Lipid Storage Disease

By IAN L. THOMPSON AND WILLIAM C. MOLONEY

IN 1954 Sawitsky, Hyman and Hyman described a lipid storage disorder in two young adults characterized by the presence in the bone marrow smears of large histiocytes with a distinctive blue staining granular cytoplasm. Subsequently, three additional cases have been reported and in this article a sixth case is presented along with a discussion of various aspects of the disorder.2

CASE REPORT

The patient, Mrs. A. C., a 34-year-old white woman of Irish extraction, was first seen at the Hematology Laboratory (Tufts) of the Boston City Hospital on November 4, 1961. She had been admitted to another hospital 5 months previously with complaints of weakness, fatigue and a severe headache. On physical examination an enlarged spleen was found. Although there were no hematologic abnormalities, a bone marrow aspiration was carried out, and large histiocytes with blue staining cytoplasm were noted in the Wright-stained smears.

Her past history was significant in that at the age of 17 she was admitted to the Boston City Hospital because of swelling of the ankles, and at that time the spleen was found to be enlarged 3 cm. below the costal margin. In 1957 when she was 1 month pregnant, the patient was admitted to a Boston hospital for investigation of fatigue and symptoms including palpitation and sweating. Cardiac, renal and thyroid studies revealed nothing of importance except a first-degree heart block. No mention of splenomegaly was made in the record of this admission.

There was no family history of splenomegaly or storage disease. The patient was gravida IX, and she had lost five infants in early pregnancy and at term for unknown causes; the four surviving children were in good health.

At the time of the present examination the patient was extremely nervous but the only positive physical finding was the presence of a spleen extending 5 cm. below the costal margin. Blood studies were within normal limits, and bone marrow aspirations were carried out from the iliac crest and the spinous process of the twelfth dorsal vertebra. These Wright-stained marrow smears showed many large storage cells with blue, granular cytoplasm, scattered among a population of normal myeloid and erythroid elements. The patient's father, three brothers and her four children were examined, but in none of these individuals were enlarged spleens noted.

The patient was lost to follow-up and was not seen again until August 12, 1964. At that time the findings were unchanged except for a slight degree of anemia and a plate-

From the Hematology Laboratory (Tufts), Boston City Hospital, Boston, Massachusetts, and the Department of Medicine, Tufts University Medical School.

This work was supported by Grant CA 07801, USPHS, National Cancer Institute.

First submitted Feb. 10, 1965; accepted for publication May 18, 1965.

IAN L. THOMPSON, M.R.C.P., M.R.A.C.P.: Clinical Fellow in Hematology, (Tufts), Hematology Laboratory, Boston City Hospital. Dr. Thompson was a Postgraduate Fellow in Hematology, NIAMD—supported by Grant T1 AM 5328. Present address: c/o Royal Australasian College of Physicians, Macquarie Street, Sydney, N.S.W., Australia.

WILLIAM C. MOLONEY, M.D., D.Sc. (Hon.): Director, Hematology Laboratory (Tufts), Boston City Hospital, and Clinical Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts.
let count of 90,000/cu. mm. In September 1964 the patient had a spontaneous abortion and during the hospital admission for a D and C, a splenic aspiration was carried out. Smears of the splenic material contained numerous storage cells identical to those noted in the bone marrow specimens.

COMMENTS AND DISCUSSION

The pertinent clinical and laboratory data in the reported cases of this unique storage disorder are listed in table 1. With one exception, all were young adults and five of the six patients were females; unlike Gaucher’s and Niemann Pick’s disease no familial, racial or hereditary factors were associated with this disorder. The disease pursues a relatively benign course, and the most serious complication, thrombocytopenia, occurred in four cases. Removal of the spleen in two patients was followed by a rise in platelets to normal levels. In the case reported by Cogan and Federman a granular lesion in the fovea was described, which these authors consider to be a retinal reticuloendotheliosis. No retinal lesions were noted in our patient, nor were similar lesions reported in other cases. The outstanding feature of this disorder, in addition to splenomegaly, was the presence of easily recognized, large, blue-colored histiocytes in bone marrow smears stained with Wright or Giemsa. These cells contained one or two small dark staining nuclei and the cytoplasm was characteristically filled with large granules varying in color from light to deep blue. In some cells, presumably older and degenerating, the cytoplasm had the colorless vacuolated appearance of Niemann-Pick cells (see fig. 1). The variations in appearance of these cells have been well described by Malinin² and more recently by Silverstein et al.⁴ In the present case the storage cells, when exposed to polarized light, showed birefringence and the cytoplasmic granules appeared red with PAS stain. Other histochemical studies, including Sudan Black B, Oil Red O, toluidine blue, peroxidase, alkaline phosphatase and an esterase method employing naphthol ASD chloroacetate as a substrate,⁵ gave negative results.

While descriptions vary somewhat, there seems little doubt that in all six cases the storage cells present a fairly uniform appearance in marrow and splenic smears stained with Wright or Giemsa. In all four of the six cases so studied, typical storage cells were described in aspirates or biopsies from the spleen. Liver biopsy was carried out in four of the six cases, and storage cells were described in hepatic sinusoids and periportal connective tissue in Malinin’s² case, but not in others. This author and Silverstein et al. also noted storage cells in biopsied mesenteric lymph nodes.²⁴

Presently available histochemical methods are inadequate for exact identification of the storage material. In all six cases PAS stains were positive, and the non-glycogenic character of the storage substance was demonstrated by diastase treatment of the cells. In three of the cases Sudan stains were positive; Malinin noted that in his case the Sudanophilia could only be shown after harsh chemical treatment of the material. In four of five cases tested the toluidine blue stain was negative and alkaline phosphatase activity was absent in all four cases in which this test was employed. It should be pointed out that in fixed tissue sections the cytoplasm of the typical histiocytes appeared colorless with eosin and hematoxylin stains. In two recently reported cases...
removal of the spleen provided the opportunity for biochemical studies of the storage material. Silverstein et al., using sialic acid chromatography, demonstrated increased amounts of sphingomyelin and cerebrosides in the splenic tissue. These authors have also noted the abnormal excretion of acid mucopolysaccharide in the urine of their patient.

In February 1965 a 24-hour urine specimen was obtained from Mrs. C. and this was sent to Dr. M. N. Silverstein at the Mayo Clinic. He arranged for determination of acid mucopolysaccharides in this specimen, and a moderately elevated value of 5 units was obtained. (Normal value 3.25 units ± 0.5 units.) If this observation is confirmed in other cases, it will be of considerable interest and may lead to further information on the underlying mechanism of this disorder. In Cogan and Federman’s case, a preliminary report on the chemical analysis of the splenic material indicated a great increase in total lipid, phospholipid and sphingomyelin.

In addition to Gaucher’s and Niemann-Pick’s disease a number of atypical storage disorders have been reported. Terry et al. described a fatal case in an elderly man which resembled Niemann-Pick’s disease, and several other cases of a similar nature have been encountered. A case in which lecithin apparently was the storage material has been described, while Baar and Hickmans reported extensive studies on two mentally defective siblings with splenomegaly and presence of lipid storage cells, most marked in the spleen. In these children chemical fractionation of the spleen gave results which indicated that the stored lipid material was inosamine phosphatide, probably linked to an amino-sugar. Landing and Shirkey described a syndrome in children consisting of recurrent infection and infiltration of viscera by pig-
### Table 1.—Clinical and Laboratory Data on Six Cases of Lipid Storage Disease

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Age</th>
<th>Sex</th>
<th>Enlarged Spleen</th>
<th>Enlarged Liver</th>
<th>Other Clinical and Laboratory Features</th>
<th>Cytologic Examination of Organs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sawitaky, Hyman and Hyman, 1964</td>
<td>34</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
<td>Asymptomatic—mild purpura</td>
<td>Smears showed storage cells</td>
<td>Biopsy—no storage cells</td>
</tr>
<tr>
<td>As above</td>
<td>26</td>
<td>M</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderately severe purpura, 20 years' duration</td>
<td>Smears showed storage cells</td>
<td>Imprint smears and sections show storage cells</td>
</tr>
<tr>
<td>Malinin, 1961</td>
<td>30</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
<td>Asymptomatic</td>
<td>Smears showed storage cells</td>
<td>Not studied</td>
</tr>
<tr>
<td>Cogan and Federman, 1964</td>
<td>24</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild anemia and thrombocytopenia; granular lesion of fovea; splenectomy</td>
<td>Smears showed storage cells</td>
<td>Storage cells in smears and sections</td>
</tr>
<tr>
<td>Silverstein, Young, ReMine and Pease, 1964</td>
<td>60</td>
<td>F</td>
<td>Yes</td>
<td>No</td>
<td>Gall stones, post-necrotic cirrhosis splenectomy</td>
<td>Smears and sections showed storage cells</td>
<td>Angiomata storage cells in sections</td>
</tr>
<tr>
<td>Thompson and Moloney, 1965</td>
<td>34</td>
<td>F</td>
<td>Yes</td>
<td>No</td>
<td>Thrombocytopenia slight</td>
<td>Smears showed storage cells</td>
<td>Aspiration smears show storage cells</td>
</tr>
</tbody>
</table>
Table 1.— (Continued)

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Wright and Giemsa Stains</th>
<th>Histochemical and Other Studies</th>
<th>Results of Biochemical Studies</th>
<th>Comment Storage Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sawitsky, Hyman and Hyman, 1964</td>
<td>Large reticuloendothelial cells, packed with blue staining granules, Foamy reticuloendothelial cells</td>
<td>PAS Positive, Sudan Black B Negative, Toluidine Blue Negative, LAP Negative</td>
<td>None</td>
<td>Mucopolysaccharides</td>
</tr>
<tr>
<td>As above</td>
<td>As above</td>
<td>Positive, Positive (after harsh treatment)</td>
<td>Not done, Not done</td>
<td>None</td>
</tr>
<tr>
<td>Malinin, 1961</td>
<td>Large reticuloendothelial cells, blue staining granules—macrophages</td>
<td>Positive Positive, Positive</td>
<td>H and E granules did not stain</td>
<td>Bound fat or fatty acid</td>
</tr>
<tr>
<td>Cogan and Federman, 1964</td>
<td>Large storage cells, 15 to 80 μ also foam cells—histiocytes</td>
<td>Positive Positive, Not done</td>
<td>Birefringence positive</td>
<td>Great increase in total lipid, phospholipid and sphingomyelin of spleen</td>
</tr>
<tr>
<td>Silverstein, Young, ReMine and Pease, 1964</td>
<td>Histiocytes with blue staining granules</td>
<td>Positive Positive, Negative</td>
<td>H and E granules did not stain</td>
<td>Sialic acid chromatography-increased sphingomyelin and cerebrosides of spleen</td>
</tr>
<tr>
<td>Thompson and Moloney, 1965</td>
<td>Histiocytes with blue granules, vacuolated looking macrophages</td>
<td>Positive Negative, Negative</td>
<td>Birefringence positive, VPO negative, esterase—negative</td>
<td>None</td>
</tr>
</tbody>
</table>
mented lipid histiocytes and raised the question of ceroid storage disorder. However, the sites of occurrence as well as the physical and histochemical characteristics of this brownish pigment make confusion with other storage disorders unlikely.9 Important contributions to many phases of the problem of sphingolipidoses are contained in a valuable monograph edited by Aronson and Volk.10 The first chapter by Landing and Rubinstein on biopsy diagnosis furnishes a comprehensive list of the lipoidoses and an excellent discussion of the subject especially in relationship to central nervous system involvement.

Storage cells have been described in the spleens of patients with ITP and in bone marrow of patients with chronic granulocytic leukemia and other hematologic disorders. Saltzstein, in a series of seven patients undergoing splenectomy for thrombocytopenic purpura noted a marked accumulation of lipid containing histiocytes in the spleen.11 In these cells the foamy material was readily stained with fat stains but the PAS stain was only faintly positive. No imprint smears from the spleens, stained with Wright or Giemsa, were described in his report and in none of these cases were typical blue pigmented histiocytes noted in bone marrow preparations. A case reported by Marshall and Adams bears a striking similarity to those described by Saltzstein.12 The patient had a splenectomy for long-standing thrombocytopenic purpura, and foamy macrophages were found in the sections of the greatly enlarged spleen. Histochemical and biochemical studies carried out by these authors indicated that the cytoplasmic storage material was phospholipid or glycolipid in character. No Wright or Giemsa stained preparations from the spleen were described, nor were blue pigmented macrophages reported in the presplenectomy bone marrow smears in this case.

Hill and his coworkers, using electron microscopy, studied foam cells in the spleen, bone marrow and lymph nodes of patients with various blood dyscrasias.13 Foam cells were found chiefly in spleens and other tissues of patients with ITP and a few other conditions associated with increased destruction of platelets and other blood elements. Typical foam cells were found in 14 cases of thrombocytopenia, six patients with acute leukemia, a case of hypoplastic anemia and a patient with Felty’s syndrome. Examination of tissues under light microscopy with H and E staining detected only cases with marked accumulation of foam cells; the electron microscope was much more effective in this regard. Hill et al. pointed out that while the foam cells resemble Niemann-Pick cells morphologically, in their biochemical studies total lipid was increased, but the proportion of lipids was not abnormal. The appearance of these cells in fresh smears or imprints stained with Wright or Giemsa was not described; in two cases histochemical studies gave positive results with Oil Red O and Sudan Black. These authors suggest that the cytoplasmic material was derived by phagocytosis of lipids from destroyed platelets and probably leukocytes and erythrocytes. Since foam cells have been noted only in material studied in recent years, Hill et al. postulate that the therapeutic use of corticosteroids played a role in the development of this storage cell phenomenon.13

Recently Sundberg and her coworkers reported that blue-green staining macrophages were found in the bone marrow in 35 cases of chronic granulo-
cytic leukemia, and in 12 cases these cells were numerous. Similar macrophages, in smaller numbers, were noted in several other disorders. The macrophages were PAS and acid phosphatase positive, and these authors state that the cells were comparable to those originally described by Moeschlin and to the cases of Savitsky et al. In our laboratory Osofsky also noted the presence of pigmented macrophages in Wright stained marrow smears in a number of patients with chronic granulocytic leukemia. However, while the cytoplasm stained a blue-green color with Wright or Giemsa, the material appeared homogeneous or somewhat striated and lacked the typical granular appearance of histiocytes found in marrow and splenic smears of our patient, Mrs. A. C.

Until the etiology has been established, an accurate classification of lipid storage disorders is impossible. However, it is evident that in Gaucher's and Niemann-Pick's disease, inborn errors of metabolism result in the storage of kerasin, on the one hand, and sphingomyelin, on the other. Storage cells, lipid containing macrophages, are also found under conditions of abnormally accelerated and prolonged breakdown of platelets and myeloid cells. The storage disorder discussed in this report does not seem to fit into either of the above categories. Recent chemical evidence obtained by analysis of splenic material indicates that a major portion of the lipid storage material is sphingomyelin. However, there is no similarity of this disorder to the fatal and genetically oriented Niemann-Pick's disease. While the four of the six cases had slight to moderate degrees of thrombocytopenia, similar thrombocytopenic states are encountered in other splenomegalic disorders without the appearance of storage cells. Moreover, in ITP the storage cells occur in the spleen and have not been described in the bone marrow smears.

It seems unlikely that the disorder which characterizes these six cases arises solely from storage of accelerated breakdown products of platelets or other hematopoietic elements. It may be due to an acquired or an inborn partial defect associated with increased lipid breakdown products. Further studies such as those of Silverstein et al. on the abnormal urinary excretion of acid mucopolysaccharide may lead to better understanding of the etiology and the pathogenesis of this disorder.

Summary

In this report a sixth case of a storage disorder of unknown etiology is described and other reported cases are discussed. No hereditary or significant etiologic factors were noted in these patients. The disease is characterized by a benign course, splenomegaly and in some cases thrombocytopenia. A lipid containing histiocyte with unique blue staining granular cytoplasm is present in bone marrow and splenic smears, and biochemically the storage material consists largely of sphingomyelin.

Summario in Interlingua

In le presente reporto un sexte caso de un disordine de thesaurisation de etiologia incognoscite es describite, e altre reportate casos es commentate. Nulle factor hereditari o etiologic de signification esseva notate in iste pa-
tientes. Le morbo es charaterisate per un curso benigne, per splenomegalia, e—in certe casos—per thrombocytopenia. Un histiocyto a contenu lipidic con singular cytoplasma granular que accepta un tincturation blau es presente in le medulla ossee e in frottis splenic. Biochimicamente le material thesaurisate consiste primarimente de sphingomyelina.

ACKNOWLEDGMENT

We are grateful to Lila Fliegelman for technical assistance.

REFERENCES

Lipid Storage Disease

IAN L. THOMPSON and WILLIAM C. MOLONEY