease. *Eur J Pediatr* 1979; 13: 133–140.
9 Hammersen G, Oppermann HC, Harms E, Blassmann K, Harzer K. Oculo-neural involvement in an enzymatically proven case of Niemann-Pick disease type B. *Eur J Pediatr* 1979; 132: 77–84.
10 Pavone L, Fiumara A, La Rosa M. Niemann-Pick disease type B: clinical signs and follow-up of a new case. *J Inherit Metab Dis* 1986; 9: 73–78.
11 Niggemann B, Rebien W, Rahn W, Wahn U. Asymptomatic pulmonary involvement in 2 children with Niemann-Pick disease type B. *Respiration* 1994; 61: 55–57.