Ceroid Histiocytosis of Spleen and Bone Marrow in Idiopathic Thrombocytopenic Purpura (ITP): A Contribution to the Understanding of the Sea-blue Histiocyte

By Arkadi M. Rywlin, Juan A. Hernandez, Doyle E. Chastain and Victoriano Pardo

Ceroid-containing histiocytes are described for the first time in the spleen and marrow of a patient with ITP. Ceroid results from the oxidation and polymerization of unsaturated lipids and may appear in histiocytes in a variety of diseases. With the Wright or Giemsa methods, ceroid granules are stained sea-blue, and ceroid-containing macrophages appear as “sea-blue histiocytes.” This sea-blue color is not pathognomonic for ceroid. Therefore, the finding of sea-blue histiocytes in the bone marrow should be followed by histochemical studies to confirm the presence of ceroid. The spleen from a case of the recently described “syndrome of the sea-blue histiocyte” showed numerous ceroid-containing macrophages. In view of the lack of specificity of the sea-blue histiocyte, it is suggested that the syndrome be renamed “idiopathic ceroid histiocytosis of spleen and marrow.”

THE TERM “CEROID,” derived from Greek, means waxlike. It was introduced by Lillie et al. in 1942 to describe a pigment occurring in experimental dietary cirrhosis in rats. Ceroid has been studied in depth by Hartroft and Porta. It is defined by its insolubility in hydrocarbon lipid solvents and its reactivity with fat stains, such as oil red O and Sudan black. It is further characterized by a pale yellow to dark brown color, autofluorescence, periodic acid–Schiff (PAS) positivity before and after diastase digestion, acid fastness, and a strong affinity for basic dyes such as fuchsin and methylene blue. Lipofuscin and ceroid share the same physical and histochemical characteristics. At present lipofuscin seems the preferred term for the naturally occurring, age-related lipochrome, while ceroid is used for a

From the Department of Pathology and Laboratory Medicine, Mount Sinai Hospital of Greater Miami, Miami Beach, Fla.; the V.A. Hospital of Miami and University of Miami School of Medicine, Miami, Fla.; and the Departments of Pathology and Medicine, Jess Parrish Memorial Hospital, Titusville, Fla.


Arkadi M. Rywlin, M.D.: Director, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital of Greater Miami, Miami Beach, Fla.; Professor of Pathology, University of Miami School of Medicine, Miami, Fla. Juan A. Hernandez, M.D.: Director, Department of Pathology, Jess Parrish Memorial Hospital, Titusville, Fla. Doyle E. Chastain, M.D.: Chief, Department of Internal Medicine, Jess Parrish Memorial Hospital, Titusville, Fla. Victoriano Pardo, M.D.: Staff Pathologist, V.A. Hospital of Miami; Associate Professor of Pathology, University of Miami School of Medicine, Miami, Fla.

Blood, Vol. 37, No. 5 (May), 1971
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similar, if not identical, pigment seen in different experimental and pathologic conditions.

We are recording a hitherto unreported observation: ceroid histiocytosis of the spleen and marrow in a patient with ITP. We stress that ceroid-containing macrophages appear as "sea-blue histiocytes"4 when treated with the Wright and Giemsa stains. The significance of this finding in relation to the recently described "syndrome of the sea-blue histiocyte"4 is discussed.

CASE REPORT

A 52-year-old, white housewife, with a Cushingoid appearance, was hospitalized to undergo splenectomy for thrombocytopenia of 9 years' duration, in the hope that her corticosteroid dosage could be reduced. The thrombocytopenia was first discovered when the site of an influenza vaccination continued to bleed. The patient was treated with prednisone for the ensuing 9 years, the latest dose being 10 mg every other day. Any reduction of this dose of prednisone caused purpura. One year prior to the discovery of thrombocytopenia, the patient was told that she had Raynaud's phenomenon. She had no rashes or signs of kidney, liver, lung, or heart disease. The medical and family history and the review of systems were noncontributory. The patient had always eaten a diet that did not contain abnormal amounts of unsaturated fats.

Physical examination was negative. No jaundice, purpura, or ecchymoses were seen. The lymph nodes, liver, and spleen were not palpable. Radiologic studies of the chest, upper gastrointestinal tract, and gallbladder were normal. On admission, hemoglobin was 13.5 gm/100 ml, hematocrit was 40 per cent, and WBC (white blood cell) count was 4000/cu mm with a normal differential count. Platelet count was 165,000/cu mm. Urinalysis, glucose, blood urea nitrogen (BUN), uric acid, calcium, inorganic phosphorus, total protein, protein electrophoresis, bilirubin, alkaline phosphatase, lactic dehydrogenase (LDH), and serum glutamic oxaloacetic transaminase (SGOT) were all normal. The serum was not lipemic, and a lipoprotein electrophoresis was normal. Cholesterol was 215 mg per cent, and triglycerides were 89 mg per cent. No acid mucopolysaccharides were found in the urine. Three lupus erythematosus (L.E.) preparations were negative. The latex test for rheumatoid arthritis was positive 1:20.

A bone marrow aspiration and a splenectomy were performed. The postoperative course was uneventful. Prednisone was discontinued after the operation. Four months after splenectomy, the platelet count was 200,000/cu mm.

Tissue Reports

Bone marrow. The particles were normocellular. Megakaryocytes were normal and showed adequate platelet production. The red cell series was normoblastic. Iron stores were decreased. The granulocytic series showed normal maturation. Giemsa-stained smears

Fig. 1.—Bone marrow smear: Histiocyte filled with blue granules. Giemsa × 1134.

Fig. 2.—Bone marrow section: Histiocytes with PAS positive granules. PAS × 1134.

Fig. 3.—Bone marrow, paraffin-embedded section: Histiocyte with Sudan black positive granules. Sudan black × 1134.

Fig. 4.—Spleen, paraffin-embedded section: Histiocytes with Sudan black positive granules. Sudan black × 720.

Fig. 5.—Spleen: Histiocytes with PAS positive granules after diastase digestion. PAS × 720.

Fig. 6.—Spleen: Histiocytes with blue-green granules closely associated with plasma cells. Giemsa × 1134.
and sections showed many histiocytes with numerous blue granules and some vacuoles (Fig. 1). The histochemical reactions of these cells were identical with those found in the spleen (Figs. 2 and 3).

**Spleen.** The spleen weighed 110 g. Capsule and cut surface appeared unremarkable on gross inspection. On microscopic examination, the Malpighian follicles and trabeculae were normal. Moderately dilated sinusoids were lined by prominent endothelial cells. Numerous histiocytes were seen in the cords of Billroth. These histiocytes, often occurring in small clumps of four or five cells, were particularly abundant around some trabeculae. They measured 15–50 μ in diameter and contained small, round or oval, paracentral or eccentric nuclei. Stained with hematoxylin and eosin, their cytoplasm was filled with small, yellow to brown granules and a few vacuoles. An occasional histiocyte appeared foamy with only a few granules. The pigmented granules were stained with oil red O and Sudan black in both frozen and paraffin-embedded sections (Fig. 4). They were PAS-positive before and after diastase digestion (Fig. 5). They demonstrated golden yellow autofluorescence and acid fastness. The Comori reaction for iron was negative. The granules were green to blue when treated with the Giemsa stain and were identical to those seen in the sea-blue histiocytes. The histiocytes were often closely associated with plasma cells (Fig. 6).

Electron microscopic examination of formalin fixed tissue showed that the ceroid granules were made up of nonmembrane-bound, electron-dense bodies surrounded by a lighter, finely granular background.

The tissue diagnoses were: ceroid histiocytosis of spleen and bone marrow; mild focal fatty metamorphosis, liver biopsy.

**DISCUSSION**

The woman in this report had thrombocytopenic purpura, Raynaud's phenomenon, a positive latex agglutination test for rheumatoid factor and repeatedly negative L.E. preparations. She may represent that type of ITP that evolves into systemic lupus erythematosus.

The patient underwent splenectomy to decrease her corticosteroid requirements. Both spleen and bone marrow showed a striking number of ceroid-containing histiocytes.

Lipid-containing foam cells in the spleens of patients with ITP have been described by several authors. Saltzstein claimed that the lipid was not ceroid. Landing et al. described some brown pigment in the splenic histiocytes of their cases. Foamy and granular splenic histiocytes, the latter containing a brown pigment, interpreted as lipofuscin, were described by Couderc et al. The occurrence of such pigmented cells in the bone marrow of patients with ITP has not been previously described.

Experimental studies have shown that ceroid is the result of oxidation and polymerization of unsaturated lipids. Its formation depends upon the presence of unsaturated lipids and oxidants or the lack of antioxidants, such as vitamin E. The histochemical reactions of ceroid reflect on its degree of oxidation and polymerization. Autofluorescence appears first, followed by PAS positivity and then by acid fastness. These considerations may explain some of the differences in the reported staining reactions of the foam cells in ITP.

The origin of the lipids in the histiocytes in ITP is not established. To us, it seems reasonable to assume that they are derived from platelets. This view is supported by Koepke et al. However, the electron microscopic study of our
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Table 1.—Conditions with Ceroid-containing Histiocytes in the Spleen and/or Bone Marrow

<table>
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<th>Condition</th>
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<tr>
<td>Batten’s disease</td>
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<td>Niemann-Pick’s disease</td>
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<tr>
<td>Tay-Sachs’ disease</td>
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<td>Adult lipidosis resembling Niemann-Pick’s disease</td>
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<tr>
<td>Wolman’s disease</td>
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<td>Ceroid accumulation in a patient with progressive neurological disease</td>
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<tr>
<td>Ceroid storage disease</td>
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<tr>
<td>Chronic granulomatous disease of childhood</td>
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<tr>
<td>Familial lipochrome histiocytosis</td>
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<tr>
<td>Ceroid histiocytosis of spleen with rupture in a vegetarian</td>
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<tr>
<td>Vascular pseudohemophilia associated with ceroid pigmentophagia in albinos</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
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<tr>
<td>Ceroid histiocytosis of spleen and bone marrow in ITP Syndrome of the sea-blue histiocyte (idiopathic ceroid histiocytosis of spleen and marrow)</td>
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<tr>
<td>Chronic granulocytic leukemia</td>
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<tr>
<td>Sickle-cell anemia</td>
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<td>Cirrhosis of the liver</td>
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Only the first case of Silverstein et al. was examined and shown to have ceroid-containing splenic histiocytes. Because the Giemsa reaction for ceroid is not specific, it is possible that in the other cases of this syndrome, the sea-blue histiocytes may contain a different pigment.

‡ These cases had sea-blue histiocytes in the bone marrow. Because the Giemsa stain is nonspecific for ceroid, the nature of the pigment is unproved.

case, performed on formalin-fixed material, failed to reveal any structures resembling platelets within the ceroid-containing histiocytes.

When ceroid-containing histiocytes are stained by the Giemsa method, they have the appearance of the “blue pigment macrophages” of Moeschlin, called “sea-blue histiocytes” by Silverstein et al.

Ceroid-containing histiocytes are not diagnostic of any disease and may be found in the spleen and/or bone marrow in different entities (Table 1). Additional clinical, laboratory, and morphologic data are necessary to establish a specific diagnosis.

In 1970, Silverstein et al. described “the syndrome of the sea-blue histiocyte.” The description was based on nine cases, including two personal and seven from the literature. The syndrome was characterized by a relatively benign course, splenomegaly, thrombocytopenia in four, purpura or bleeding in seven, and cirrhosis in two patients. All nine patients had numerous sea-blue histiocytes in the bone marrow. Dr. Silverstein kindly permitted us to examine the spleen of his first case of “the sea-blue histiocyte syndrome.”

The histiocytes had all the histochemical criteria of ceroid and were identical with those illustrated in this paper.

“The syndrome of the sea-blue histiocyte” seems an inappropriate name for the following reasons: First, “sea-blue histiocyte” merely describes the staining reaction of a cell by the Wright or Giemsa methods. It does not give any clue to the nature of the cytoplasmic granules. Second, we have been shown that the sea-blue histiocytes contain ceroid in the first case of Silverstein
et al.\textsuperscript{15} Third, sea-blue histiocytes are seen in the marrow and/or spleen in many different diseases (Table 1). Fourth, the sea-blue histiocyte may not always represent ceroid, because the Giemsa reaction is not specific for this lipochrome. Thus, hemosiderin and melanin are stained blue-green by the Giemsa method. When sea-blue histiocytes are found, histochemical studies must be carried out to further characterize the pigment.

The syndrome described by Silverstein et al.\textsuperscript{4} may, however, represent a specific entity. It differs from the case reported here and from other instances of ITP with splenic foam cells by splenomegaly as contrasted to relatively normal sized spleens in ITP. But, before a new disease is postulated, the conditions listed in Table 1 must be ruled out. This is not possible in some of the reported cases, because of lack of data such as serum lipids, dietary habits, and the histochemical characterization of the sea-blue granules. Until the syndrome described by Silverstein et al.\textsuperscript{4} is validated, it seems best to call it "idiopathic ceroid histiocytosis of spleen and bone marrow."

ACKNOWLEDGMENT

We wish to thank Dr. Murray N. Silverstein and Dr. Arnold L. Brown, from the Mayo Clinic, for having allowed us to study the spleen of their first case of the "syndrome of the sea-blue histiocyte."

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