Ceroid Histiocytosis of the Spleen in Hyperlipemia: Relationship to the Syndrome of the Sea-blue Histiocyte

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ABSTRACT

Rywlin, Arkadi M., Lopez-Gomez, Alfredo, Tachmes, Pablo, and Pardo, Victoriano: Ceroid histiocytosis of the spleen in hyperlipemia: Relationship to the syndrome of the sea-blue histiocyte. Amer. J. Clin. Path. 56: 572-579, 1971. Morphologic findings in a patient with primary, type 5 hyperlipoproteinemia of Fredrickson and Lees, reported for the first time, include marked splenomegaly with extensive ceroid histiocytosis, fatty metamorphosis and early fibrosis of the liver, and increased numbers of foam cells in the bone marrow. Diseases associated with accumulation of ceroid in various tissues are tabulated. We stress that, with the Wright or Giemsa methods, ceroid granules are stained sea-blue and ceroid-containing macrophages appear as "sea-blue histiocytes." This staining reaction is not pathognomonic for ceroid. The spleen from a patient with "the syndrome of the sea-blue histiocyte" contained numerous ceroid-containing macrophages. In view of the lack of specificity of the "sea-blue histiocyte," it is suggested that, pending its validation, "the syndrome of the sea-blue histiocyte" be renamed "idiopathic ceroid histiocytosis of spleen and marrow" or "Silverstein's syndrome."

Fredrickson and Lees have clarified the complex problem of the hyperlipidemias by classifying them into five types on the basis of lipoprotein electrophoresis. Relatively few morphologic data describing the five groups of hyperlipoproteinemias are available. Some of the older reports lack adequate information to assign them to one of the five types.

No pathologic findings in patients with clearly established type 5 hyperlipoproteinemia seem to have been recorded. We describe histologic characteristics of the spleen, liver, and bone marrow of a patient with type 5 hyperlipoproteinemia. We stress that ceroid-containing macrophages are identical to sea-blue histiocytes when treated with the Wright or Giemsa stains. The significance of this finding in the evaluation of the recently described syndrome of the sea-blue histiocyte is discussed.

Report of a Case

A 35-year-old, Caucasian Cuban accountant was admitted to the hospital for evaluation of hepatosplenomegaly. Enlargement of the spleen, first noted when the patient was 7 years old, had been attributed to...
FIG. 1 (upper, left). Foam cell in bone marrow smear. Giemsa stain. × 1,134.

FIG. 2 (upper, right). Histiocytes containing granules and vacuoles in spleen. Hematoxylin and eosin. × 720.

FIG. 3 (lower, left). Clump of histiocytes in spleen with PAS-positive cytoplasmic granules. Periodic acid-Schiff stain. × 720.

FIG. 5. Ultrastructural appearance of ceroid-containing histiocyte in spleen, adjacent to sinusoid (S): A = whorls of unit membranes; B = bodies consisting of electron dense material. Formalin fixed, epon 812 embedded, stained with uranyl and lead. $\times 5,400$. C = area magnified ($\times 38,000$) in inset.
malaria. Enlargement of the liver and mild hypertension had been discovered 4 and 2 years before admission. As a child, the patient had several bouts of malaria and typhoid fever. His parents are not consanguineous. The father is 65 years old, and has diabetes mellitus, hypertension, and questionable hepatomegaly. The mother and two siblings are healthy. The patient is married and has three healthy children. He drinks alcoholic beverages occasionally and does not smoke.

The patient was moderately obese, weighed 190 pounds, and was 5' 11" tall. Blood pressure was 140/80 mm. Hg. There was no arcus senilis, lipemia retinalis, skin lesions, or lymphadenopathy. The liver was palpated 4 cm., and the spleen 12 cm., below the costal margins. There were no premature arteriosclerotic changes in the retinal arteries.

**Laboratory Data**

Hemoglobin was 16 Gm. per 100 ml., hematocrit 47%, leukocyte count 3,600 per cu. mm. with a normal differential, platelet count 90,000 per cu. mm., and reticulocyte count 3.4%. BUN, fasting blood glucose, calcium, phosphorus, total protein, albumin, bilirubin, alkaline phosphatase, LDH, and SGOT were normal. Uric acid was 9.5 mg. per 100 ml. and cholesterol, 310 mg. per 100 ml. No acid mucopolysaccharides were found in the urine.

A bone marrow aspirate was normal, except for the presence of an increased number of foam cells (Fig. 1).

Splenectomy and liver biopsy were performed because of hepatosplenomegaly of unknown cause with hypersplenism, as evidenced by thrombocytopenia, leukopenia, and an elevated reticulocyte count.

Postoperatively, a nonpruritic, erythematous, papular rash appeared on the chest, shoulders, back, and buttocks. The platelet count rose to 760,000 per cu. mm. on the eighth postoperative day.

A lipid profile was done 3 months after surgery because of repeatedly high cholesterol levels, reports of lipemic serum, and puzzling histologic findings in the spleen and liver. After a 2-week period of a regular diet, a 12-hour fasting serum specimen was lipemic. Filter paper lipoprotein electrophoresis showed chylomicrons and hyperbetalipoproteinemia. Cholesterol was 787 mg. per 100 ml. and triglycerides were 5,900 mg. per 100 ml. A glucose tolerance test was normal. The lipid studies were repeated after 1 month of a special diet for hyperlipoproteinemia type 5, and 500 mg. of clofibrate, t.i.d. Cholesterol was 355 mg. per 100 ml. and triglycerides were 687 mg. per 100 ml. The serum was lipemic, and lipoprotein electrophoresis was unchanged. The clinical diagnosis was hyperlipoproteinemia, type 5 of Fredrickson and Lees.

**Histologic Examination**

The spleen was markedly enlarged and weighed 1,230 Gm. The capsule and cut surface were unremarkable. Microscopic examination disclosed normal Malpighian follicles and trabeculae. The sinuses were of normal caliber and had prominent endothelial cells. In the red pulp, there were numerous histiocytes, located predominantly in the cords of Billroth. These histiocytes were 15 to 50 μ in diameter and were assembled in clumps of four to five cells, often intermingled with plasma cells. Their nuclei were relatively small and unremarkable. Their cytoplasm contained various amounts of small granules which, in hematoxylin and eosin stained sections, ranged in color from pale yellow to gray-brown. Many of the cells were densely packed with these granules; others had a few vacuoles associated with the granules (Fig. 2).
These granules demonstrated all the histochemical reactions characteristic of ceroid. They were stained by oil red O and Sudan black in frozen and in paraffin-embedded sections, and they were PAS positive before and after diastase digestion (Fig. 3). The peracetic acid-Schiff reaction was positive. The granules were acid fast, autofluorescent, and stained dark blue with Luxol-fast blue and Nile blue sulfate. Stained by the Giemsa method, the granules appeared sea blue (Fig. 4). The Gomori reaction for iron was negative. Small amounts of lipids were demonstrated in some splenic arterioles.

Electron microscopic examination of formalin-fixed tissue showed the ceroid granules as whorls of electron dense unit membranes identical to myelin figures. Other granules appeared as electron dense bodies in a finely granular background (Fig. 5).

A needle biopsy of the liver disclosed severe fatty metamorphosis, particularly marked in the inner two thirds of the liver lobule. Thin fibrous septa extending from the portal spaces into liver lobules were present. There was no significant inflammatory reaction. The Kupffer cells were normal and no ceroid-containing histiocytes were seen (Fig. 6).

The diagnoses were: (1) ceroid histiocytosis of the spleen; (2) fatty metamorphosis with early fibrosis of the liver; (3) foamy histiocytes in the bone marrow.

Discussion
Although more than 30 patients with familial type 5 hyperlipoproteinemia have been studied by Roberts and associates, none have died and no biopsies have been performed. It is possible that patients with type 5 hyperlipoproteinemia have been reported, but a compilation from the literature is impossible because of lack of specific information about lipoprotein pat-
Table 1. Conditions Associated with Accumulation of Ceroid

- Neuronal ceroid-lipofuscinosis (Batten's disease)
- Tay-Sachs' disease
- Niemann-Pick's disease
- Adult lipidosis resembling Niemann-Pick's disease
- Gaucher's disease
- Metachromatic leukodystrophy
- Globoid leukodystrophy
- Wolman's disease
- Ceroid accumulation in progressive neurologic disease
- Visceral histiocytic glycolipidosis with mental retardation
- Ceroid storage disease
- Chronic granulomatous disease of childhood
- Familial lipochromic histiocytosis
- Vascular pseudohemophiliia associated with ceroid pigmentophagia in albino
- Hyperlipoproteinemia
- Idiopathic thrombocytopenic purpura
- The syndrome of the sea-blue histiococyte
- Chronic granulocytic leukemia
- Sickle cell anemia
- Cirrhosis of the liver

Malabsorption syndromes with probable vitamin E deficiency:
(a) cystic fibrosis of pancreas
(b) Whipple's disease
(c) sprue
(d) chronic pancreatitis
(e) regional enteritis
Miscellaneous: ceroid-like colonic histiocytosis, hemochromatosis, old hemorrhage and endometriosis

* Conditions in which ceroid-containing histiocytes have been demonstrated in the spleen and/or bone marrow.
† Only the first case of Silverstein et al. was examined and shown to have ceroid in splenic histiocytes.
‡ Sea-blue histiocytes in the bone marrow reported. Ceroid nature of pigment unproven, because specific histochemical stains were not recorded.

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used for a similar pigment seen in a variety of pathologic conditions (Table 1).

The name “ceroid” is, by now, well established in medical literature. Objection to its use has been voiced by Wolman, who prefers Ciaccio’s “chromolipoid,” because it is more inclusive and has historical preference.

Splenic ceroid-containing histiocytes have also been reported in idiopathic thrombocytopenic purpura, in “the syndrome of the sea-blue histiocyte,” and in other conditions (Table 1).

In 1970, Silverstein and co-workers described “the syndrome of the sea-blue histiocyte,” characterized by splenomegaly, thrombocytopenia, cirrhosis of the liver in two of nine patients and numerous “sea-blue histiocytes” in the bone marrow in all patients. Dr. Silverstein kindly permitted us to examine the spleen from his first patient with “the syndrome of the sea-blue histiocyte.” The spleen was markedly enlarged and infiltrated with histiocytes filled with granules exhibiting all the histochemical criteria of ceroid. These histiocytes were identical to those in our patient. The lipid profile of the patient was normal.

Ceroid-containing histiocytes in the spleen or bone marrow are not diagnostic and may be seen in a variety of conditions (Table 1). Furthermore, the Giemsa reaction is not pathognomonic for ceroid, and, therefore, the presence of “sea-blue histiocytes” should be followed by histochemical studies to confirm the ceroid nature of the pigment. Melanin and hemosiderin are stained green-blue by the Giemsa method and resemble ceroid granules.

In view of these considerations, the appellation “syndrome of the sea-blue histiocyte” appears inappropriate and should be replaced, pending elucidation of etiology or pathogenesis, by “idiopathic ceroid histiocytosis of spleen and marrow” or “Silverstein’s syndrome.”

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References


