Niemann-Pick disease, type B with TRAP-positive storage cells and secondary sea blue histiocytosis

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We present 2 cases of Niemann Pick disease, type B with secondary sea-blue histiocytosis. Strikingly, in both cases the Pick cells were positive for tartrate resistant acid phosphatase, a finding hitherto described only in Gaucher cells. This report highlights the importance of this finding as a potential cytochemical diagnostic pitfall in the diagnosis of Niemann Pick disease.

Key words: Niemann pick disease, Gaucher disease, tartrate resistant acid phosphatase, sea blue histiocytosis.

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We present two unrelated patients who were referred to the Hematology OPD from Gastroenterology during work-up of long-standing splenomegaly 2 years apart and whose details are presented in Table 1. Neither had any neurological complaints or a history suggestive of developmental delay. Family history was negative for similar illness. Their bone marrows were examined when preliminary work-up for chronic haemolysis was negative and the hemograms revealed varying combinations of cytopenias. Liver and renal function tests were normal in both cases.

The marrow smears in both patients showed abundant classical Niemann Pick cells (foamy cytoplasm positive for the lipid stain Sudan black B, small central to eccentric nucleoli) with many sea-blue histiocytes, a well-recognized secondary phenomenon (Golde *et al.*, 1975) (Figures 1 and 2). Diagnostic uncertainty arose when enzyme cytochemistry on the marrow smears showed intense tartrate resistant acid phosphatase (TRAP) activity in the foamy cells, periodic acid Schiff positive material and haemophagocytosis in the sea-blue histiocytes, findings hitherto described only in Gaucher cells (Weisberger *et al.*, 2004) (Figures 3 and 4). No classical Gaucher cells were seen in multiple Romanowsky stained smears.

The diagnostic puzzle was resolved when both patients showed normal beta-glucocerebrosidase levels, very low levels of HDL cholesterol with low acid phosphatase, and in the one patient where it could be performed, a reduced but recordable level of sphingomyelinase activity (as seen in type B form), thus confirming clinico-pathologically the diagnosis of Niemann Pick disease, type B.

A literature search reveals that although serum TRAP levels may be mildly elevated in patients with Niemann Pick disease, the enzyme has not been localized cytochemically to these cells previously

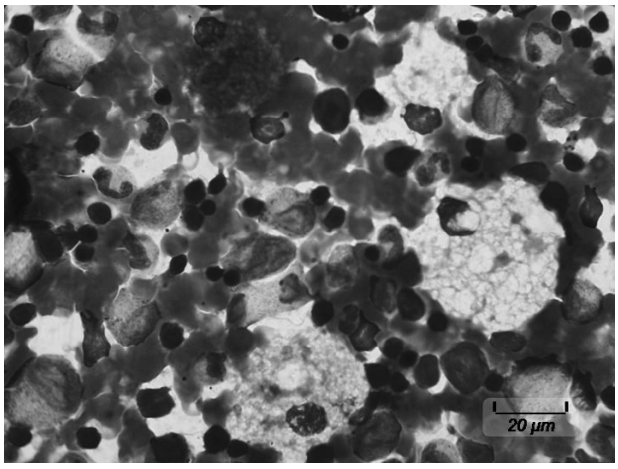

Figure 1. The bone marrow aspirate shows numerous Niemann Pick cells with abundant foamy cytoplasm and fewer and smaller sea-blue histiocytes (Jenner-Giemsa).

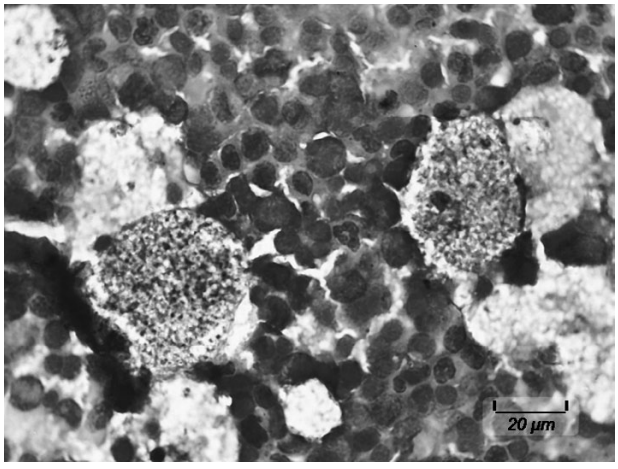

Figure 2. The multi-vacuolated Niemann Pick cells are positive for the lipid stain Sudan Black B. (Giemsa counterstaining).

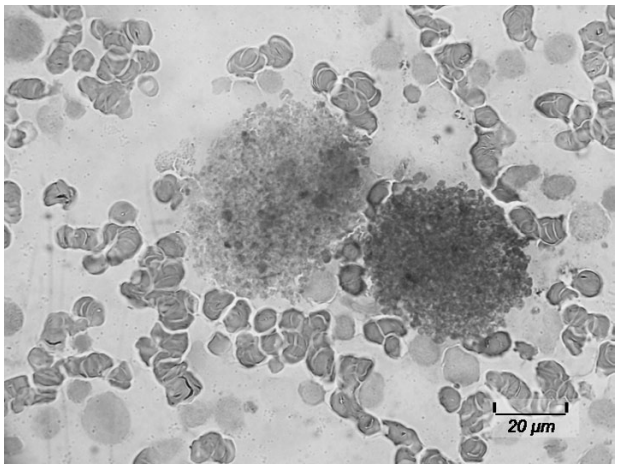

Figure 3. The Niemann Pick cells variably measure 20-50 micrometers in greatest diameter. They are uniformly and intensely positive for tartrate resistant acid phosphatase. (Methyl green counterstaining). The sea blue histiocytes' acid phosphatase is inhibited by tartaric acid (image not shown).

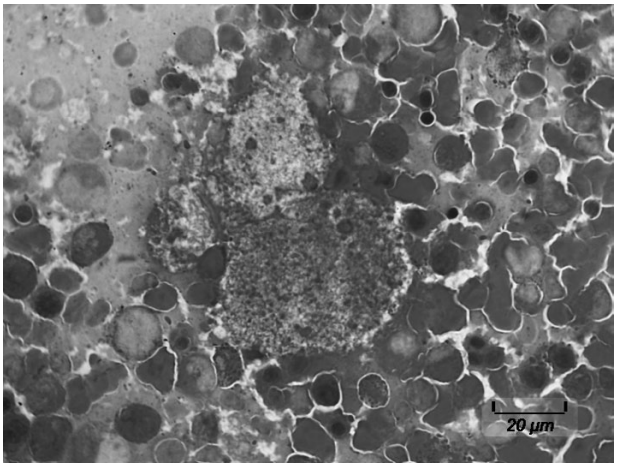

Figure 4. The Niemann Pick cells are only weakly positive for periodic acid Schiff stain. Gaucher cells would be expected to be brilliantly positive. (Haematoxylin counterstaining).

(Chambers *et al.*, 1977). Interestingly, a recent publication using sequence profiling and fold recognition methods suggests a remote evolutionary relationship between the phosphoesterase domain of acid sphingomyelinase (deficient in Niemann Pick disease) and purple acid phosphatases (mammalian form of which is TRAP) (Seto *et al.*, 2004). The importance of this relationship is unclear but it is interesting to speculate whether there could be an upregulation of a related enzyme in face of congenital deficiency of acid sphingomyelinase in our cases. The iron content and the haemo-phagocytosis were possibly simply pointers towards the intrinsic histiocytic nature of the sea-blue histiocytes.

The major lesson from these cases is to alert the pathologist to the possibility of TRAP and iron positive histiocytic and storage cells other than Gaucher cells that may display haemophagocytosis. This is especially relevant to avoid incorrect diagnosis in resource-restricted settings in India where specialized diagnostic tests may be inaccessible or omitted if the morphological and cytochemical findings are felt to be characteristic of Gaucher disease.

Table 1. Clinical, pathological and biochemical findings in the two patients.

	Patient 1	*Patient 2*
Age, sex	14 yr/F	18 yr/F
Presenting complaints	Pain, awareness of mass in left upper abdomen x12 years	Low grade fever on and off, abdominal discomfort x2 yrs
Hb (gm%), TLC (/μL), platelets (/μL)	7.3, 4500, 153000	12, 6900, 47000
Liver / Spleen	Not palpable / 14 cm below costal margin	Not palpable / massive enlargement (span 20 cm)
Ultrasound abdomen	Massive splenomegaly, multiple hyperechoeic foci, no evidence of EHPVO or HVOTO	Splenomegaly, mesenteric lymphadenopathy
CECT abdomen	Not done	Splenomegaly, pre-aortic lymphadenopathy (? lymphoma infiltration)
Serum bilirubin, alkaline phosphatase, SGOT, SGPT, total protein, Albumin, urea, creatinine, sodium, potassium	Normal ranges	Normal ranges
Hemoglobin HPLC, direct and indirect antiglobulin tests, 24-hour incubated osmotic fragility test, G6PD deficiency screening	Normal	Normal
RK-39 antigen test for Leishmaniasis, HBsAg, anti HCV, anti HIV 1 & 2	Negative	Negative
HDL Cholesterol (normal 40-50 mg%)	12 mg%	23 mg%
Fundoscopic examination	Normal	Bilateral cherry red spots
Acid phosphatase (normal >6.5 U/L)	5.5 U/L	4.2 U/L
Bone marrow examination	Aspirate: Cellular smears with normal marrow elements, foamy histiocytes present along with numerous sea blue histiocytes, some foamy histiocytes show haemophagocytosis Biopsy: hypercellular, foamy cells and other histiocytes prominent	Diluted marrow with many foamy histiocytes and sea blue histiocytes, normal marrow elements seen Biopsy: normocellular, foamy cells and other histiocytes present
Cytochemistry	Foamy cells positive for Sudan Black B, acid phosphatase (AP), tartrate resistant acid phosphatase (TRAP), weak hue with periodic acid Schiff (PAS), sea blue histiocytes strongly positive for PAS and AP	Foamy cells positive for Sudan Black B, acid Phosphatase, TRAP, weak positive with PAS; sea blue histiocytes positive for PAS, AP
Enzyme assay	Normal beta-glucocerebrosidase level, sphingomyelinase- not done	Normal beta-glucocerebrosidase level, sphingomyelinase- 9 nmol/17 hr/mg protein (normal 10-47 nmol/17 hr/mg protein)

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