Hermansky-Pudlak syndrome with special reference to lysosomal dysfunction

A case report and review of the literature

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Summary. In addition to the triad in the Hermansky-Pudlak syndrome (tyrosine-positive oculocutaneous albinism, mild bleeding tendency with a normal platelet-count and widespread accumulation of ceroid-like pigment in various organs), we document severe pulmonary fibrosis, pseudomelanosis coli and deeply pigmented renal cortex. In the liver, innumerable number of pigment-laden Kupffer cells and macrophages in the Glisson capsule were seen. Interestingly, many intralysosomal accumulations of the pigment within the hepatocytes were found by electron microscopy, suggesting that these configurations possibly resulted from a dysfunction of the lysosome itself, especially with regard to loss of digestive and secretory activity. The triad and other complications may also be resultants of a lysosomal dysfunction.

Key words: Hermansky-Pudlak syndrome – Intralysosomal pigment – Lysosomal dysfunction

Hermansky-Pudlak syndrome is an autosomal recessively inherited disorder, which consists of tyrosine-positive oculocutaneous albinism, mild haemorrhagic tendency associated with prolongation of bleeding time and a normal platelet-count, and widespread accumulation of ceroid-like pigment in various organs (Hermansky and Pudlak 1959; Bednar et al. 1964; Witkop et al. 1983). Frequent pulmonary fibrosis and granulomatous colitis have also been reported as complications of this syndrome (Hermansky and Pudlak 1959; Davies and Tuddenham 1976; Garay et al. 1979; Hoste et al. 1979; Schinella et al. 1980). In a detailed review (Witkop et al. 1983), approximately 200 patients with the disease were reported or were known to the authors, but little effort has been made to clarify the fundamental pathogenesis of the pathomorphology of the disease. In the present study of the Hermansky-Pudlak syndrome, we describe the detailed pathological findings of an autopsy case and discuss the pathogenesis, with special reference to a possible lysosomal dysfunction in this disorder.

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Case Report

Clinical abstracts. (Respir. Clin., Jichi Medical School Hosp., No. 178435.)

The patient was a 34-year-old Japanese welder. He was the first child of non-consanguineous parents. In the relatives up to third pedigree, there was no family history of the same clinical signs with the patient.

Since his childhood, albinism with pale-brown hair, visual disturbance and photophobia have been pointed out. A haemorrhagic diathesis was frequently manifest since a school-boy. Easy fatigability was complained of from February 1980. Exertional dyspnoea and cough had deteriorated since December 1980. Reticulo-nodular shadows in the lung fields, which were different from those of usual interstitial pneumonia, were discovered by a medical practitioner, and the patient was admitted to the Shimotsuga Hospital, Tochigi, Japan, on February 9, 1981. He was placed on anti-tuberculous treatment, but streptomycin and INAH did not improve symptoms or remove the abnormal shadows in the lung. He was transferred to the Jichi Medical School Hospital on June 8, 1981. Albinism of classical oculocutaneous type was present and the irides were pale-brown in color. Visual acuity was markedly decreased on both sides. A haemorrhagic diathesis with prolonged bleeding time was disclosed (Table 1). Blood cell count and haemogram were within the normal range, and platelets showed no abnormality in number and appearance. Aggregation studies revealed that the platelets had decreased response to potent aggregating agents such as collagen (3 μg/ml), ADP (2.25 and 9.0 μM) and adrenalin (0.1 μg/ml). Histological examinations of aspirated bone marrow showed deposition of a ceroid-like pigment in the cytoplasm of macrophages (Fig. 1). The histological findings along with clinical data and symptoms led to the diagnosis of Hermansky-Pudlak syndrome. Electron microscopically, a ceroid-like pigment was detected in the cytoplasm of macrophages; irregular-sized clear fat globules and highly electron-dense granules depicting neither lamellar nor membranous structures (Fig. 2). By transbronchial lung biopsy, marked fibrosis was found, but no pigment-laden cells were seen in the small fibrotic specimen. Pulmonary function tests explained a restrictive ventilatory and diffusion disturbance with hypoxemia and mild pulmonary hypertension (Table 2). Other laboratory data were within the normal range. Urinalysis showed no abnormality and urine was normal in color. He did not complain of constipation, diarrhoea or bloody stool during admission. After discharge in December 1981, oxygen inhalation was carried out at home. An emergency admission was made on January 10, 1982, because of high fever, chillness, cough and dyspnoea. Administration of antibiotics and oxygen inhalation were not effective treatment for the pneumonia which was clinically suspected. Blood gas data deteriorated in association with extended reticulonodular shadowing. He died of respiratory insufficiency on January 16, 1982.

Morphological observations and methods for investigations. (Dept. Pathol., Jichi Medical School. A-1200.)

The autopsy was carried out about 7 h after death. The essential findings of Hermansky-Pudlak syndrome were not prominent macroscopically. The bone marrow, spleen and liver were obviously brown in color. The bone marrow was hypercellular, and there was no hepatosplenomegaly. Lymph node swelling was not found. The kidney, especially the cortex, was deeply brown in color, but cortico-medullary structure was well recognized. The lung showed very interesting findings: they were small and firm in consistency with marked contraction of the lower lobes. The pleural surface was grossly nodular and had many bullous lesions. The cut surface presented irregular and severe fibrosis which was to some extent different from that of usual interstitial pneumonia: irregular, partly subpleural and markedly islet-like and nodular fibrosis of the parenchyma was seen (Fig. 3a). There were scattered lesions of honeycomb appearance with small cysts up to 5 mm in diameter (Fig. 3b). Evidence of several infections, granulomatous and ulcerative bronchiolitis and/or bronchitis accompanied by haemorrhage, were all seen in certain places. In the large bowel, a severe pseudomelanosis coli was found through the entire length, but no granulomatous colitis was demonstrated. There was no evidence of Hermansky-Pudlak syndrome in the other organs supported macroscopically. We were not permitted to examine the brain.