

Pediatric Non-neuronopathic Gaucher Disease- A Case Report

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Abstract: Gaucher disease an uncommon autosomal recessive disorder, caused by deficiency in the activity of the lysosomal enzyme glucocerebrosidase, responsible for the degradation of glucosylceramide, resulting from the breakdown of red and white cell-membranes. In the absence of enzyme, glucosylceramide accumulates in lysosomes of macrophages, leads to hepatomegaly, splenomegaly with haematologic abnormalities -leucopenia, anaemia, thrombocytopenia and bone manifestations. Three types of Gaucher disease are described: type 1, most common, non-neuronopathic form, type 2 and 3 are associated with neurologic symptoms. With the advent of enzyme replacement therapy and substrate reduction therapy the natural history of the disease has been changed with a marked decrease in morbidity, especially for type I patients. We report this case of a 14 year old boy referred to Haematology department with massive splenomegaly. Hematological workup revealed pancytopenia. Bone marrow study showed the characteristic Gaucher cells and diagnosis of Type I (non-neuronopathic) Gaucher disease was given. Patient underwent splenectomy

Keywords: Gaucher, Glucocerebrosidase, Non-neuronopathic, Pancytopenia, Splenomegaly.

INTRODUCTION

Gaucher disease was first described in 1882 by French physician, Philippe Charles Ernest Gaucher, after he evaluated a deceased 32-year-old woman with an enlarged spleen, one of the disorder's distinguishing signs. This is a lysosomal storage disorder caused by mutation in the gene responsible for the production of the enzyme β -glucocerebrosidase which breaks down glycosphingolipids derived from physiological turnover of membranes, particularly of blood cells. More than 200 mutant alleles have been identified [1].

As a result of mutation, β -glucocerebrosidase activity is insufficient to prevent accumulation of a glycosphingolipid called glucocerebroside in the lysosomes of cells, mainly of the tissue macrophage system. Glucocerebroside-engorged macrophages, termed Gaucher cells, accumulate in organs. Gaucher cell storage leads to a further cascade of physiopathologic events, including the elicitation of a chronic inflammatory and hypermetabolic state. Clinically, this may translate into infiltration with masses of Gaucher cells of the organs of the reticuloendothelial system with secondary consequences such as hepatomegaly, splenomegaly, thrombocytopenia, anaemia, skeletal pathology, pulmonary hypertension and interstitial lung disease, and in a minority central neurological involvement [2].

Gaucher disease probably affects fewer than 10,000 people worldwide [3]. Recognizing the signs and symptoms of Gaucher is critical as early diagnosis and intervention.

CASE REPORT

A fourteen year old boy, Muslim by religion and born to parents with non-consanguineous marriage presented with pain abdomen and shortness of breath since one week, admitted in acute medical care unit and referred to haematology department in view of massive splenomegaly. Past history revealed recurrent episodes of fever, jaundice since one year and progressive distension of abdomen since two years. General examination showed short stature, pallor, icterus, petechia and massive splenomegaly extending upto right iliac fossa.

Laboratory data revealed thrombocytopenia and slightly elevated bilirubin level (1.68 mg/dl). Haemoglobin on admission was 9.0 grams per decilitre of blood. Complete blood counts showed red blood cell count of 3.12 million per cubic mm of blood, white blood cell count of 3400 cells/mm³ blood and platelet count of 40000 cells/mm³ of blood. An impression of pancytopenia was given. Bone marrow study showed characteristic Gaucher cells. Ultrasound examination revealed hepatosplenomegaly. Computerised tomography evaluated the size of the spleen 40x 20 x

12 cm. To confirm diagnosis of Gaucher disease enzyme test was performed. Glucocerebrosidase activity in leucocytes was 4.8nmol/mg protein/hr and was below the normal range (12.5 to 16.9 nmol/mg protein/hr). Low glucocerebrosidase activity in cultured fibroblasts confirmed the diagnosis of Gaucher disease. No skeletal, pulmonary or neurological involvement was found. Family history was not significant.

Splenectomy was done due to the severe cytopenia caused by hypersplenism and prophylactic antibiotics against capsulated organisms was given. Spleen weighed about 6 kilograms and size was 42×20×12 centimeters. Histopathological examination showed depletion of lymphoid follicles, replaced by sheets of large histiocytes with eccentrically placed nucleus and fibrillary cytoplasm-gaucher cells and intervening fibrosis. Periodic Acid Schiff stain showed magenta pink fibrillary cytoplasm in gaucher cells of spleen. Percutaneous liver biopsy also showed gaucher cells. Postoperatively the patient's condition was uneventful with improved blood counts-Hemoglobin 10.9 gms/dl, red blood cell count 3,9 million per cubicmm, white blood cell count 11600 cells per cubicmm and platelet count 4.1 lakhs per cubicmm of blood.



Figure 1: Chest x-ray PA and Pelvis AP view- Hepatosplenomegaly and no skeletal involvement respectively



Figure 2: Splenectomy specimen- Huge spleen with surface nodularity. Weight 6kgs and size 40×20×12 cms

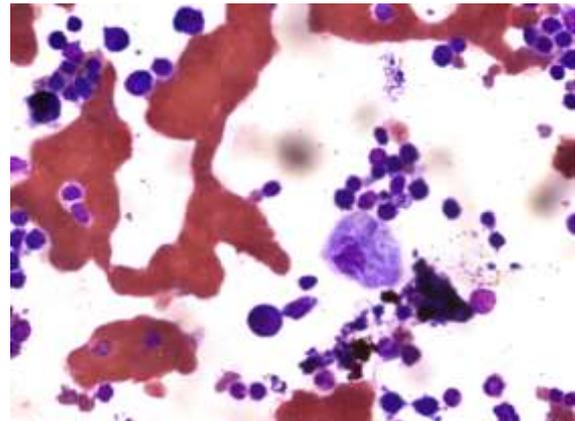


Figure 4: Leishman stain: Bone marrow aspirate showing Gaucher cell.

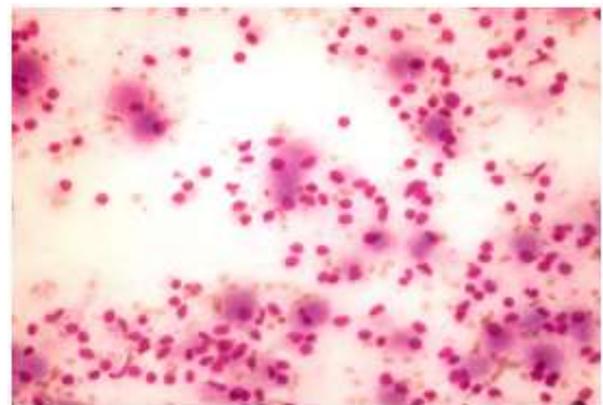


Figure 3: Splenic aspirate showing Gaucher cells- Large cells with eccentric nucleus and abundant eosinophilic fibrillary cytoplasm

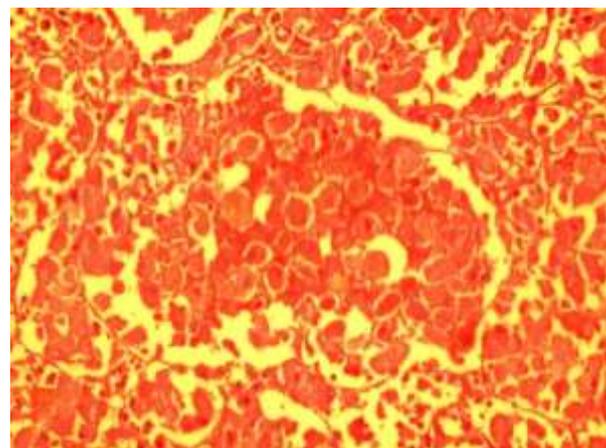


Figure 5: Histopathological sections of spleen: Hematoxylin and eosin stain - 40× showing sheets of Gaucher cells.

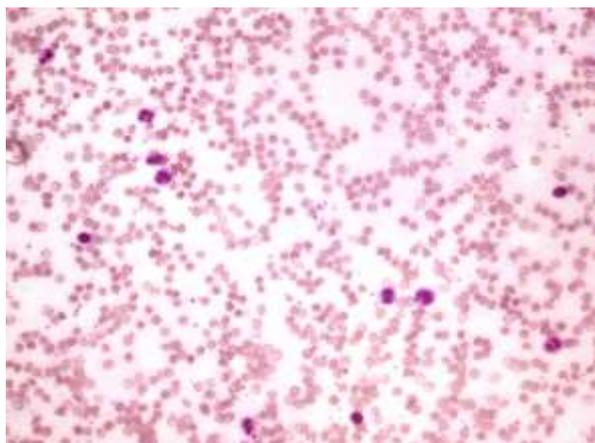


Figure 6: Post operative Peripheral smear: Leishman stain 10x-Neutrophilia and thrombocytosis.

DISCUSSION

Gaucher's disease, the most frequent sphingolipid storage disease, is an autosomal recessive disorder caused by mutations in the beta-glucocerebrosidase gene leading to deficient activity of this lysosomal enzyme. It is most prevalent in the Ashkenazi Jewish (AJ) population (1/450). The clinical features of the condition principally reflect the distribution of abnormal macrophages (Gaucher cells) within affected organs and tissues. In this clinicopathological syndrome, storage of glucocerebroside occurs principally in mononuclear phagocytes, which is derived from exogenous membrane components released by phagocytosis of haematopoietic cells [4].

Gaucher disease is a multisystem disorder associated with striking variation in its clinical manifestations, severity and course. Three phenotypes of Gaucher disease, based on the presence or absence of neurological symptoms, were first proposed in 1962 [5]. Type I Gaucher disease is caused by partial glucocerebrosidase deficiency with no discernible neuronopathic manifestations. The clinical features of type I Gaucher's disease are inconsistent. It is associated principally with parenchymal disease of the liver, spleen, bone marrow and, in severe cases, the lung. Hypersplenism can lead to anaemia, bleeding due to thrombocytopenia and recurrent bacterial infection associated with neutropenia.

Traditionally, type I Gaucher disease has been referred to as the 'adult type'; however, 66% of individuals with symptomatic non-neuronopathic Gaucher disease manifest in childhood. Onset in childhood is usually predictive of a severe, rapidly progressive phenotype and children with non-neuronopathic Gaucher disease are at high risk for morbid complications. Enzyme therapy with recombinant human glucocerebrosidase in childhood

can restore health in reversible manifestations and prevent the development of irreversible symptoms. A heightened focus on pediatric Gaucher disease is therefore needed [6].

Mutations in the glucocerebrosidase gene that severely affect its function are additionally associated with neurological manifestations in acute neuronopathic Gaucher disease (type II) and chronic neuronopathic Gaucher disease (type III) [7].

Knowledge of the genotype allows limited prediction of the severity of disease. For instance, certain mutations indicate that the patient has severe disease (e.g. homozygosity for L444P). Other mutations, such as the N370S allele are almost never associated with neuronopathic disease and the presence of one copy of this allele is almost invariably associated with type I Gaucher disease. However, while mutations, in the human glucocerebrosidase gene are necessary for the development of the condition, they are not tantamount to, or sufficient for, a diagnosis of symptomatic Gaucher disease. Homozygosity or compound heterozygosity for some mutant alleles of glucocerebrosidase may be detected in otherwise asymptomatic or apparently healthy people. Thus, clinical expression of the disease cannot be accurately predicted by mutation analysis alone, although knowledge of the glucocerebrosidase genotype may contribute to prognosis and provide a broad guide to clinical behaviour [8].

A demonstration of Gaucher cells in bone marrow aspirate can lead to misdiagnosis, even when combined with clinical symptoms typical of the disease. Gaucher-like cells have been described in a number of other conditions, including multiple myeloma, myeloid leukaemia, thalassaemia and Hodgkin disease [9]. Therefore, histological examination of the spleen, bone marrow and other organs is insufficient for the definitive diagnosis of Gaucher disease. Biochemical and molecular techniques are more specific and less invasive. In patients with symptoms associated with evidence of tissue injury, the definitive diagnosis of Gaucher disease requires the demonstration of deficient glucocerebrosidase activity in mixed leukocyte preparations or fibroblast cultures. Most patients with Gaucher disease have demonstrated glucocerebrosidase activity $\leq 15\%$ of mean normal activity [10].

Ours is a 14 year old boy who presented with pain abdomen, shortness of breath and the predominant clinical presentation was pancytopenia and splenohepatomegaly with splenomegaly greater than hepatomegaly. Bone marrow examination showed gaucher cells. Enzyme assay confirmed the diagnosis with low levels of glucocerebrosidase in fibroblasts. Spleen was huge weighing 6 kilograms, measuring

42×20×10cms and characteristic gaucher cells on histopathology. Liver biopsy also showed gaucher cells. Postoperatively the patient is stable and advised regular followup. Type 1 gaucher disease has been referred to as the 'adult type' but symptomatic non-neuronopathic Gaucher disease can manifest in childhood like the present case.

CONCLUSION

Gaucher's disease is an unusual disorder, with ill-defined incidence in our environment. Diagnosing Gaucher disease can pose a challenge. Despite the availability of accurate, non-invasive diagnostic tests - enzyme activity assays and DNA analysis, the initial diagnosis may be challenging and considerable diagnostic delays are not unusual. The difficulty arises in part because of the relative rarity of the disease--some practitioners may not even consider testing specifically for Gaucher disease, since clinical signs and symptoms may suggest other diseases. Moreover, Gaucher disease's clinical course can be unpredictable: signs and symptoms may take years to emerge and it may progress at varying rates. A thorough approach to baseline assessment will improve the understanding of childhood Gaucher disease, optimizing management to minimize impairment of growth and development and prevent irreversible symptoms.

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