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Idiopathic Ceroid Histiocytosis of Spleen: Syndrome of the Sea-Blue Histiocyte*

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The term ceroid was first applied by Lillie et al[7] to a wax-like, coarse, yellow pigment noted in the cirrhotic livers of rats maintained on a low protein, low fat diet. Endicott and Lillie[1] subsequently described this pigment as having a bronze brown color in gross preparations. Microscopically, it appears as yellow globules 1 to 20 micra in diameter. Histochemical characteristics of ceroid were studied extensively and were described, in part, as follows:

1. It is stained by oil soluble dyes both in frozen sections and paraffin prepared tissues. Oil soluble dyes are readily removed by acetone and alcohol. Following removal of the dye, the preparation may be restained.

2. It demonstrates greenish yellow autofluorescence which fades to pale yellow on frozen sections.

3. It shows golden brown autofluorescence of unstained paraffin sections.

4. It stains positively with the periodic acid, peracetic acid and performic acid, using the Schiff procedure.

5. It retains acid fast stains.

6. It is insoluble in dilute acids and alkalis but it is saponified by boiling in 10 percent NaOH. Fatty acids are precipitated from solution by acids.

7. It is insoluble in alcohols, acetone, ether, aliphatic and aromatic hydrocarbons, chloroform, carbon tetrachloride, pyridine, acetic anhydride, glycols and glycerol.

8. It is not bleached by permanganate, chromic acid, hydrogen peroxide, bromide or chlorine water.

9. The Prussian blue reaction is usually negative, but iron positive pigment is sometimes associated with it.

10. It stains strongly with basic fuchsin and methylene blue.

Experimental studies have shown that ceroid is the result of oxidation and polymerization of unsaturated lipids.[2] At the present time its exact chemical structure is

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unknown. Depending upon the degree of oxidation and polymerization the histochemical reactions may differ somewhat. Autofluorescence appears first, followed by PAS positivity and then acid-fastness.[3]

Lipofuscin and ceroid seem to have similar histochemical characteristics. Different physical characteristics have been postulated by some.[18] At present lipofuscin seems the preferred term for the naturally occurring, age-related pigment, while ceroid is used for a similar pigment in experimental and pathologic conditions. Objection to the term ceroid has been voiced by Wolman[17] who prefers Ciaccio's chromolipoid because it is more inclusive and has historical preference. The term, however, is well established in medical literature.

Recent delineation of a peculiar syndrome characterized by splenomegaly, thrombocytopenia and sea-blue histiocytes has evoked considerable interest. Silverstein et al[16] has called this entity syndrome of the sea-blue histiocyte. Rywlin et al[12] have shown that the pigment in one of Silverstein's cases was ceroid and have proposed that the syndrome be renamed idiopathic ceroid histiocytosis of spleen and marrow, since ceroid containing histiocytes can accumulate in the spleen and bone marrow under different circumstances including both dietary intake of unsaturated fats, hyperlipoproteinemias, ITP, various hemolytic processes and other lipid histiocytoses.

Case Report

A 27 year old married white man (J.M.H. 948981) had a history of pain in the left lower quadrant of the abdomen of three days duration. Medical history included an appendectomy three years ago at which time splenomegaly was noted. Since the appendectomy, the patient has had recurrent episodes of left lower quadrant pain, stabbing in nature, occurring about once monthly and lasting for 15 to 20 seconds. The episodes of pain increased gradually in frequency and severity; recently, the attacks occurred 15 to 20 times daily. There was weight loss of an unstated amount in the past 5 to 6 weeks. There was nausea but no emesis. The patient denied melena, hemoptysis, diarrhea, steatorrhea or anorexia. The patient denied excessive alcohol intake but smoked 1 to 1.5 packs of cigarettes daily. There was a history of poliomyelitis as a child. Family history was noncontributory. Dietary habits were unremarkable, and there was no apparent excessive intake of lipids.

Pertinent findings on physical examination revealed a mild enlargement of upper cervical lymph nodes and a smooth nontender spleen felt 8 cm below the costal margin. Retinal examination was not recorded.

Extensive laboratory investigation revealed no significant positive findings. This included complete blood count including differential count, platelets, urinalysis, prothrombin time, partial thromboplastin time, SMA-12 panel, serum iron and serum iron binding capacity, antinuclear antibody, heterophile, Coombs tests, lipase, amylase, fetal hemoglobin, haptoglobin, G-6-PD, methemalbumin, serum protein electrophoresis and immunoelectrophoresis, hemoglobin electrophoresis, and lipid fractionation. Serum cholesterol was 180 mg per 100 ml, and triglycerides were 68 mg per 100 ml. Lipoprotein electrophoresis was within normal limits.

Radiological examination revealed a normal upper gastrointestinal series with splenomegaly. Splenic arteriogram outlined an enlarged spleen without evidence of a discrete mass. An IVP was normal.

Needle biopsy of liver was normal. Smears of a sternal bone marrow aspiration were normal, no foam cells or sea-blue histiocytes were seen.

A splenectomy was done (S-71-856) which revealed a spleen weighing 450 gm. The capsule was smooth, thin and intact. The cut surfaces were firm, slightly bulging, and homogeneous dark red. Trabecular structures and lymphoid follicles were not prominent.

A frozen section diagnosis of "lipid histocytosis, type undetermined" was rendered. On microscopic examination of permanent sections there were well-demarcated follicles and trabecular structures. The red pulp contained innumerable large histocytic cells occurring singly and in small groups, predominantly in the cords of Billroth. Their cytoplasm was finely and coarsely vacuolated to granular; frequently, small regular brown granules were visible in some of the cells. They were grouped principally around trabecular structures. No abnormal plasma cell infiltrate was noted.

Histochemical characteristics:

1. Hematoxylin and eosin stains: finely to coarsely vacuolated cells, some of them containing a fine, uniform brown granularity.

2. Periodic acid-Schiff reaction-positive with and without diastase digestion.

3. Oil red O-positive in frozen and paraffin processed tissues.

4. Sudan Black B, positive in frozen sections and in paraffin processed tissues.

5. Acid fast stains positive.

6. Giemsa stain: granular sea blue cytoplasm seen on splenic imprints.

7. Fluorescence microscopy: tan brown fluorescence seen in formalin fixed unstained sections and in the granules of the sea blue histiocytes of the splenic imprints.

Final pathological diagnosis was "ceroid histiocytosis, idiopathic."

Review of Literature

Moeschlin[10] first described the occurrence of "blue pigment" macrophages in a splenic puncture and in a marrow film. It was Sawitzky, Hyman and Hyman[14] who first described a clinical syndrome associated with an unidentified reticuloendothelial cell in the bone marrow and spleen in two patients. They divided the cells into two morphologically distinct types: (1) a large reticuloendothelial-like cell with a single nucleus usually eccentrically placed whose cytoplasm was packed with blue staining pigmented granules of variable size and shape whose stain intensity varied from a very light azure blue to a deep sea blue; and (2) a large foamy reticuloendothelial cell with scattered dark granules. This appeared to be a macrophage of the type not uncommonly noted in the bone marrow. Histochemically, the granules were PAS

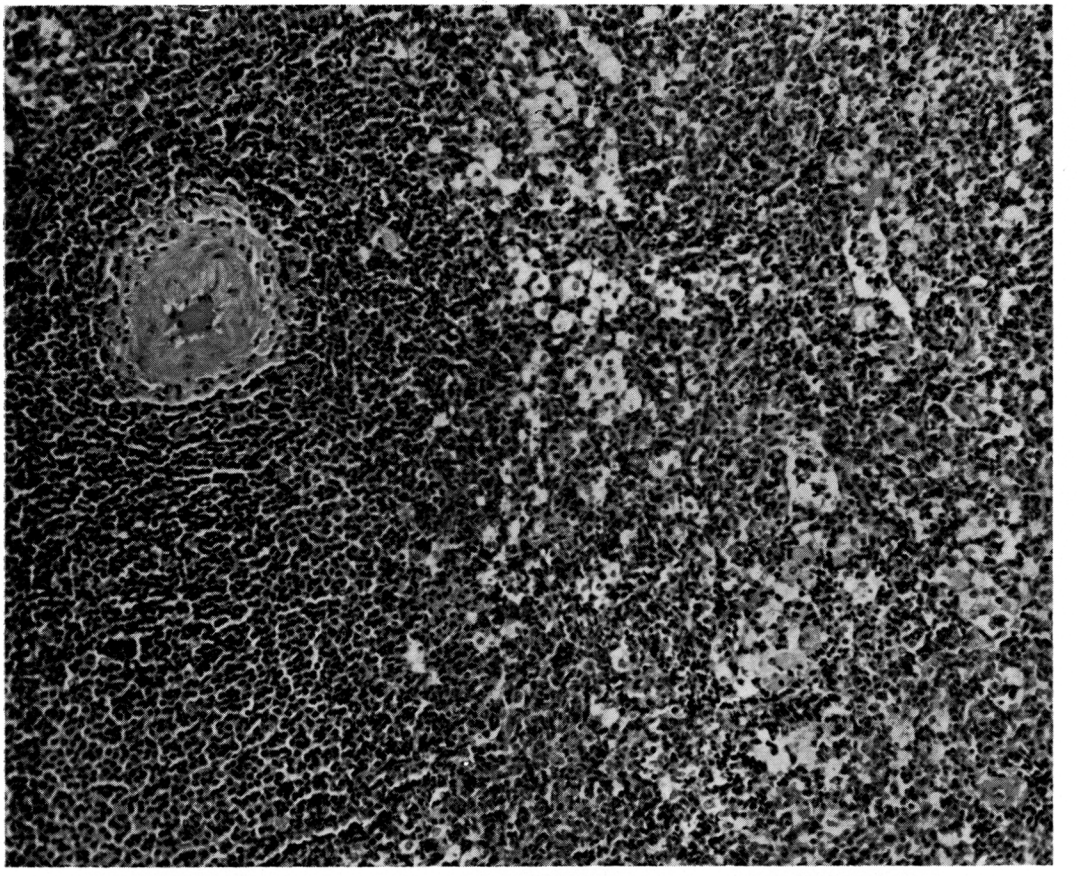

FIGURE 1. Low power photomicrograph of spleen showing preservation of the general architecture with numerous foamy histiocytes in the red pulp. (H&E ×176)

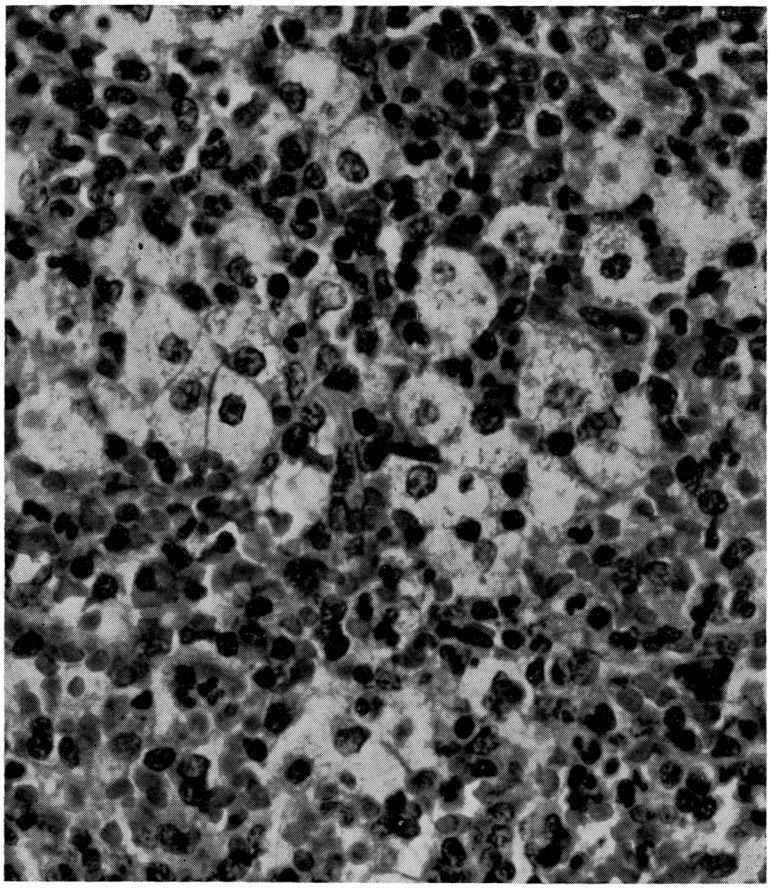

FIGURE 2. Red pulp of the spleen containing numerous large histiocytes with foamy cytoplasm. (H&E × 666)

positive before and after diastase, toluidine blue negative, alkaline phosphatase negative, acetic-carbol-sudan III negative, Feulgen negative, and iron negative. The authors felt that the granules contained mucopolysaccharides. They suggested a syndrome consisting of asymptomatic splenomegaly, normal hematological findings and a benign course.

Marshall and Adams[9] observed a patient with an unusual form of lipidosis associated with thrombocytopenia and angiomas of the spleen. The patient had a normal bone marrow, normal liver and splenomegaly. Three types of macrophages were described: (1) with coarsely vacuolated cytoplasm; (2) with clear or finely vacuolated cytoplasm; and (3) with brownish yellow pigment diffusely spread throughout the cell. Biochemically, there was an increase in phospholipid and glycolipid. Histochemically, the coarse granules were considered to be saturated phospholipids, the pigmented granules nonreducing lipofuscin (ceroid), and the fine granules saturated glycosphingoside or glycolipid.

Malinin[8] in 1961 presented a case report of a 30 year old female with hepatosplenomegaly. The bone marrow contained two abnormal cell types: (1) a prominent cell representing a large reticuloendothelial-like cell with a small eccentrically placed nu-

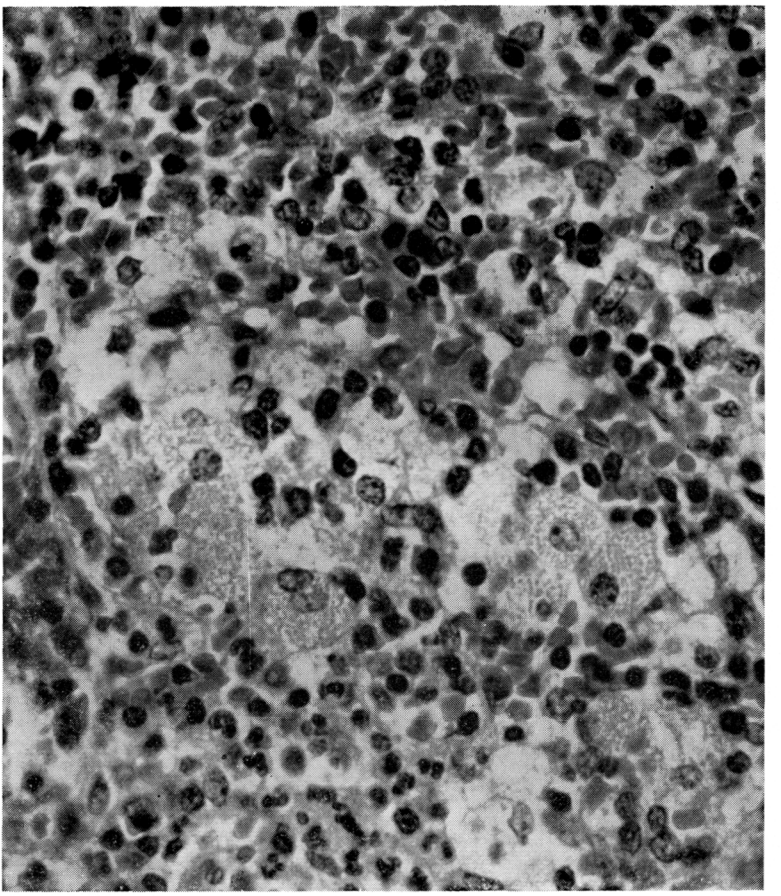

FIGURE 3. Red pulp of the spleen. Many of the large histiocytes contain well-defined ceroid granules. (H&E ×666)

cleus whose cytoplasm contained numerous dark sea blue, densely packed round and oval granules; (2) a cell with a foamy cytoplasm, scattered dark blue granules and an eccentric nucleus with a prominent nucleolus; and (3) an intermediate stage represented by cells whose cytoplasm contained vacuoles as well as dark blue granules. In the liver, abnormal cells were noted in the sinusoids and in periportal connective tissue. Histochemically, the cells were PAS positive with and without diastase, Feulgen negative, and sudanophilic in both paraffin and frozen sections after boiling in acetate buffer at pH 4. Metachromasia was absent with toluidine blue. Malinin concluded that the granules were composed of an insoluble unknown chemical complex containing lipid and protein.

Silverstein, Young and ReMine in 1964[15] presented a case report of a 60 year old white female with hepatosplenomegaly, easy bruising and bleeding. Lipid profile was normal. The bone marrow contained large histiocytes with a cyptoplasm packed with large blue staining granules. A few of the well granulated histiocytes contained pale yellow pigment. Histochemically, the cells were PAS positive both before and after diastase digestion, were Sudan Black positive and iron negative. The granules were considered to be a phospholipid or

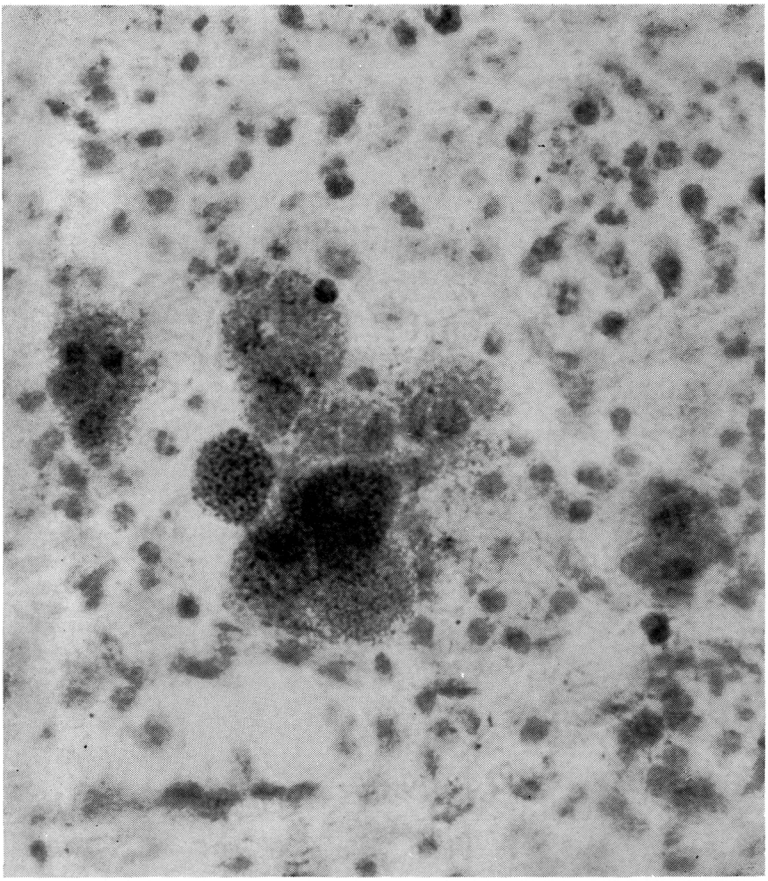

FIGURE 4. Splenic histiocytes containing Oil Red O positive granules. Frozen section material. (×1664)

glycolipid. The authors considered this to be a syndrome characterized clinically by splenomegaly and morphologically by the presence of a distinct unusual histiocyte. They found no evidence for a familial or congenital basis. This case was reexamined by Rywlin et al[12] and splenic histiocytes were shown to contain abundant ceroid.

Holland[4] discussed chronic reticuloendothelial cell storage disease and presented a case report of a six year old child with asymptomatic hepatosplenomegaly, normal serum lipid profile, and with normal serum triglycerides. Studies were done on bone marrow aspiration smears and paraffin sections. He described two morphologically distinct but probably related storage cell types: (1) Cells varying from 20 to 50 micra with numerous blue granules scattered throughout the cytoplasm; (2) Cells 20 to 60 micra in diameter without cytoplasmic granules but with a foamy vascuolated cytoplasm; and (3) Intermediate forms present with only a few granules in a vacuolated cytoplasm. The cells were PAS positive with and without diastase digestion, toluidine blue negative, and Sudan Black B positive which suggested that the lipid was primarily a phospholipid.

Silverstein, Ellefson, and Ahers[16] in 1970 coined the term "syndrome of the sea-blue histiocyte" and described the case of a black

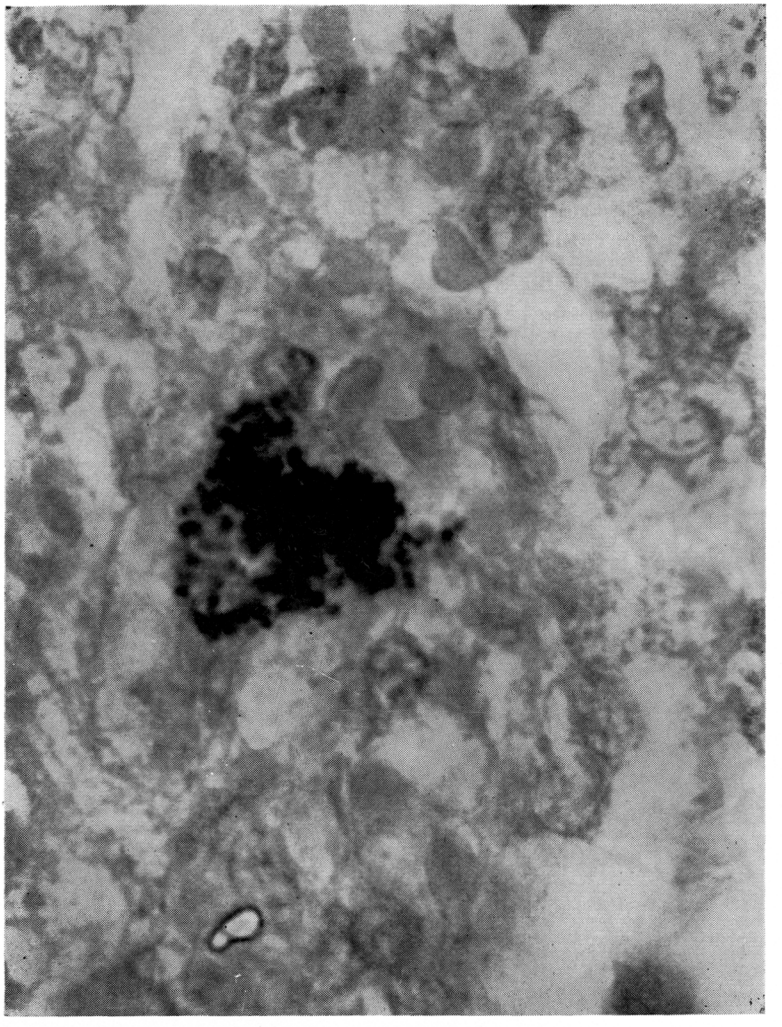

FIGURE 5. Splenic histiocytes with acid-fast positive granules in the cytoplasm. Acid fast stain. (×1664)

girl observed from 16 months to 10 years of age. She presented with hepatosplenomegaly and persistent thrombocytopenia. Bone marrow examination revealed a moderate number of sea-blue histiocytes. Splenomegaly was done during the course of the child's illness. Final admission at 10 years of age was preceded by fever and deepening jaundice. At necropsy the liver showed obvious cirrhosis and fatty vacuoles in parenchymal cells. Previously recorded cases were reviewed and delineated a syndrome characterized by occurrence of a rare, morphologically distinct blue, granulated histiocyte associated with splenomegaly. It was postulated that the syndrome represented a definite metabolic abnormality characterized by a relatively benign course with mild purpura or bleeding tendency secondary to thrombocytopenia. It was thought that progressive cirrhosis with hepatic failure and death could occur.

Jones, Gilbert, Zugibe and Thompson[5] described two siblings, ages 10 and 12 years

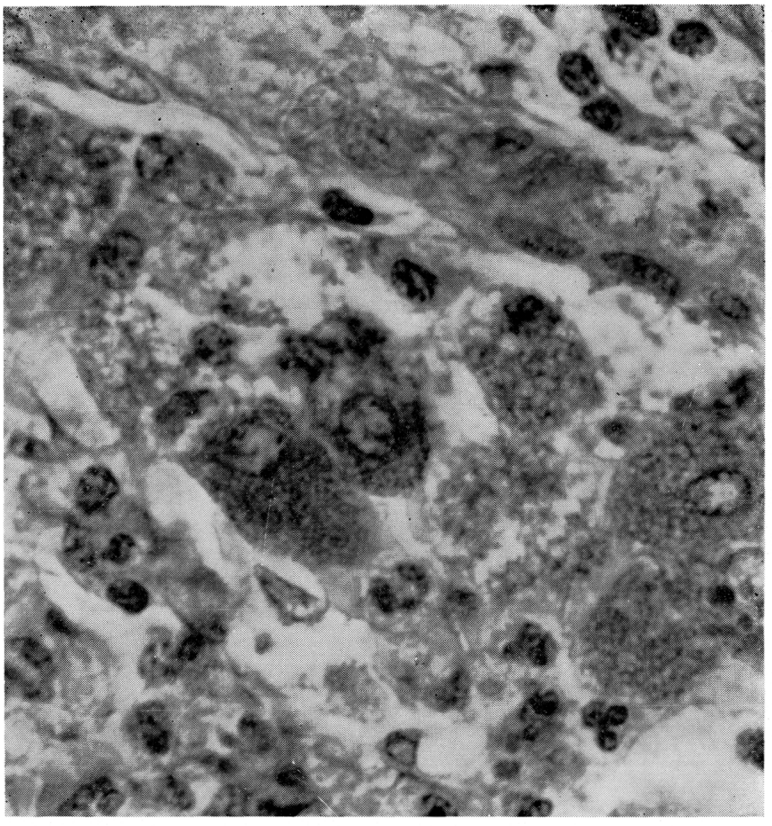

FIGURE 6. Splenic histiocytes with PAS positive granules in the cytoplasm. Periodic acid Schiff stain. (×1664)

with the sea-blue histiocyte syndrome. The diagnosis was made on the basis of bone marrow aspirates. Findings of bone marrow material in the parents and one sibling were normal. The authors postulated that the disease was a hereditary disorder of lipid metabolism similar to Gaucher's disease and transmitted as an autosomal recessive trait.

Saidi et al[13] published the account of a 16 year old Iranian boy admitted for hepatosplenomegaly which had been noted since early childhood. There was no documented case of hepatosplenomegaly in the family. Bone marrow aspirate contained many large histiocytes with many cytoplasmic granules of varying size and varying stain intensity from light azure to deep blue. Liver biopsy revealed cells similar to those seen in the bone marrow. The granules were weakly PAS positive. No further histochemical reactions were carried out.

Rosner et al[11] presented a short case report of a 20 year old black man admitted because of grand-mal seizures, fever, right supraclavicular adenopathy and a large nontender firm spleen. Biopsy of the supraclavicular node showed coalescent epithelioid granulomas. No acid fast or fungal organisms were noted. The patient was given antitubercular therapy. A bone marrow aspiration showed moderate numbers of "sea-blue histiocytes." Histochemical staining reactions were similar to those previously described by other authors.

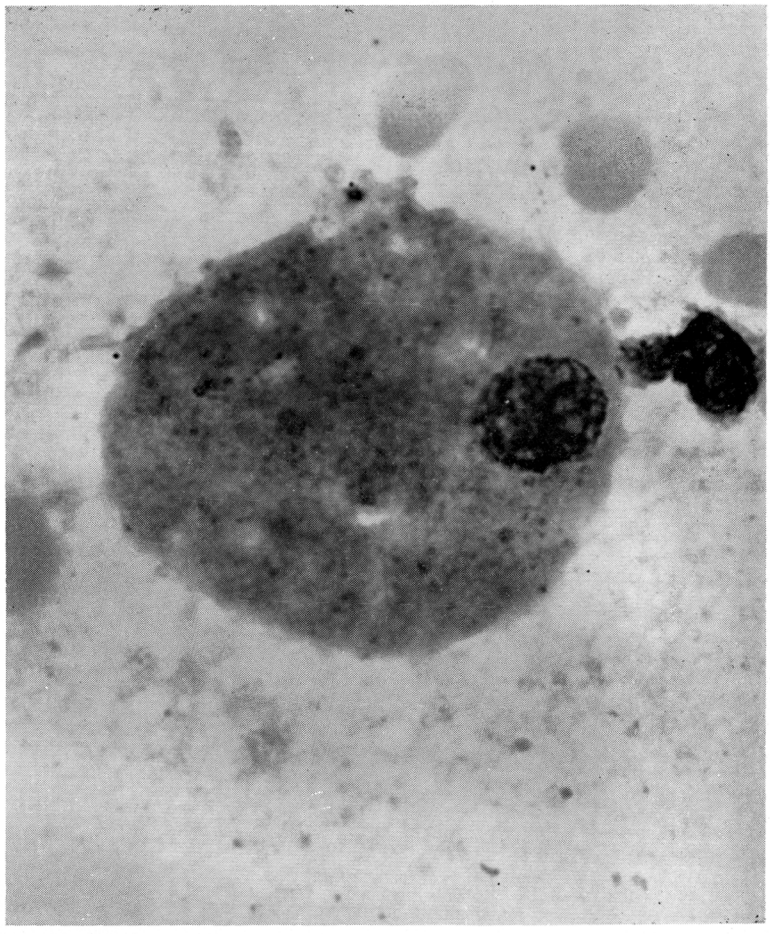

FIGURE 7. Splenic imprint containing a large histiocyte cell with blue granular cytoplasm (sea-blue histiocyte) Wright's stain. (×1664)

Comment

A seemingly divergent group of cases are reviewed here which have as a common denominator lipid-containing histiocyte occurring in the spleen and sometimes in the liver and bone marrow and unaccompanied by any of the biochemical alterations known to give rise to such cells. Splenic lipid histiocytes may be associated with hyperlipoproteinemia, idiopathic thrombocytopenic purpura, Felty's syndrome, aplastic anemia, acute granulocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and a number of diverse conditions as outlined by Rywlin et al[12] or may be idiopathic as in the patient presented in this paper.

The studies of Sawitsky et al[14] were based on bone marrow and splenic smears. The type I cell contained blue staining pigmented granules when stained with Giemsa stain. Since the Giemsa reaction for ceroid is nonspecific[12] and since histochemical stains for ceroid other than the PAS reaction were not investigated by Sawitsky, it is entirely possible that his cases fall into the category of what is here called ceroid histiocytosis.

The type III cell described by Marshall and Adams[9] contained brownish yellow pigment diffusely spread throughout the cell. Histochemically, the pigmented granules were considered to be nonreducing lipofuscin (ceroid).

In the case presented by Malinin,[8] a type II cell in the bone marrow was described with a foamy cytoplasm and scattered dark blue granules. The granules were PAS positive both before and after diastase digestion and sudanophilic in both paraffin and frozen sections after boiling in acetate buffer. This combination of histochemical properties strongly suggests the presence of a ceroid-like pigment.

The patient described by Silverstein et al[15] contained histiocytes in the bone marrow. These cells exhibited a cytoplasm with large, blue staining granules and occasionally with pale yellow pigment. The cells were PAS positive before and after diastase digestion, were Sudan Black positive and iron negative. Silverstein considered the granules to be a phospholipid or glycolipid.

The sections of the spleen of the first patient described by Silverstein as "syndrome of the sea-blue histiocyte"[16] were examined. The histiocytes had all the histochemical criteria of ceroid and were identical with those in the patient presented in this paper.

In the case of Holland et al,[4] cells were described in the bone marrow as having numerous blue granules throughout the cytoplasm. These granules were PAS positive with and without diastase digestion, and were Sudan Black B positive, suggesting the presence of ceroid but precluding its identification because of insufficient data.

In the two patients described by Jones et al,[5] the granules of the sea-blue histiocytes of the bone marrow were PAS positive, Sudan Black B positive, Oil Red O positive before and after cold acetone extraction. It was concluded that the histiocytic cytoplasm contained a glycophospholipid complex.

A critical review of the published case reports leads one to the following tentative conclusions:

1. Ceroid histiocytosis may be seen in a variety of clinical states and probably therefore represents a nonspecific morphologic response to a diversity of biochemical alterations.

2. Although ceroid containing histiocytes may appear in a number of diseases, the syndrome described by Silverstein et al[16] may represent a specific entity characterized clinically by splenomegaly and anatomically by the presence of numerous ceroid-containing histiocytes in the spleen and/or bone marrow in the absence of any of the known biochemical alterations known to give rise to such cells.

3. The presence of ceroid cannot be ascertained in all the cases reported as syndrome of the sea-blue histiocyte because of incomplete histochemical data. However, none of the histochemical reactions reported were inconsistent with ceroid. Furthermore, ceroid-containing histiocytes stain blue with Giemsa and appear as sea-blue histiocytes. Also, in five of the cases, including, the present report accepted as syndrome of the sea-blue histiocyte, the histochemical reactions indicated the presence of ceroid.

4. The following cases along with the presently reported case can then be reasonably accepted as examples of idiopathic ceroid histiocytosis or "syndrome of the sea blue histiocyte":

Sawitsky, Hyman and Hyman,[14] Marshall and Adams,[9] Malinin,[8] Silverstein, Young and ReMine,[15] Holland, Hug and Schubert,[4] Silverstein, Effelson and Ahers,[16] Jones, Gilbert, Zugibe and Thompson,[5] Rosner, Kagen, Dana,[11] Saidi, Azizi, Scarlati and Sayer,[13] and Teloh and Rywlin.

Summary

The general chemical and histochemical nature of ceroid is discussed. A case report of "idiopathic ceroid histiocytosis of spleen" is presented. A review of case reports of idiopathic ceroid histiocytosis is presented.

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When griping grief the heart doth wound,
And doleful dumps the mind oppress,
Then music with her silver sound,
With speedy help doth lend redress.

Shakespeare. *Romeo and Juliet.*