Pulmonary involvement in Niemann-Pick type B disease

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A six-year-old girl presented with complaint of episodic dyspnoea. Physical examination showed marked splenomegaly and hepatomegaly. Cardiovascular and neurological examinations were normal.

The chest radiograph showed a fine bilateral reticular pattern. Pulmonary function tests showed normal lung volumes and a decreased diffusing capacity. High resolution computed tomographic (CT) scan of the chest showed smooth thickening of the interlobular septa and extensive bilateral ground-glass attenuation. There was no mediastinal lymphadenopathy (Figures 1a and 1b).

Bone marrow biopsy showed infiltration by numerous histiocytes. Some of the histiocytes contained vacuolated cytoplasm whilst others contained granules that stained deep blue with the May-Grünwald-Giemsa stain (Figure 2). This histological pattern was indicative of Niemann-Pick disease. Confirmation of this diagnosis was obtained by lysosomal enzyme assay that showed undetectable sphingomyelinase activity. Histological examination of the pulmonary biopsy specimen revealed foamy macrophages located in the alveoli and thickening of the alveolar walls. Macrophages also filled the lymphatic spaces around the peripheral bronchi and peripheral pulmonary artery branches, and the sub-pleural and interlobular connective tissues. These cells had small dense nuclei and a fine vacuolated cytoplasm (stained with Giemsa stain). Some giant cell forms were rarely observed. Neither granulomatous reaction nor fibrosis was seen, which confirmed the pulmonary localization of the Niemann-Pick disease.

As the patient had presented with visceral disease without neurological involvement, she was presumed to belong to subtype B of the Niemann-Pick disease.

Discussion

The Niemann-Pick disease is a rare inherited autosomal reces-
sive disorder characterized by accumulation of sphingomyelin resulting from deficiency in the production of sphingomyelinase. The excessive sphingomyelin is deposited in the liver, spleen, lungs, bone marrow or brain.\textsuperscript{1,2}

There are several clinical subdivisions of this disorder according to the predominant organs affected. Severity ranges from a clinically obvious acute neuronopathic phenotype (Type A) to a chronic visceral phenotype (Type B), with intact nervous system and moderate sphingomyelinase deficiency. Subacute forms, Niemann-Pick Types C and D, present with involvement of central nervous system without a clear sphingomyelinase deficiency.\textsuperscript{1}

The case reported here corresponds to subtype B of the disease. This entity seems to be pan-ethnic without gender predilection and it may manifest at any age, although it is more frequent before the age of 20 years.\textsuperscript{1,4} Symptoms of subtype B appear to remain generally trivial over a long period, with the late development of a restrictive ventilatory defect. Diagnosis can be made in childhood or adulthood by finding hepatosplenomegaly or chronic pulmonary interstitial infiltration on chest radiographs. Other systemic manifestations, such as skin pigmentation, bone involvement, macular abnormalities, and gastrointestinal disorders related to malabsorption, have all been reported in this phenotype.\textsuperscript{1-2}

The radiological appearance of this affection is non-specific, consisting classically of linear strands associated with nodular infiltrates, producing a honeycombing effect that spreads diffusely throughout the lung fields, with a predominance in the bases.\textsuperscript{1-3} High resolution CT findings have been described recently in adults.\textsuperscript{3,4} The high resolution CT pattern consisted of a thickening of the interlobular septa without nodularity, mainly predominant in the lower parts of the lungs, associated with ground-glass opacities that predominated in the upper and middle pulmonary zones.

Pathological examination helps to understand the high resolution CT pattern. The characteristic microscopic feature is an infiltration of lipid-storing foam histiocytes (Pick cells), usually seen within the alveoli, the alveolar walls, and lymphatic interlobular and subpleural spaces, while the pulmonary architecture remains normal.\textsuperscript{4} The presence of histiocytes in the interstitial spaces, without granulomatous formation, may account for the smooth thickening of secondary lobe margins in a polygonal distribution as they are seen on high resolution CT slices.\textsuperscript{3} Ground-glass opacity seen on high resolution CT slices may be explained by partial filling of the alveolar spaces with Pick cells or by intense cellular infiltration in inter-alveolar walls.\textsuperscript{4}

Such high-resolution CT findings remain non-specific. Association of splenomegaly or hepatomegaly should suggest the diagnosis of a storage disease. Demonstrating typical sea-blue histiocytes in the bone marrow aspirate or from the liver in biopsy material and a low sphingomyelinase activity by enzyme assay will confirm the diagnosis.

Other radiological abnormalities have been described in Niemann-Pick Type B disease, such as low-intensity non-enhancing coarse bone marrow pattern on MR imaging, osteoporosis, long bone marrow cavity expansion, metacarpal widening, and massive splenomegaly with low-density splenic nodule(s); but these are less frequent than lung infiltrates.\textsuperscript{1}

Evolution of Type B Niemann-Pick disease is usually, but not always, benign. Though the disease may be present for decades, in certain cases a less good prognosis has been observed progressing to hepatic failure and death. Progressive pulmonary infiltration is a major cause of morbidity and mortality. To date, no successful treatment of pulmonary involvement by Niemann-Pick disease has been documented. Whole-lung lavage appears to be a potentially useful treatment.\textsuperscript{5}

References