Rare cause of huge splenomegaly: Gaucher's Disease- 2 cases

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ABSTRACT

Often patients with splenomegaly present as diagnostic challenge to the clinicians. Even extensive laboratory investigations fail to yield the diagnosis. In 1908 Williams Osler correctly stated "all diseases of the spleen are of secondary in nature". Here we outline two such cases of huge splenomegaly. They were diagnosed as Gaucher's disease only after bone marrow study.

Key words: Gaucher's disease, splenomegaly, bone marrow biopsy

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INTRODUCTION

Gaucher's disease (GD), an autosomal recessive lipid storage disorder resulting from accumulation of glucocerebrosidase in the cells of macrophage-monocyte system. It was first described by Gaucher in 1882. 1 The metabolic defect is due to the deficiency of the lysosomal hydrolase, acid B-glucosidaseencoded by chromosome 1.2 GD is a rare type of disease with prevalence of 1:40,000.3The disease is characterized by continuum of phenotypes. Some present in childhood with all complications while other remains asymptomatic even in eighth decade. Here we report 2 cases of Gaucher's Disease with massive splenomegaly due to disease rarity in Indian subcontinent. We also highlight the presentation for early diagnosis and management to prevent the further complications.

CASE REPORT

CASE 1- A9 years old hindu girl born out of non consanguinous marriage presented with history of gradually increasing abdominal girth and paleness since 2 years of age. There was easy bruisability for last6 months but no history of bleeding from any other sites.She also complained of bone pain over both upper and lower limbs. Umbilical sepsis or catheterization and blood transfusion in the past could not be elicited. On clinical examination, her anthropometric values lagged behind3rd percentile despite adequate calorie intake.Abdominal examination revealed hepatomegaly (liver- 4 cm below right costal margin, firm in consistency without any tenderness, surface smooth and margin was sharp) and huge splenomegaly (spleen- 9 cm below costal margin along its' axis, firm, nontender

with smooth surface) . No significant lymphadenopathy and bony tenderness were present. Multiple bruises over back and legs were spotted. Complete blood count, liver function tests, renal function tests were done. Only peripheral blood picture revealed pancytopenia (Hb-7.5 gm/dl, total count 3800 (N37 L58 E3 M2 B0) , platelet 80,000). No abnormal cell was seen in peripheral smear. Reticulocyte count was 0.9%. Coagulation profile did not show any abnormality. Blood for malaria parasite and RK 39Ag for kala-azar came out to be negative. Ultrasonography with colour Doppler study showedhepatospleenomegaly with normal flow in portal vein and there was multiple hypoechoeic lesions in spleen(Fig 1a) . Upper GI endoscopy and results of Hb electrophoresis were within normal limits. Ultimately bone marrow study was conducted. Trephine biopsy showed large storage cells having small lobulated nuclei and pale eosinophilic cytoplasm with wrinkled paper appearance suggestive of Gaucher's cells with focal myelofibrosis(Fig 1b) . For confirmation of our diagnosis dried blood spot was sent for enzyme assay which showed level of glucocerebrosidase markedly low(0.27 nmol/hr) with raised chitotriosidase level 279.41 nmol/hr/ml consistent with GD. The child was started on Enzyme replacement therapy (ERT) with cerezyme. With 4 months of treatment there has been marked improvement in her blood picture with increament in Hbby 1.5gm/dl and platelet increased to 2.1 lakks/cu.mm. There was also reduction in spleen size by 20% with complete sudsidence of bone pain.

Fig 1a :Multiple hypoechoeic lesion in spleen

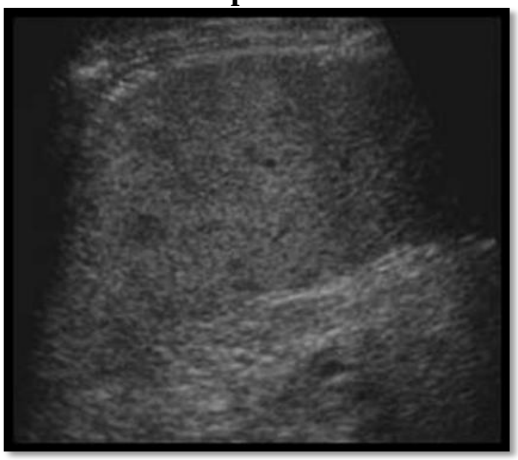
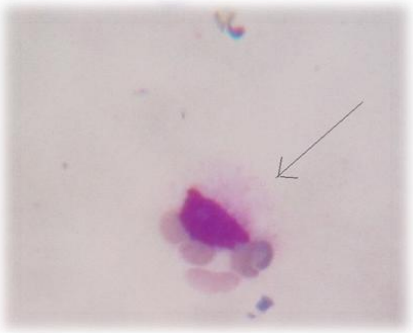


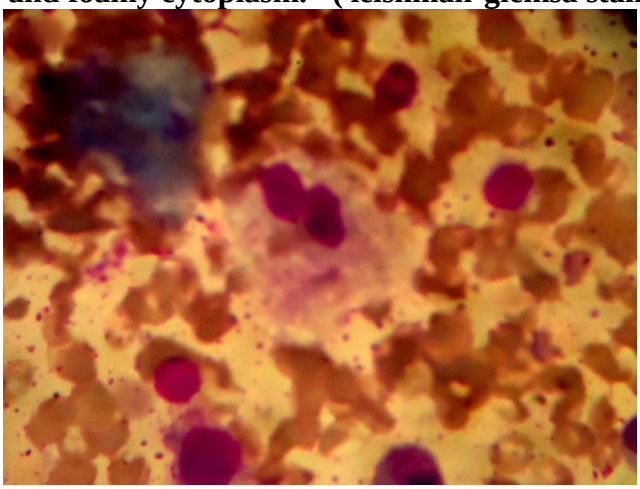
Fig 1b : Large Storage Cells Having Small, Lobulated Nuclei And Pale Eosinophilic Cytoplasm With Wrinkled Paper Appearance (Leishman-Giemsa Stain-10 X100)



CASE 2-1yr 2months old baby presented with chief complaints of gradual swelling of left hypochondriumfrom her 20 days of life with delayed developmental milestones. She was born out of non consanguinous marriage with uneventful earlyneonatal period. No history of seizure or feeding difficulty was present. She achieved head holding at 8 months of age, sitting with support at 12 months of age, crawling at13 months, monosyllable words at 8 months age. On clinical examination child was alert, active and playful with gross lag in her anthropometric parameters. Liver was 2.5 cm below costal margin, soft and non-tender. 4 cm firm non tender spleen could be palpated with no evidence of ascites, lymphadenopathy and bony tenderness. Blood picture showed only thrombocytopenia (platelet 90,000). All other investigations to find out cause of spleenomegaly came out to be non-conclusive. Finally

bone marrow biopsy showed cells with crumpled tissue paper like appearance and eccentric nuclei suggestive of Gaucher's cells (Fig 2). Her glucocerebrosidase level was markedly low (0.21 nmol/hr) with raised chitotriosidase level 291.5 nmol/hr/ml. Enzyme level confirms the diagnosis of GD. She is on her way of ERT.

Fig 2: Fair number of storage cells having crumpled tissue paper like appearance, eccentric nucleus and foamy cytoplasm. (leishman-giemsa stain-10 x100)



DISCUSSION

GD is a rare multisystem disorder that can have variable clinical presentations. 4Challenge in diagnosing the disease lies in its ability to present in several unique clinical scenarios. It has been divided traditionally into three cilinical subtypes delineated by the absence or presence of neurologic involvement and its progression. Type I or non neuronopathic form, type 2- the infantile onset acute neuronopathic form, type 3 the juvenile onset neuropathic form.5 All forms are panethnic. However type I is more common specially among the Ashkenazi Jews.6

Type I GD presents in childhood withhepato-splenomegaly and pancytopenia which was evident in our first patients. It is less rapidly progressive. Child may have chronic fatigue secondary to anemia, pathologic fractures and easy bruisability. If splenomegaly is progressive child may be of short stature because of the energy expenditure by the enlarged spleen. Radiologic evidence of skeletal deformity in the form of Erlenmeyer Flask may be noted. Type II GD presents in infancy with all features of type I along with seizure. There may be increased tone, strabismus, laryngospasm and developmental delay. Severe form may present with hydropsfetalis or congenital icthyosis or both. It usually fatal within 2 years of age. Type III GD can present in infancy or childhood with neurologic involvement in the form of myoclonic epilepsy, learning disabilities or horizontal saccades. Our 2nd patient presented with developmental delay with hepatospleenomegaly. Swallowing abnormalities, occulomotorapraxia, stridor due to laryngospasm typically found in GD type 2 were absent in our patients. Therefore she can be considered to fall within the GD type III phenotypic continuum.7, 8

All forms of GD are caused by glucocerebrosidase activity deficiency due to mutations in GBA gene. More than 200 different mutations have been identified.9 Bone marrow examination is the hallmark of GD but all suspected cases should be confirmed by enzyme assay in isolated leucocytes or cultured fibroblast to rule out the possibility ofpseudo Gaucher's cells found in CML, congenital dyserythropoeitic anaemia and multiple myeloma.10Prenatal diagnosis is available by determination of enzyme activity and/or the specific family mutations in chorionic villi or cultured amniotic fluid cells. 11

Treatment of patients of GD type I is enzyme replacement therapy with cerezyme (60 IU/kg) intravenously every other week. Two other preparation are recently approved by USFDA, namely velaglucerasealfa and teliglucerasealfa. In cases of GD type II &III, ERT can be used as a palliative measure as it cannot alter the neurological progression of the disease. Bone marrow transplantation may be curative in a small number of patients. 7, 12

CONCLUSION

GD should be considered in the differential diagnosis of patients with unexplained splenomegaly. Through these case series we reinforce the importance of bone marrow analysis and exclusion of other possibilities for early recognition of the disease and institution of ERT to arrest the disease process and prevention of complications.

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