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LIPIDOSIS WITH SEA-BLUE HISTIOCYTES*
Report of Two Siblings with Lung Involvement

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Two siblings, an eight-year-old girl and a three-year-old boy with lipid storage disease, most likely non-neuropathic Niemann-Pick disease (NPD) with sea-blue histiocytes, are presented. Both of them had foamy and sea-blue histiocytes in their bone marrow smears and reticulo-nodular appearance of both lungs on their chest X-rays. Case 1 had diffuse, biopsy-proven, pulmonary involvement associated with sea-blue histiocytes. Although diffuse reticulo-nodular pulmonary infiltration of non-neuropathic NPD (type B) is frequently detected on chest X-rays, to our knowledge there is only one reported adult case of lipidosis resembling NPD in which severe pulmonary involvement associated with pigmented histiocytes and Niemann-Pick cells were demonstrated at autopsy. *Key words: non-neuropathic Niemann-Pick disease, adult Niemann-Pick disease, sea-blue histiocyte syndrome.*

Histiocytes containing distinctive blue-green intracytoplasmic granules were first reported in a splenic aspirate by Moeshlin[1] in 1947. Later they were detected in the bone marrow of some patients with hepatosplenomegaly, and it was suggested that this might represent a specific syndrome with a benign course[2-4]. But it is now clear that they can be seen in a variety of conditions including inborn errors of lipid metabolism[5-15].

We report here two siblings with lipid storage disease, most likely non-neuropathic Niemann-Pick disease (NPD) with sea-blue histiocytes. One of them had diffuse biopsy-proven pulmonary involvement associated with sea-blue histiocytes. Although diffuse reticulo-nodular pulmonary infiltration of non-neuropathic NPD (type B) is frequently detected on chest X-rays, to our knowledge there is only one reported adult case of lipidosis resembling NPD in

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which severe pulmonary involvement associated with pigmented histiocytes and Niemann-Pick cells were demonstrated at autopsy[9-11,15-18].

Case Reports

Case 1

An eight-year-old girl was admitted to Hacettepe Children's Hospital for the evaluation of a diffuse reticulo-nodular appearance of both lungs on chest X-ray and splenomegaly. She had been underweight since infancy. When she was seen at the same hospital at the age of 14 months because of failure to thrive, iron-deficiency anemia and urinary tract infection were detected. She did not have hepatosplenomegaly at that time. Her parents were healthy and distantly related. Her three-year-old brother had also had failure to thrive since infancy.

The patient was 108 cm in length (< 5th percentile) and weighed 17 kg (< 5th percentile). Her spleen was palpable 8 cm below the costal margin. The liver was not palpated. The neurological examination was normal, and there was no evidence of intellectual impairment. Laboratory tests (including whole blood count and liver function tests) were found to be within normal limits. The chest X-ray showed a diffuse reticulo-nodular pattern in both lungs (Fig. 1). An open lung biopsy was performed because of a suspicion of miliary tuberculosis. Microscopic examination of the formalin-fixed lung tissue revealed many nodular clusters of oil-red O and Sudan-black B positive foamy histiocytes in the alveoli, located prominently in the perivascular, peribronchial and subpleural areas (Fig. 2). Some cells had cytoplasmic, faint yellow-brown pigments that were blue-green in color, with Giemsa stain giving them an appearance of sea-blue histiocytes. These granules were PAS-positive after diastase treatment and iron-stain-negative. An

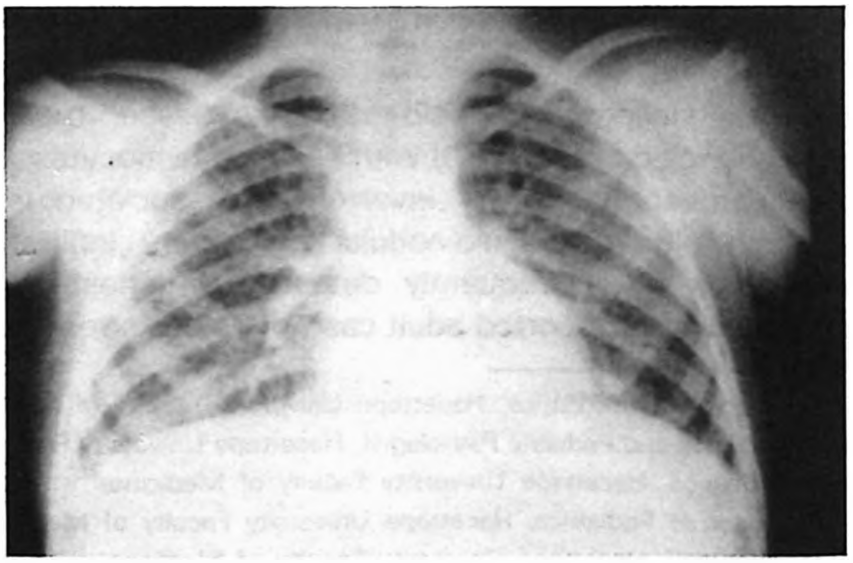

Fig. 1: Case 1- Chest X-ray showing reticulo-nodular appearance of lung fields.

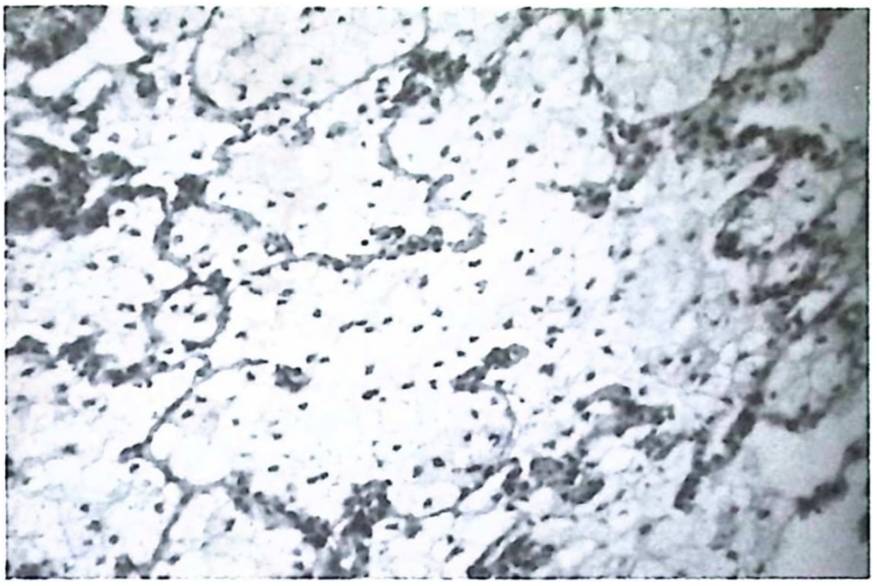

Fig. 2: Case 1- The alveolar spaces are filled with foamy histiocytes in the lung (H + E x 400).

electron microscopic study with formalin-fixed tissue was attempted. Ultrastructurally the intracytoplasmic-stored material was represented by either lamellated membranous bodies or fine granular materials (Figs. 3, 4).

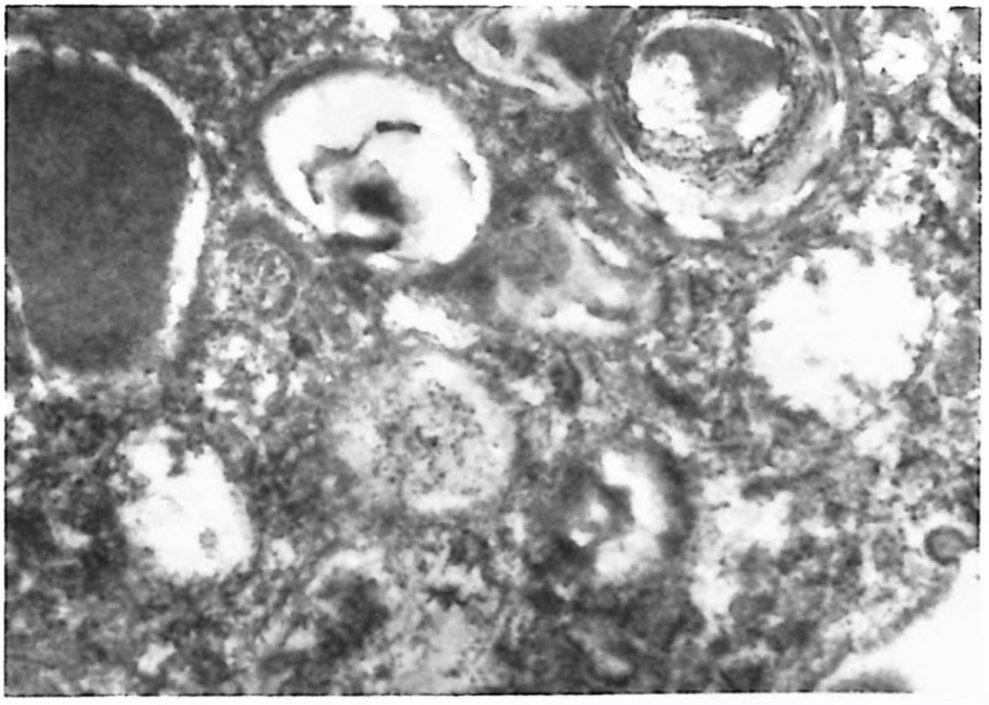

Fig. 3: Case 1- Electron micrograph of lung biopsy. Lamellated membranous material in the histiocytes (x 8300).

A bone marrow specimen stained with Wright stain also showed many sea-blue histiocytes and foamy histiocytes similar to Niemann-Pick cells (Fig. 5).

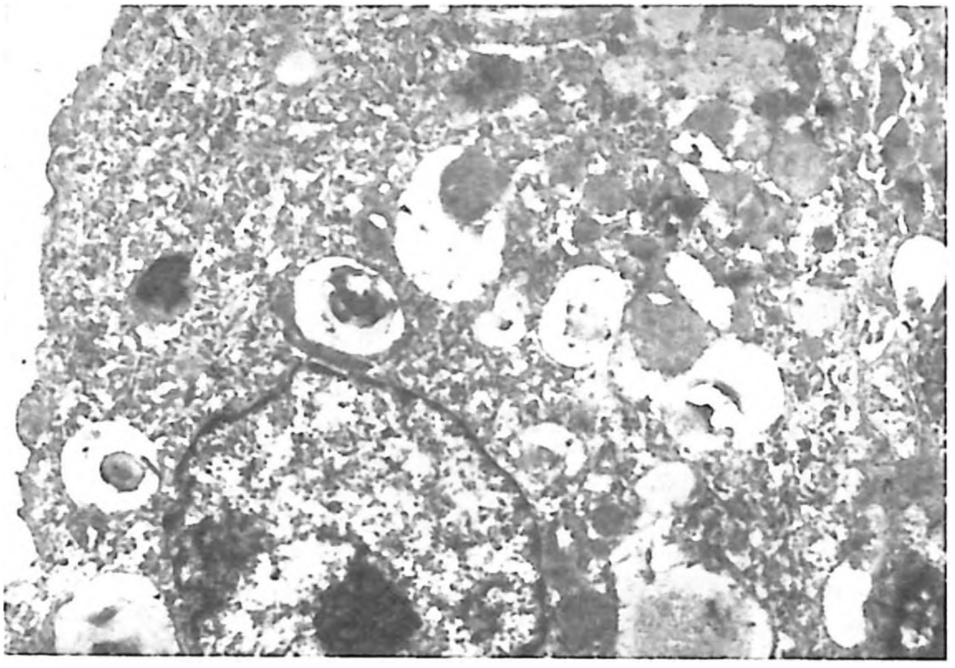

Fig. 4: Case 1- Electron micrograph of lung biopsy. Fine granular material in the histiocytes (x 8300).

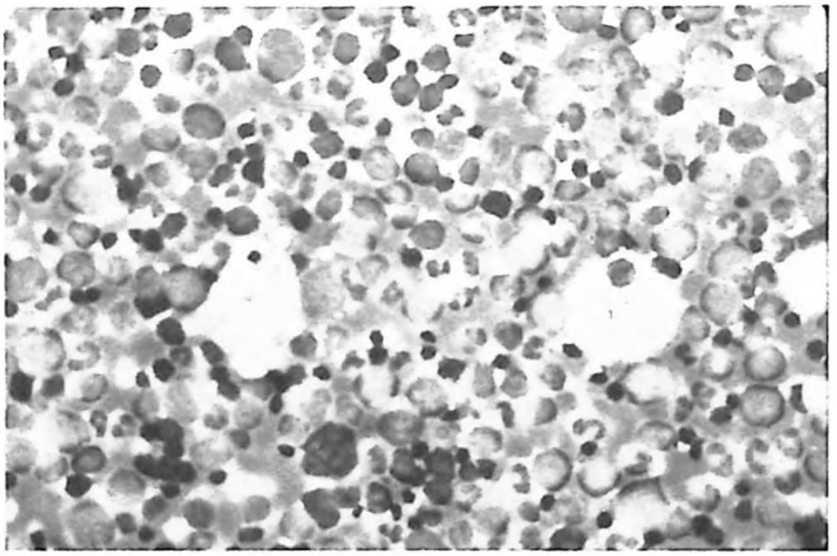

Fig. 5: Bone marrow of Case 1 showing foamy histiocyte (Wright x 650).

Case 2

The three-year-old brother of Case 1 was called for examination. He was 90 cm tall (10^{th} percentile) and weighed 13.5 kg (25^{th} percentile). His liver and spleen were palpated 2.5 cm below the respective costal margins. The neurological examination was normal. Bone marrow examination revealed many foamy histiocytes similar to Niemann-Pick cells and sea-blue histiocytes. The chest X-ray

showed a fine reticular appearance in both lung fields. Other routine laboratory tests were all within normal limits.

Despite the same appearance of their chest X-rays, the patients had no complaint during the follow-up of two and one-half years.

Discussion

Sea-blue histiocytes have been associated with a variety of systemic, hematological and neurological syndromes[6-15]. The primary syndrome is quite rare[8]. Recently, many authors have suggested that this term should be discarded, as it leads to confusion[6,7]. They recommended that the presence of such cells in abundance should initiate a search for an underlying defect because it is becoming clear that variants of NPD are common causes of this uncommon clinical picture in adults and children[6-13]. The actual origin of sea-blue histiocytes is unknown. Though the precise biochemical defect cannot always be identified, it seems reasonable to suggest that in most instances, a structurally defective or partially or completely absent enzyme leads to an accumulation of its natural substrate within the cell. It is shown that the sea-blue color on Giemsa stain is due to the presence of ceroid[9].

Sea-blue histiocytes have been reported in many forms of NPD (types B, C, D, E, F)[6,9-13,15]. They have been observed in the bone marrow, spleen, liver or lymph nodes in nine of 17 cases of well-documented chronic non-neuropathic NPD (type B) in the literature[9]. The age ranges of these patients varied from two to 17 years. They all had hepatosplenomegaly associated with moderate anemia and sometimes thrombocytopenia. A reticulonodular appearance was noted on the chest X-rays in seven of the cases. None of the patients had abnormal neurological signs or mental impairment. NPD type B is manifested by a subacute or chronic course and hepatosplenomegaly. The chronic form, however, may reveal only slight visceromegaly, sometimes only splenomegaly, and may take an inapparent and rather benign course[10]. Chronic forms frequently contain a conspicuous amount of ceroid, thereby hindering diagnosis and misleading one to the diagnosis of the sea-blue histiocyte syndrome[10]. The incidence of this form is low. However, because of the absence of neurologic changes, the diagnosis may be unsuspected clinically. Traumatic rupture of an enlarged spleen is frequently the first sign. It is important, therefore, for the pathologist to recognize this condition in surgically removed spleens or at autopsy.

Clinical, histopathological and electron microscopic findings of Case 1 and the clinical and bone marrow findings of Case 2 revealed a lipid storage disease, most likely non-neuropathic NPD type B with sea-blue histiocytes. To our knowledge, this is the first reported lung-biopsy-proven case of lipid storage disease with sea-blue histiocytes. We were not able to do biochemical investigations nor could

we confirm the diagnosis by enzyme assays; however, we believe the diagnosis can be established with reasonable certainty from formalin-fixed tissue. Because of the reticulo-nodular appearance of its pulmonary involvement, NPD must be considered in the differential diagnosis in countries where tuberculosis and consanguinity are fairly common.

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