CORRESPONDENCE

To the Editor,

A recent article in this journal purportedly identified the granules of the sea-blue histiocyte as ceroid-containing and further stated that "ceroid-containing histiocytes are not diagnostic of any disease and may be found in the spleen and/or bone marrow in different entities."

Since we first described the presence of sea-blue histiocytes in two unrelated individuals and suggested that these patients may represent a previously undescribed syndrome of a lipid-storage disease, almost 36 more cases have been reported and probably an equal number have been seen but not yet reported. Because of our studies of such patients and after a review of the literature we believe that there can be no doubt that the sea-blue histiocyte syndrome is indeed a real entity. Silverstein has recently summarized much of the evidence and has emphasized this point of view. The syndrome, insidious and relatively benign at onset, may coexist with or be precipitated by a more overt and different disease state; but recurring reports indicate that the sea-blue histiocyte syndrome itself may produce abnormalities in lung and liver besides accumulating cells in the bone marrow. A possible variant of the syndrome may be associated with neurological disease. There are two distinct clinical groupings of patients. The first consists predominantly of children or young adults clinically well or with minor complaints and brought to the physician’s attention by their splenomegaly. Investigation of this sign with bone marrow study uncovers the presence of sea-blue histiocyte syndrome. The second group of patients are diagnosed by bone marrow study, having been brought to the medical clinic because of complaints referable to a basic disease such as rheumatoid arthritis, sickle cell anemia, myeloproliferative syndrome, thalassemia, thrombocytopenic purpura. This latter group usually includes the older patients even to the age of 83.

There is now evidence in the literature and in our clinic that the first group of patients represents a genetically determined group in whom a defect in lipid metabolism is basic to the disease syndrome. This clinical syndrome is characterized by splenomegaly, mild anemia, and thrombocytopenia, frequent but not easily defined lung disease and less frequently, eye findings. When bone marrow examination is carried out in siblings, parents and children, a high family incidence of sea-blue histiocytes in the bone marrow is found. The sea-blue histiocyte syndrome is frequently found in family members where no palpable splenomegaly or abnormal peripheral blood values are detected. Although the genetics are not yet worked out, it would appear that this group represents a homozygous, recessive form of the disease, whereas the second group or "acquired" type is a form first precipitated into clinical view by the presence of a different basic disease.

The nature of the lipid within the granules of the sea-blue histiocyte is yet to be determined and "ceroid" may partially describe the material but more than histochemical identification is necessary if the underlying pathogenesis is to be understood. Histochemistry helps more in the localization of a given compound within a cell than in defining structure or function.

It has been stated that when ceroid-containing histiocytes are stained by the Giemsa method, they have the appearance of a blue-pigmented macrophage. It has also been stated that ceroid manifests autofluorescence and is acid-fast staining material. These qualities are characteristic for ceroid. The literature and our own experience state that not all sea-blue histiocytes stain acid-fast. Autofluorescence is a characteristic not limited to ceroid but reflects the presence of multiple unsaturated carbon bonds in that particular spatial arrangement that allows for excitation by ultraviolet light. Bone marrow aspirate smears obtained from a child with Niemann-Pick’s disease also showed mild autofluorescence. Autofluorescence is thereby a nonspecific characteristic.
addition, tissue lipid analyses by either thin layer chromatography or other biochemical techniques, are all in agreement that total tissue lipids are increased in this disease and that phospholipid and particularly sphingomyelin is increased in all spleens and livers examined to almost eight times the amount found in normal spleens. Electron microscopy studies of the cells have also indicated the presence of sphingomyelin in such tissue.

Although one cannot say that ceroid is not present within these histiocytes, to label the histiocyte as "ceroid histiocytosis" and to suggest the syndrome be named "idiopathic ceroid histiocytosis" is to further muddy understanding of a disease pattern better labeled for the present by the nonspecific descriptive term "sea-blue histiocyte syndrome."

References


Reply

Some of the questions raised by Sawitsky et al. are due to misconceptions about ceroid. Ceroid is a pale yellow to dark brown pigment which results from the peroxidation and polymerization of unsaturated lipids. Unsaturated lipids are ubiquitous in biologic material, being present in membranes of subcellular organelles, red blood cells, platelets, etc. Ceroid can be formed whenever there is a supply of unsaturated lipids, oxidants, or a lack of antioxidants. Experimental production of ceroid has been studied in vivo and in vitro. The histochemical reactions of ceroid vary and reflect its degree of oxidation and polymerization. The sine qua non for the identification of ceroid is insolubility in hydrocarbon lipid solvents and reactivity with fat stains such as Oil Red O and Sudan Black. The other histochemical reactions develop as the pigment ages: autofluorescence first,
followed by PAS positivity and acid-fastness last. To my knowledge, no one has claimed that autofluorescence was pathognomonic for ceroid and that acid-fastness was absolutely necessary for its identification.

Ceroid may accumulate in neurons, muscle cells, epithelia, and histiocytes. Ceroid-containing histiocytes have been found in the spleen and bone marrow in a variety of conditions. One might speculate that ceroid-containing histiocytes result from an excessive phagocytosis of unsaturated lipids (hyperlipoproteinemias, diets rich in unsaturated fats, idiopathic thrombocytopenic purpuras, known lipid histiocytoses) and/or a congenital inability of the histiocyte to catabolize unsaturated lipids. Idiopathic ceroid histiocytosis is diagnosed, when ceroid-containing histiocytes accumulate in the absence of one of the above mentioned conditions. Ceroid, whether idiopathic or secondary, is tinctorially a striking by-product of a variety of disturbances in lipid metabolism.

Sawitsky et al. attempt to cast doubt on the ceroid nature of the granules in sea-blue histiocytes or blue-pigment macrophages, a term that has historical preference. We have demonstrated unequivocally that ceroid granules are blue and that ceroid-containing macrophages appear as sea-blue histiocytes with the Giemsa-Wright stain. We have shown this in a patient with idiopathic thrombocytopenic purpura and in another patient with hyperlipoproteinemia and hypersplenism. We have further confirmed this finding in old hematomas where ceroid is abundant. Teloh and have corroborated this observation in a case of idiopathic ceroid histiocytosis of the spleen.

Through the kindness of Dr. Murray N. Silverstein, we were able to establish the ceroid nature of the sea-blue granules in the spleen of his first case of the syndrome of the sea-blue histiocyte. Furthermore, in the cases of Malinin and Marshall and Adams, which are generally accepted as examples of the syndrome of the sea-blue histiocyte, the reported histochemical reactions identify the sea-blue granules as ceroid. Whether all the cases of the syndrome of the sea-blue histiocyte are examples of ceroid histiocytosis cannot be ascertained because of lack of specific histochemical data. In the two cases of Sawitsky et al., the reported histochemical reactions are consistent with, but not diagnostic of, ceroid. The authors concluded, without proof, that the granules "appear to contain mucopolysaccharides."

If the syndrome of the sea-blue histiocyte is indeed a single entity, then the sea-blue granules must be identical in all cases and their ceroid nature must be accepted, since it has been documented in four cases. Therefore, the more precise term "idiopathic ceroid histiocytosis" is fully justified for this syndrome.

A warning, however, must be sounded. The Giemsa-Wright stain is not specific for ceroid and gives a blue color to other brown pigments and to other substances such as mast cell granules. With the Giemsa-Wright stain, all ceroid-containing macrophages appear as sea-blue histiocytes, but whether all sea-blue histiocytes contain ceroid remains to be proven.

If the syndrome of the sea-blue histiocyte represents several entities and the sea-blue granules differ in composition, then the term "syndrome of the sea-blue histiocyte" has even less justification.

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REFERENCES
4. —, Lopez-Gomez, A., Tachmes, P., and
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ERRATA: In A Study of Aplastic Anemia in an Autopsy Series With Special Reference to Atomic Bomb Survivors in Hiroshima and Nagasaki, by Kirshbaum et al. (Blood: No. 1, July, 17-26, 1971) page 21, Table 5, the top part of the table under the heading should read as follows:

<table>
<thead>
<tr>
<th>Bone Marrow</th>
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In Leukemic Reticuloendotheliosis, by Trubowitz, Mason, and Frasca Blood: No. 3, September, 288-298, 1971) on page 295, Fig. 8 should read Fig. 9; Fig. 9 should read Fig. 8.