Rare Variant of Lipid Storage Disorders

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In 1954 Sawitsky, Hyman and Hyman reported an unidentified lipid storage disorder in two young adults characterized by the presence in the bone marrow smear of large histiocytes with numerous blue staining cytoplasmic granules. By 1966 only six such cases had been reported in the literature. A summary of clinical and laboratory findings of these cases were compiled and discussed by Thompson and Moloney. In the present paper, a seventh case is reported which presents additional clinical findings, further confirming the impression that these cases do indeed represent a rare but distinct variant of the lipid storage disorders.

Case Report

The patient, A.Y., a 16-year-old boy from Garmsar, in the central part of Iran, was admitted to the First Medical Service of Pahlavi Hospital (Teheran University) on February 26, 1966, for evaluation of hepatosplenomegaly which had been noted since early childhood. Except for occasional low grade fever and rare epistaxis, his general health had been good, but his physical growth and development was somewhat retarded. There had been a history of geophagia for at least one year during his early childhood. His mental development had been fair, but he never managed to go beyond the third grade.

The patient's father had died six months previously of a "stroke." His mother and two sisters were living and well. There had been no known illnesses in the family and no other documented cases of hepatosplenomegaly.

On admission the patient's physical examination showed a young boy with an apparent age of 13 and in no distress. His height was 137 centimeters; his weight, 35.5 kilograms; blood pressure, 100/65; pulse 72 per minute and temperature 36.8° C. There was patchy, brownish pigmentation of the face and bilateral pingueculae of the eyes. The fundi showed increased tortuosity of the vessels. There was a doughnut-shaped gray discoloration of the macular region bilaterally, separated by a narrow yellow inner ring from the fovea, and surrounded by a wider yellow zone around its periphery (Fig. 1). There was no peripheral adenopathy. The liver was enlarged to 7 cm. below the right costal margin and the spleen to 12 cm. below the left costal margin. Both organs were smooth and nontender. Neurologic examination was within normal limits. Affect and intelligence were grossly normal but the patient demonstrated frequent outbursts of unexplained crying and laughing spells.

Laboratory examinations showed a hemoglobin of 12 Gm./100 ml.; RBC of 4,400,000/mm³; WBC of 7,300/mm³; with 53 per cent neutrophils, 4 per cent bands, 31 per cent lymphocytes, 7 per cent eosinophils, and 5 per cent monocytes. The platelet count was 150,000/mm³. Urinalysis was within normal limits. Serum cholesterol was 280 mg./100 ml.; calcium 9.9 mg./100 ml.; phosphorus 4.2 mg./100 ml.; thymol turbidity 15 units; cephalin flocculation 3+ in 24 hours and alkaline phosphatase 15 Bodansky units. VDRL was non-
reactive. Prothrombin time was 19 seconds (normal 13.5 sec.); bleeding time 1.3 minutes; and clotting time 4 minutes. Serum electrophoresis showed a total protein of 7.2 Gm./100 ml. with 49.5 per cent albumin, 5.2 per cent alpha1 globulin, 7.8 per cent alpha2 globulin, 10.0 per cent beta globulin, and 27.5 per cent gamma globulin. Stool examination showed no ova, parasite or occult blood. X-ray studies of the chest, skull, long bones and upper gastrointestinal series were normal. Bone age as shown on a film of the wrists was consistent with the chronologic age of 16.

Bone marrow aspiration showed normal cellularity. The erythroid and myeloid elements appeared normal. Interspersed among these cells, however, were large histiocytes which with Wright’s stain showed one or two small dark staining nuclei with prominent nucleoli and many cytoplasmic granules of varying size and varying stain intensity from light azure to deep blue (Fig. 2). In some of these cells, some of the cytoplasmic granules seemed to have been replaced by small vacuoles giving the cells a foamy appearance. Liver biopsy indicated an essentially normal liver architecture, but cells similar to the histiocytes described in the bone marrow were again seen, which on PAS stain gave a weakly positive reaction (Fig. 3).

**COMMENTS**

The clinical, histologic and laboratory findings of the present case and the six previously described cases indicate a rare but distinct clinical entity which, in all probability, is a variant of the lipid storage disorders.

Lipid containing histiocytes, commonly referred to as foam cells, have been noted in the spleen and bone marrow in association with a variety of conditions with or without detectable disturbances of lipid metabolism.\(^6\)\(^-\)\(^1\) Where the primary disease process is a blood dyscrasia with increased destruction of the formed elements of blood such as leukemia or thrombocytopenia, it is presumed that the foam cells contain phagocytized accumulations of the released...
intracellular contents (phospholipids) of destroyed cells. However, even in such cases the underlying mechanism is undoubtedly complex and does not represent a simple quantitative relationship between accelerated breakdown products and appearance of lipid containing histiocytes. Genetic predisposition and extraneous factors such as steroid therapy have already been implicated as causative adjuncts. The foam cells in these varied conditions have a nonspecific appearance and only rarely are they present in the bone marrow. Macrophages with blue-green granular cytoplasmic inclusions in the bone marrow of patients with chronic myelogenous leukemia have been reported, but morphologic and obvious diagnostic distinction is possible. In contrast, the abnormal histiocytes described in the present case and the six previously reported cases have a distinct and unmistakable appearance and are present in abundance in the bone marrow as well as other reticuloendothelial organs. Histochemical analyses of these cells have indicated an increase in glycolipids and phospholipids, and increased splenic content of sphingomyelin and cerebrosides have been demonstrated. Abnormal urinary excretion of muco-
polysaccharides have also been noted, which, together with Sawitsky's finding of a suggestive increase in the mucopolysaccharide content of the abnormal histiocytes, may point to the underlying mechanism of this disorder.

The additional clinical findings in our case of brownish pigmentation of the skin and suggested mental retardation are of particular interest since these findings are often associated with the more common variants of the lipid storage disorders, such as Gaucher's disease, Niemann-Pick's disease and Tay-Sachs disease. These findings, however, have not been reported in the six previously presented cases of the entity under discussion. Bilateral pingueculae were described only in one of Sawitsky's patients. Macular degeneration, also seen in our case, was noted in only one of the previously reported cases. It is of particular interest that the macular changes of our case resemble those of Cogan's patient, which were distinct and different from the typical macular changes of Niemann-Pick's disease. Similar macular changes have recently been described in a 12-year-old boy thought to have the chronic form of Niemann-Pick phosphatide lipidosis. However, histologic details and morphologic descriptions of the storage cells were not given. The clinical findings of our case, together with those of the previously described patients, fit the characteristic spectrum of the multifaceted clinical picture of the lipid storage disorders. It is also of interest that although liver biopsies had been performed in four of the six previously presented cases, only one had shown the presence of abnormal histiocytes within the liver parenchyma. Our case also showed on biopsy the presence of these cells within the liver parenchyma, possibly explaining the impairment of his liver function. Gall stones and postnecrotic cirrhosis were reported in Silverstein's patient, but it is of inter-
est that storage cells were not seen in the liver biopsy of this patient. Hepatic dysfunction is certainly not a common denominator of these patients.

The ethnic origin and family histories of the cases reported so far eliminate familial, hereditary, or racial factors. The clinical courses of all of the seven patients have been relatively benign. Thus, it seems probable that whatever the defect in lipid metabolism in these cases, its consequences are relatively mild, and do not threaten the general health or survival of the patient. It is also possible that, as with the other more common variants of the lipid storage disorders, there is a clinical spectrum and only the mild cases have been detected so far, suggesting interesting genetic implications and the possibility that severe cases may be incompatible with life. It is of interest that in the case reported by Thompson and Moloney, the patient lost the product of 5 of her 9 pregnancies early in the course of the pregnancy or at term for unknown causes. On the other hand, Malinin’s case was described as gravida VI, para VI, but no details were given about the results of these pregnancies. Fertility information was not available in the remaining four cases reported.

Adult Niemann-Pick disease as a rare and benign sphingolipidosis may offer many points in common with the entity under discussion. Granular histiocytes in the lymph node of the patient reported by Lynn and Terry, and the macular changes in the patient described by Sebestyen and Galfi, are strong points in favor of such a speculation. However, despite the common eponym and the abnormal storage of sphingomyelin in both the infantile and the adult forms of Niemann-Pick’s disease, the two conditions in all likelihood represent different metabolic disorders rather than varying severities of the same defect. Until more is known about the specific biochemical abnormalities of adult Niemann-Pick disease and the entity under discussion, a clinical separation of these two disorders may be justified.

Recent investigation into the pathogenesis of the lipid storage disorders has pointed to the exact site of the metabolic bottleneck in some of these disorders, and has demonstrated reduced activity of specific catabolic enzymes. It is hoped that with better clinical appreciation more cases of the type discussed will be recognized, allowing the eventual understanding of the exact pathogenesis of this disorder.

**Summary**

A 16-year-old boy with brownish pigmentation of the skin, bilateral pingueculae, macular degeneration, hepatosplenomegaly, suggested mental retardation, and abnormal histiocytes in the bone marrow and liver is presented. The morphologic appearance of the histiocytes is unique and specific, and so far only six similar cases have been reported in the literature. The contents of these histiocytes are thought to be phospholipids and glycolipids of sphingomyelin and cerebroside variety, respectively. The significance of the clinical and laboratory findings of these cases and the possible relationship to the lipid storage disorders are discussed.
ADDENDUM

Since this paper was submitted for publication, an additional case was reported by Silverstein, M. N., Ellefson, R. D., and Ahern, E. J.: New Eng. J. Med. 282:1–4, 1970. These authors included in their review of previous cases two patients not cited in our paper. The findings reported by Holland, P., Hug, G., and Schubert, W. K.: Amer. J. Dis. Child. 110:117–124, 1965, are in conformity with our observations and the six other cases cited by us. However, the case reported by Marshall, A. H. E., and Adams, C. W. M.: J. Path. Bact. 76:159–164, 1958, because of the associated findings of thrombocytopenia and splenic angiomata and lack of information regarding the bone marrow morphology, cannot be included on the basis of our present knowledge of the entity described.

REFERENCES

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