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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 mannifest 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 hypoxoemia 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.

Table 1. Tests of haemostasis

Bleeding time	16.0 min
Prothrombin time	10.6 s
A-PTT	37.3 s
Thrombotest	100%
Fibrinogen	235 mg/dl
Clot retraction	80.4%
Prothrombin consumption test	<3.15%

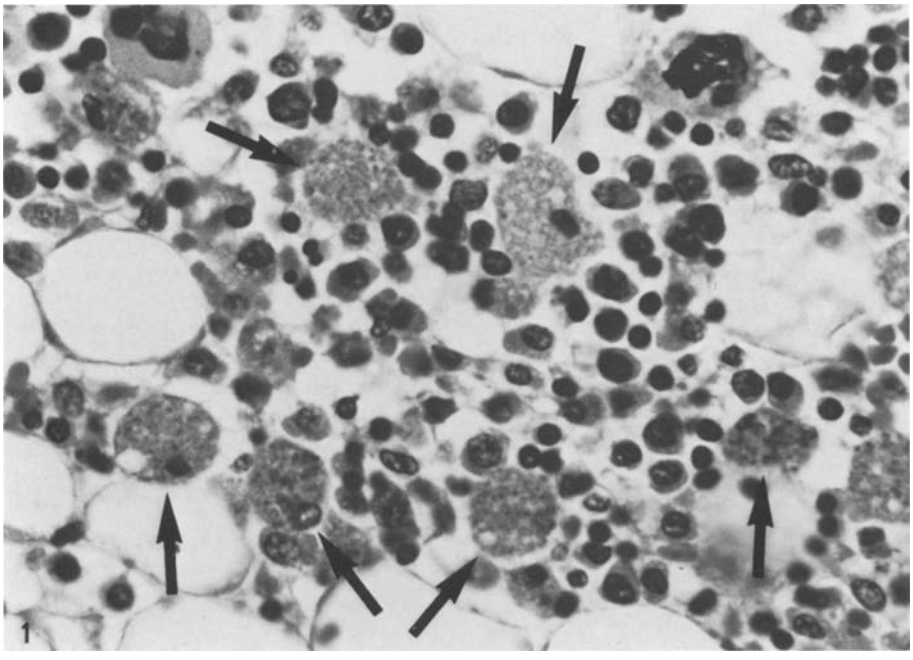

Fig. 1. Bone marrow aspirate. Macrophages filled with ceroid-like pigment granules (*arrows*). H-E, ×400

Specimens from various organs were obtained and fixed in 10% formalin. Paraffin-embedded sections were stained with the following methods (Table 3): haematoxylin and eosin (H-E), periodic acid-Schiff (PAS), Azan-Mallory, Giemsa, Ziehl-Neelsen, Nile blue, periodic acid-methenamine silver-Masson trichrome (PAM-MT), Luxol fast blue, Prussian blue, Masson-Fontana, and Schmorl for lipofuscin. After treatment by potassium permanganate, sections were stained with H-E, PAS and Masson-Fontana. Frozen sections were stained with Sudan III, Sudan black B, oil red O and Nile blue for lipid staining.

A slice from the left lung, about 2 cm in thickness, was embedded in 25% gelatine solution after fixation in formalin. According to the method reported by Gough and Wentworth (1949), the hilar part was cut at about 100 μm by Tetrander-Microtome (Jung, FRG), depicting the whole length from the apex to the base. The specimens were not stained.

At the time of autopsy, small pieces from various organs were fixed in 2.0% glutaraldehyde in 0.2 M s-collidin for 60 min, following by fixation for 2 h in 1.0% osmium tetroxide in 0.2 M s-collidin for the electron microscopic studies. Selected ultra-thin sections were stained

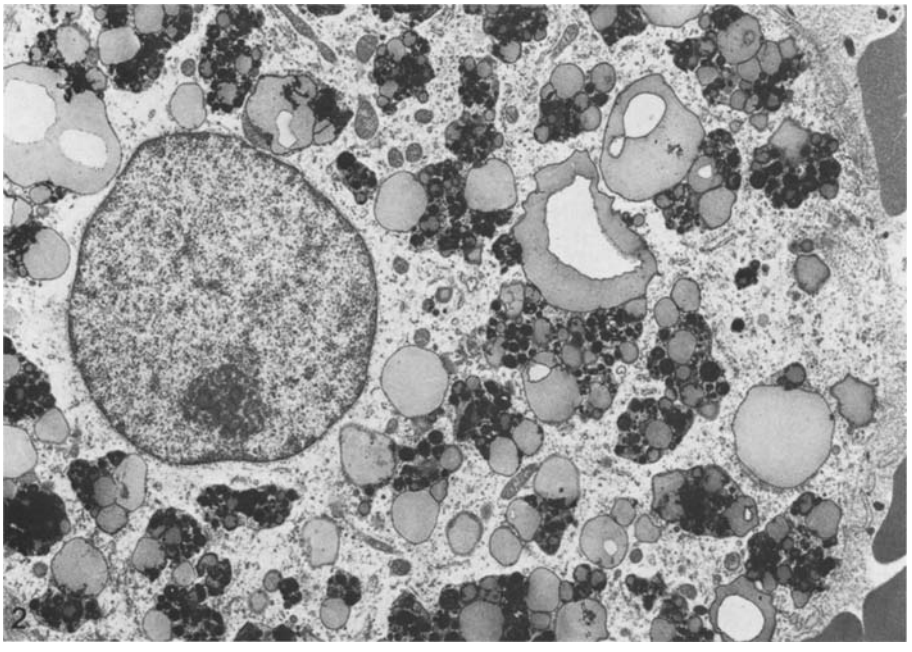

Fig. 2. A bone marrow macrophage with electron-dense and -lucent configurations, closely resembling ceroid or lipofuscin. × 5,500

Table 2. Pulmonary function tests

VC	1.50 litter (l)
% VC	39.7%
FRC	1.59 l
RV	0.78 l
TLC	2.28 l
RV/TLC	34.2%
FVC	1.21 l
% FVC	32.0%
$FEV_{1.0}$	1.10 l/s
$FEV_{1.0\%}$	91.1%
MMF	2.05 l/s
PEFR	5.21 l/s
$\dot{V}_{50}$	2.90 l/s
$\dot{V}_{25}$	0.62 l/s
$\dot{V}_{50}/\dot{V}_{25}$	0.24
Z_{rs} (3 Hz)	5.5 $cmH_2O/l/s$
ΔN_2	0.2%
PMI	1.0%
D_{LCO}	4.0 ml/min/mm Hg (20%)
D_{LCO}/V_A	1.87 ml/min/mm Hg/l

Blood gas analysis (room air)	
pH	7.394
PaO_2	63.9 Torr
$PaCO_2$	40.3 Torr
HCO_3^-	23.5 mEq/l
SaO_2	89.7%
$A\text{-}aDO_2$	35.7 Torr (R = 0.8)

Exercise test (Ergometer; 30 watt, 5 min)		
	before	after
pH	7.404	7.436
PaO_2	57.3	33.1 Torr
$PaCO_2$	42.5	37.7 Torr
HCO_3^-	26.5	25.3 mEq/l
SaO_2	89.7	66.7%

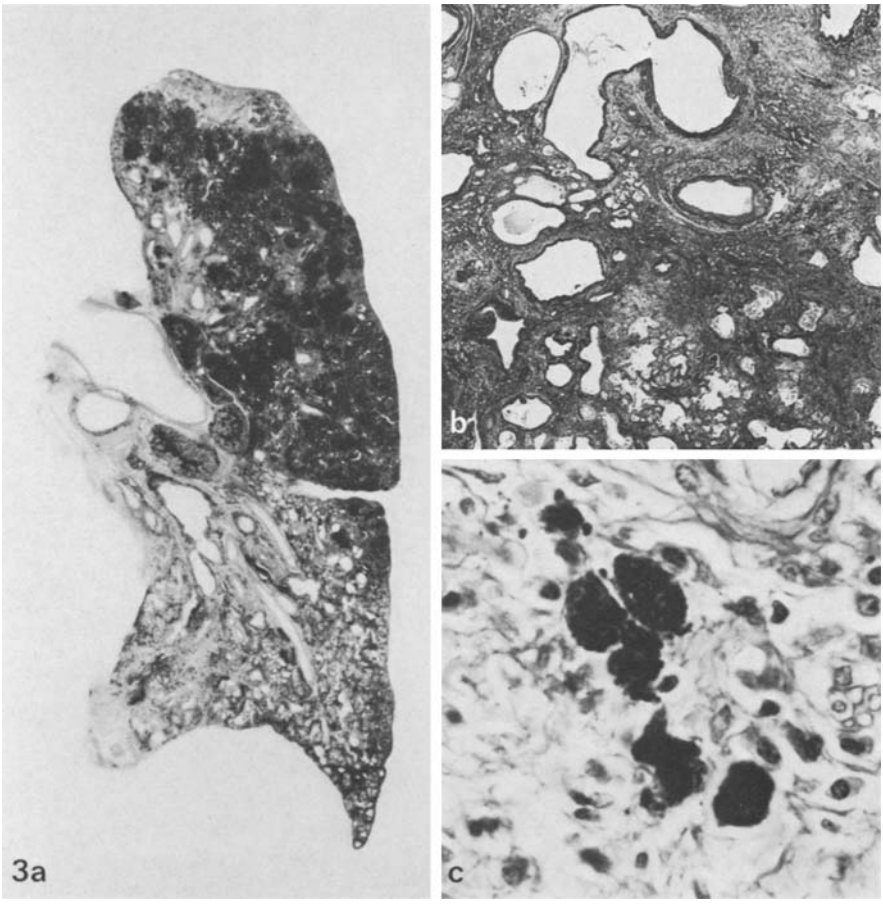

Fig. 3. a A Gough-Wentworth section of the left lung, showing irregular fibrosis with honeycomb-appearance and hemorrhage. **b** Higher magnification of left lower lobe **a** with honeycomb-appearance. PAM-MT ×50. **c** Macrophages filled with ceroid-like pigment granules in a fibrotic area of the lung. PAS ×400

with uranyl acetate and lead citrate, and examined by an electron microscope (JEOL-Model 100 CX, Japan).

Light microscopic observations. A ceroid-like pigment was demonstrated in large quantities mainly in the reticuloendothelial system. Innumerable number of macrophages were revealed in the bone marrow and in the perifollicular area and red pulp of the spleen. In the liver, there were many swollen Kupffer cells and macrophages in Glisson capsule filled with the pigment, and hepatocytes had also tiny pigment granules of the same nature (Fig. 4). In the tubular epithelia and interstitial tissue of the kidney, a large amount of pigment had accumulated and tubular cells were mostly effaced. No pigment granules was found in the glomerular tufts. Although no lymph node was abnormally swollen, a moderate number of pigment-laden macrophages were disclosed, showing a ballooned appearance. In the fibrotic area of the lung, a considerable number of macrophages with the same pigment were revealed (Fig. 3c). These cells were apparently distinguishable from alveolar epithelial cells of type II. In the

Table 3. Histochemical property of ceroid-like pigment

H-E	pale-brown
PAS	brownish-purple
Schmorl	blue
Giemsa	dark-green
Nile blue	yellowish-green
Ziehl-Neelsen	weakly brown
PAM-MT	black
Azan-Mallory	dark-blue
Masson-Fontana	brown with black granules
Sudan III[a]	yellowish-orange
Sudan black B[a]	black
Oil red O[a]	reddish-orange
Nile blue[a]	brownish-blue
H-E[b]	pale-blue or gray
PAS[b]	purple
Masson-Fontana[b]	brown
Luxol fast blue	not stained
Prussian blue	not stained

[a] Frozen section
[b] After removal of melanin by potassium permanganate

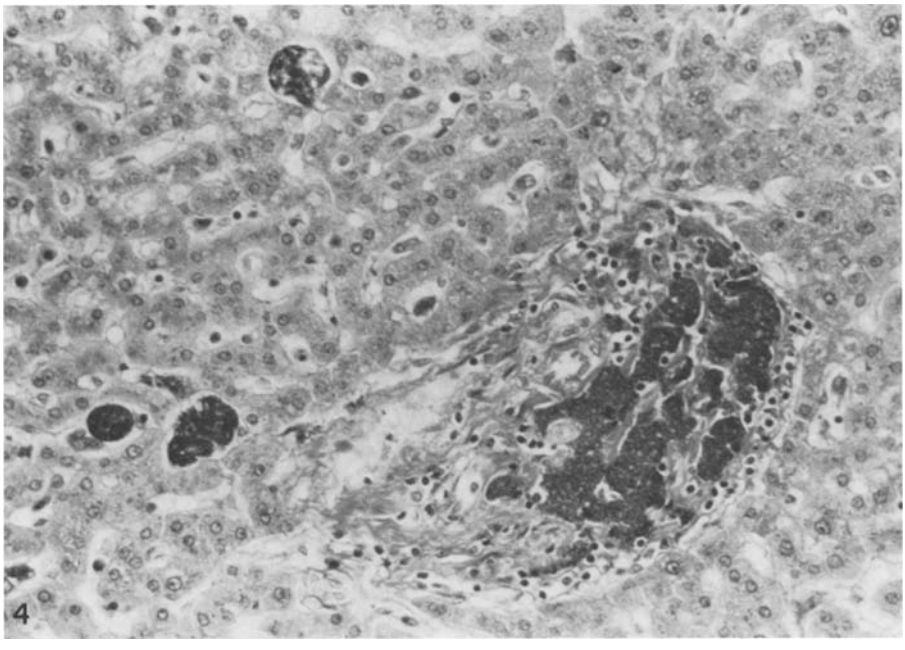

Fig. 4. Kupffer cells and macrophages in the Glisson capsule, filled with ceroid-like pigment granules. PAS ×200

infectious lesions and the alveolar lumina lined by thick hyaline membrane, macrophages with relatively transparent cytoplasm and a small amount of pigment granules were noted. In the markedly fibrotic lesions, alveolar architecture with elastic fibers was still recognizable. In the lamina propria of the large bowel, innumerable pigment-accumulated macrophages were seen, but no granulomatous colitis was discovered. A moderate number of ballooned

Table 4. Distribution of cells loaded with ceroid-like pigment

Organ	Degree of accumulation	Organ	Degree of accumulation
Bone marrow	+ + +	Pancreas	+
Spleen (130)	+ + +	Oesophagus	+
Liver (1,400)	+ + +	Stomach	+
Lymph node	+ +	Small bowel	+
Lung (570:910)	+	Large bowel	+ + +
Kidney (130:120)	+ + +	Testis	+
Heart (340)	+	Prostate	+
Adrenal (6.5:6.5)	+	Urinary bladder	+

+ + + severe, + + moderate, + slight, ( ) weight of organ (g), left:right

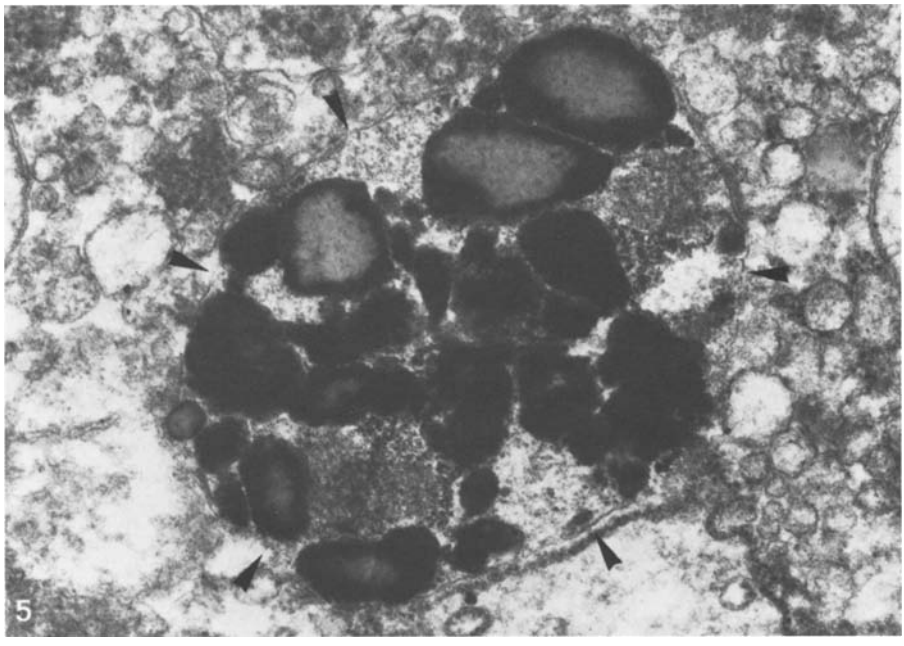

Fig. 5. Intralysosomal electron-dense and -lucent congeries encircled by a thin membrane in a hepatocyte (*arrow heads*). × 37,500

macrophages filled with the pigment were exhibited in the heart, adrenals, pancreas, oesophagus, stomach, small bowel, testes, prostate and urinary bladder (Table 4).

Histochemical analysis of the pigment was made as described above, and the results were listed in Table 3. It was very clear that the pigment possessed lipid components, because every lipid staining methods showed an excellent staining. The Schmorl method for lipofuscin showed that the pigment appeared to be closely similar to lipofuscin or ceroid. Moreover, the pigment was different from melanin or its metabolites, because it was still stained slightly pale with H-E, PAS and Masson-Fontana following treatment with potassium permanganate. Luxol fast blue displayed no lipoid. Prussian blue staining showed no iron component. Other staining methods failed to indicate a specific nature for the pigment.

Electron microscopic observations. Specimens from bone marrow, liver, spleen, kidney and lung were examined. Principally, macrophages in Hermansky-Pudlak syndrome had numerous, relatively small, highly osmiophilic granules and irregular-sized, bubble-like transparent and amorphous substances. The latter were apparently lipid droplets. The structure of the electron-dense granules which were more compacted in the severely affected cells was difficult to discern. Neither a lamellar nor a membranous structure was found in any cell, indicating that Hermansky-Pudlak syndrome was a different disease entity from the so-called storage diseases such as sphingolipidosis. In the ballooned cells, the limiting membranous residues were difficult to detect. In the hepatocytes, however, electron-dense and -lucent collections were often encircled by a complete thin membrane (Fig. 5), obviously representing lysosomal membrane. Autophagosomes were frequently present in close proximity to the pigment granules. Megakaryocytes obtained from bone marrow aspirate showed no abnormality in appearance. One dense body per platelet at most was seen in electron micrographs.

Discussion

An analogy has been drawn between the pigment in Hermansky-Pudlak syndrome and lipofuscin or ceroid usually seen in aged nerve cells. The nature of the pigment has not been clarified since the first report of an autopsy case (Bednar et al. 1964) and other subsequent cases (Verloop et al. 1964; White et al. 1972). These authors did not differentiate the configuration of the pigment from that of lipofuscin or ceroid by electron microscopy. In needle aspirates, bone marrow macrophages containing erythrocytes in various stages were documented (White et al. 1972). Most of bone marrow macrophages were presumable in the late stage of pigment accumulation and had already burst in our case. We presumed that the pigment was not morphologically different from lipofuscin or ceroid, although its exact nature has not been determined. No abnormalities in lysosomal enzymes in the leukocytes in this disorder have been shown biochemically (Gerritsen et al. 1979). On the assumption that the pigment in Hermansky-Pudlak syndrome is physiologically produced and is the same substance found in aged nerve cells and other cells, the following possible conclusion may be drawn: Hermansky-Pudlak syndrome is not caused by a defect of special lysosomal enzymes but from abberant lysosome function in an autosomal recessive trait. The heavy deposit of brown pigment granules in the cytoplasm may result from a lysosomal dysfunction: a failure of digestion and loss of the extracytoplasmic excretion property. In our case, reticuloendothelial cells and renal tubular cells were ballooned and few limiting membranous residues were revealed. Furthermore, pigment granules encircled by a thin membrane were demonstrated in the hepatocytes. These findings support the concept that the pigment was phagocytized but remained undigested within the lysosome.

Electron microscopic examination of hair bulb melanocytes in Hermansky-Pudlak syndrome disclosed that they contained numerous atypical pheomelanosomes similar to those seen in normal red hair (Witkop et al. 1974). In those cells, melanosomes up to stage III were abundant, but fully formed stage IV melanosomes were rare (Witkop et al. 1973 and 1974).

Melanosomes up to stage III in the hair bulb were converted to fully pigmented melanosomes after incubation in L-tyrosine and microassay of tyrosinase activity ranged from zero to low normal levels (King et al. 1979). A more recent study of two patients with Hermansky-Pudlak syndrome revealed a weak tyrosinase activity after incubation of hair bulbs and epidermis in L-dopa and showed the presence of numerous giant lysosomes (Frenk and Lattion 1982). It was concluded that hair bulb melanocytes had an ability to form mature melanosomes and the tyrosinase step was intact but reduced in activity. However, it may be presumed that premelanosomes and melanosomes, if fully pigmented or not, are not transported to keratinocytes of the skin. In the Chediak-Higashi syndrome, it has been suggested that the disease directly affected transport or packing of hydrolases (Lutzner et al. 1966), or that there might be abnormalities in membranes that influenced the patterns of fusion among lysosomes and endocytic or autophagic bodies (Brandt et al. 1974; Essner and Oliver 1974; Holtzman 1976). Is it impossible to conjecture that lysosome itself are affected in the Hermansky-Pudlak albino with the same mechanism as the Chediak-Higashi albino?

A storage pool deficiency with platelet dysfunction was reported in which disturbance of adenosine diphosphate (ADP) release was found (Hardisty and Hutton 1967; Weiss 1967). In the Hermansky-Pudlak syndrome, platelet dysfunction was also referred to as a storage pool deficiency (Maurer et al. 1972). Normal platelets had storage organelles for serotonin (5-hydroxytryptamine, 5-HT), adenine nucleotide (ADP and ATP) and calcium (Da Prada and Pletscher 1968; Logan et al. 1971; Maurer et al. 1972). It was suggested that when normal platelets contacted potent aggregating agents such as epinephrine or collagen, these stored substances were released to aggregate (Witkop et al. 1983). In platelets obtained from "Hermansky-Pudlak patients", a marked decrease of dense bodies was demonstrated (Maurer et al. 1972; Gerrard and White 1975). Azuropholic granules, i.e. dense bodies of platelets, were lysosome containing acid hydrolases, acid phosphatases, arylsulfatases, etc. which destroyed platelets during blood coagulation by activation of lysis of lysosomes (Kowalski et al. 1967, Bentfeld and Bainton 1975). Normal platelet had 1.1 to 1.4 dense bodies on the average (Gerrard and White 1975). Hence, it may be assessed that mild bleeding tendency associated with a normal platelet-count and coagulation abnormality arise from a dysfunction of the lysosome itself, in which 5-HT, ADP, collagen, are stored in insufficient quantity and from which these substances are unsatisfactorily released by haemorrhage.

The first autopsy case had an idiopathic pulmonary fibrosis associated with many macrophages filled with ceroid-like pigment (Bednar et al. 1964). Subsequently, it was mentioned that pulmonary fibrosis with restrictive disturbance of respiratory function tests was frequently found in the disease (Davies and Tuddenham 1976; Garay et al. 1979; Hoste et al. 1979). The findings of the lung in those patients were not always described sufficiently, but most of the patients showed an irregular fibrosis which was to some

extent different from that of usual interstitial pneumonia. In our case, pulmonary fibrosis was also extensive and irregular in distribution. Small amount of macrophages filled with ceroid-like pigment were found in the fibrous area. Another essential observations in the lung was as follows: (1) marked ulcerative and granulomatous bronchiolitis and/or bronchitis accompanied with bleeding and accumulation of a large amount of macrophages without ceroid-like pigment, (2) remarkable atelectasis and carnification showing remnants of irregular construction of alveolar elastic fibers, (3) exceedingly thick hyaline membrane. These lesions might result from lysosomal dysfunction of alveolar and free macrophages. Repeated bleeding may be induced in the lung in view of the systemic haemorrhagic diathesis in Hermansky-Pudlak syndrome. When haemorrhage or infection occurs in the interstitium, if not severe, associated with lysosomal dysfunction of macrophages, red blood cells, exudate and debris of inflammatory lesion are not removed and are followed by fibroblastic proliferation. Consequently, diffuse fibrosis of the lung may develop during the long clinical course. Thus, we consider that the pulmonary fibrosis in Hermansky-Pudlak syndrome is the result of haemorrhage and an intrinsic dysfunction of macrophage lysosome itself.

Granulomatous or ulcerative colitis developed in four patients with Hermansky-Pudlak syndrome, which was the first recognized complication (Schinella et al. 1980). They speculated that the colitis was related to the syndrome and was aetiologically dependent on lysosomal dysfunction. In the present case, colitis did not occur, but there was a severe pseudomelanosis coli. The latter has not been reported in Hermansky-Pudlak syndrome to date. We examined several cases of pseudomelanosis coli found in autopsy cases, and found after careful examination (histochemical and electronmicroscopic,) that pseudomelanosis coli in this case did not differ from that in other cases. Ultrastructural studies of pseudomelanosis coli elucidated that the pigment was lipofuscin, i.e. residual bodies derived from materials sequestrated and digested within cytolysosome (Ghadially and Parry 1966; Ghadially 1982). It seems that lysosomal digestive and secretory activity was extremely deranged in our case.

As in the first autopsy case of the disease (Bednar et al. 1964), the kidney in our case exhibited a deeply pigmented cortex. Histologically, severe accumulation of ceroid-like pigment was recognized in the tubular cells, not in the glomerular tufts. When lysosome in the tubular epithelium is functionally disturbed, reabsorption, digestion and excretion of pigment granules may not be properly processed. Consequently, a great amount of pigment may be accumulated in the cytoplasm effacing cellular architecture.

From the above-described facts, we consider systemic biopsies to be very useful for the diagnosis of the Hermansky-Pudlak syndrome. The pigment is documented in the bone marrow, liver, spleen, lymph nodes, kidney, lung and so forth. In some cases, further examination of colonic biopsies may be helpful. Concerning the pathogenesis of the disease, it is clear that the hereditary defect in the patients might be an abnormality of lysosomal dysfunction (Schinella et al. 1980).

References

Bednar B, Hermansky F, Lojda Z (1964) Vascular pseudohemophilia associated with ceroid pigmentophagia in albinos. Am J Pathol 45:283–294

Bentfeld ME, Bainton DF (1975) Cytochemical localization of lysosomal enzymes in rat megakaryocytes and platelets. J Clin Invest 56:1635–1649

Brandt EJ, Zeigel R, Swank R (1974) Abnormal control of a lysosomal enzyme in mice with Chediak-Higashi syndrome. J Cell Biol 63:35a

Da Prada M, Pletscher A (1968) Isolated 5-hydroxytryptamine organelles of rabbit platelets: Physiological properties and drug-induced changes. Brit J Pharmacol 34:591–597

Davies BH, Tuddenham EGD (1976) Familial pulmonary fibrosis associated with oculocutaneous albinism and platelet function defect. Q J Med 45:219–232

Essner E, Oliver C (1974) Lysosome formation in hepatocytes of mice with Chediak-Higashi syndrome. Lab Invest 30:596–607

Frenk E, Lattion F (1982) The melanin pigmentary disorder in a family with Hermansky-Pudlak syndrome. J Invest Dermatol 78:141–143

Garay SM, Gardella JE, Fazzini EP, Goldring RM (1979) Hermansky-Pudlak syndrome. Pulmonary manifestations of a ceroid storage disorder. Am J Med 66:737–747

Gerrard JM, White JG (1975) The influence of prostaglandin endoperoxides on platelet ultrastructure. Am J Pathol 80:189–201

Gerritsen SM, Akkerman JWN, Staal G, Roelofsen B, Koster JF, Sixma JJ (1979) Biochemical studies in Hermansky-Pudlak syndrome. Scand J Haematol 23:161–168

Ghadially FN (1982) Ultrastructural pathology of the cell and matrix. Butterworth, London Boston Sydney Wellington Durban Toronto

Ghadially FN, Parry EW (1966) An electron-microscope and histochemical study of melanosis coli. J Pathol Bact 92:313–317

Gough J, Wentworth JE (1949) The use of thin sections of entire organs in morbid anatomical studies. J Roy Microscop Soc 69:231–235

Hardisty RM, Hutton RA (1967) Bleeding tendency associated with "new" abnormality of platelet behaviour. Lancet 1:983–985

Hermansky F, Pudlak P (1959) Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: Report of two cases with histochemical studies. Blood 14:162–169

Holtzman E (1976) Lysosomes: A survey. Springer, Wien New York

Hoste P, Willems J, Devriendt J, Lamont H, van der Straeten M (1979) Familial diffuse pulmonary fibrosis associated with oculocutaneous albinism. Report of two cases with a family study. Scand J Respir Dis 60:128–134

King RA, Olds DP, Witkop CJ Jr (1979) Enzyme studies in human oculocutaneous albinism. In: Klaus SN (ed) Pigment cell pathophysiology of melanocytes. Karger, Basel, p 16

Kowalski E, Kopec M, Wegrz-Ynowicz S, Hurwic M, Budzynski AZ (1967) A lysosomal concept of the platelet release reaction and viscous metamorphosis. In: Kowalski E, Niewiarowski S (eds) Biochemistry of blood platelets. Academic Press, New York p 91

Logan LJ, Rapaport SI, Maher I (1971) Albinism and abnormal platelet function. New Eng J Med 284:1340–1345

Lutzner MA, Tierney JH, Benditt EP (1966) Giant granules and widespread cellular inclusions in a genetic syndrome of aleucian mink; and electron microscopic study. Lab Invest 14:2063–2079

Maurer HM, Wolff JA, Buckingham S, Spielvogel AR (1972) "Impotent" platelets in albinos with prolonged bleeding times. Blood 39:490–499

Schinella RA, Greco MA, Cobert BL, Denmark LW, Cox RP (1980) Hermansky-Pudlak syndrome with granulomatous colitis. Ann Intern Med 92:20–23

Verloop VMC, Wieringen AV, Vuylsteke J, Hart HCL, Huizinga J (1964) Albinismus, hämorrhagische Diathese, und anomale Pigmentzellen in Knochenmark. Med Clin 59:408–412

Weiss H (1967) Platelet aggregation, adhesion and adenosine diphosphate in thrombopathia (Platelet factor 3 deficiency). Am J Med 43:570–578

White JG, Witkop CJ Jr, Gerritsen SM (1972) The Hermansky-Pudlak syndrome. Ultrastructure of bone marrow macrophages. Am J Pathol 70:329–344

Witkop CJ Jr, Hill CW, Desnick SJ, Thies JK, Thorn HL, Jenkins M, White JG (1973) Ophthalmologic, biochemical, platelet, and ultrastructural defects in the various types of oculocutaneous albinism. J Invest Dermatol 60:443–456

Witkop CJ Jr, White JG, King RA (1974) Oculocutaneous albinism. In: Nyham WL (ed) Heritable disorders of amino acid metabolism. John Wiley & Sons, New York p 177

Witkop CJ Jr, Quevedo WC Jr, Fitzpatrick TB (1983) Albinism and other disorders of pigment metabolism. Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS (eds) The metabolic basis of inherited disease. McGraw-Hill, New York p 301

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