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BONE MARROW EXAMINATION IN GAUCHER'S DISEASE: A CASE REPORT IN A 1 YEAR OLD CHILD

Pathology

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ABSTRACT

Gaucher's disease is an autosomal recessive lysosomal storage disorder due to defect in the gene GBA1, characterized by glucosylceramide accumulation in macrophages owing to the deficiency of glucocerebrosidase. These macrophage can infiltrate numerous organ and leads to multiorgan damage. Depending on the neuronal involvement Gaucher disease is classified in to three types. They are Type I(non-neuronopathic) and Type II and III(acute on chronic neuronopathic).The non-neuronopathic usually present with splenomegaly, henceforth evaluation of bone marrow in such cases clinch the diagnosis and helps in targeted treatment. Here we report one such a case with the complaints of anemia with splenomegaly was evaluated and diagnosed as Gaucher's disease with the help of bone marrow examination.

KEYWORDS

Macrophage, Splenomegaly, Bone marrow

INTRODUCTION:

Gaucher's disease is an autosomal recessive lysosomal storage disorder affecting early childhood.[1] This disease is due to the accumulation of glucoceramide in macrophages due to the deficiency of the enzyme β glucosidase.[2] Mutation in chromosome 1q21-p31(GBA1) results in Gaucher's disease.[2] The global incidence is about 1/40000 to 1/60000 among total live births and in Askenazi Jews it is about 1/800 live births.[3] Based on the neuronal involvement Gaucher's disease is classified into non-neuronopathic (Type I) and neuronopathic(Type II and Type III).[2] Among these Type II has the worst prognosis.[1] Early diagnosis helps to prevent the development of neuronal complications. Since early manifestation of Gaucher's disease is anemia with splenomegaly, evaluation of these symptoms with a bone marrow study will help to diagnose Gaucher's disease definitely and exclude the other causes for these symptoms.

CASE REPORT:

A one year old male child presented with the complaints of easy fatigability and abdominal distension for 1 month. On examination child was anemic and had hepatosplenomegaly. Routine blood examination revealed a hemoglobin of 5.6g/dl, red blood cell count of 3.28 millions/cumm, total white blood cell count of 13,700cells/cu mm and platelet count of 2.3lakhs/cumm. Peripheral smear showed microcytic hypochromic anemia with reactive lymphocytosis. Since the patient was clinically suspected to have a hematological or storage disorder G6PD(Glucose-6-Phospho Dehydrogenase) enzyme quantification, High Performance Liquid Chromatography for Hb variant analysis and serum iron studies were done. All these results were within reference range. To exclude bone marrow pathology bone marrow aspirate and biopsy was performed. The bone marrow aspirate showed a picture of reactive marrow with trilineage hematopoiesis. The biopsy revealed a cellular marrow infiltrated by large macrophages with cytoplasm showing wrinkled tissue paper appearance and the nucleus at the periphery with suppressed trilineage hematopoiesis suggestive of Gaucher's disease. The macrophages and the storage material were further confirmed by doing special stains Periodic acid Schiff(PAS) which were positive and not digested by diastase(Periodic acid Schiff-Diastase resistant-PAS-D)Fig:2a&2b. The macrophage were positive for CD68 by immunohistochemistry. (Fig:3)

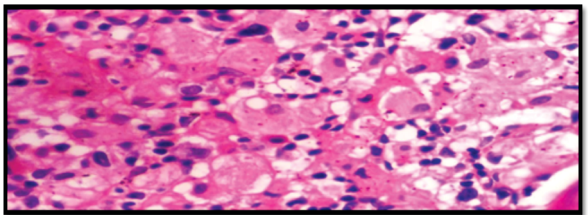

Fig 1. Gaucher's cells – Large cells with abundant cytoplasm showing wrinkled tissue paper appearance cytoplasm and peripheral nucleus (H&E X 400)

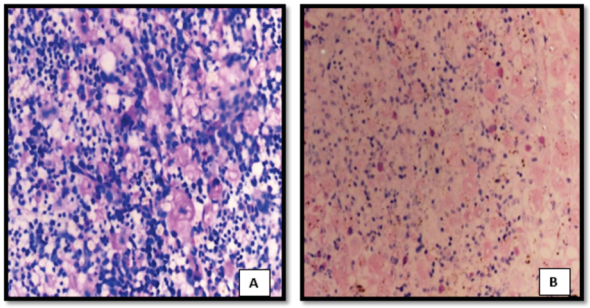

Fig 2a&2b. Special stains highlights the Gaucher's cells (PAS X 200(a)(PAS-D X 200(b))

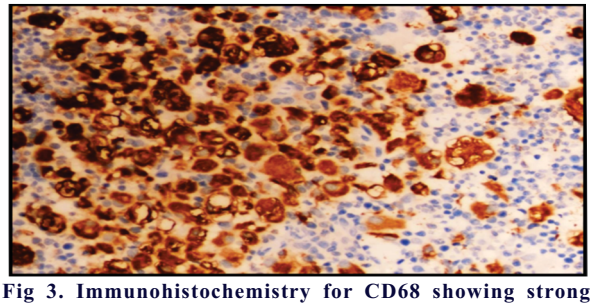

Fig 3. Immunohistochemistry for CD68 showing strong cytoplasmic positivity in the macrophages (IHC-CD68 X 200)

DISCUSSION:

Gaucher disease is the most common lysosomal storage disorder.[2] It is an autosomal recessive disorder affecting children.[3] Mutation in

chromosome 1q21-p31 results in Gauchers disease.[1] In 1882 Gaucher noted a large cell in spleen and he thought it could be a evidence of neoplasm.[2] Further in 1924 Epstein found that this large cell is due to the accumulation of glucocerebroside.[1] Later on Brady et al found that this storage material was due to the deficiency of enzyme β glucosidase.[2]

Gaucher cell is a large macrophage, which occur due to the defective degradative action of lysosome leading to accumulation of toxic substrate (glucocerebroside) in cells.[3] These cells infiltrate various organs such as bone marrow, liver, spleen, lung, kidney and brain resulting in various clinical manifestation.[2] They are bone pain, bone infarct, pathological fracture, pancytopenia, massive hepatosplenomegaly, diffuse infiltrative pulmonary disease, nephropathy and neurodegenerative disease. Severe deficiency of β hydrolase results in accumulation of glycosphingolipid in neuronal cell leading to neuronal cell death resulting in neurodegenerative disease.[4]

Based on the neuronal involvement , Gaucher disease is classified in to non-neuronopathic and neuronopathic type.[5] Depending on the mutation and clinical progression non–neuronopathic type is subclassified into type I and neuronopathic type into type II and type III. In Type I is further classified in to asymptomatic and symptomatic and type II in to neonatal and infantile type and type III in to 3a,3b and 3c.[2] Of these types type II has the worst prognosis causing neonatal or infant death.

The clinical findings such as hepatosplenomegaly and hematological manifestation seen in Gaucher disease can occur with other diseases too, for which bone marrow examination needs to be done to evaluate the cause . So early detection of Gaucher can be made with the identification of Gaucher cells in bone marrow with the morphology being a large cell with peripheral placed nucleus and wrinkled tissue paper appearance of cytoplasm.[6] Similar morphologically resembling cells (Pseudo –Gaucher cell) can be seen in other diseases such as hematological malignancies, multiple myeloma and AIDS.[2] Further special stains (PAS and PAS D) can be done to show the presence of carbohydrate inside the large cells.[1] The macrophage origin of these large cells can be confirmed by immunohistochemistry for CD 68.[7] Identifying the Gaucher cell in a biopsy is an indication for estimation of enzyme assay (β glucosidase) in blood leukocytes which is the gold standard for diagnosis of Gaucher's disease.[3] However it was not done for our patient.

Molecular diagnosis can be done to confirm the diagnosis and for prognostication. Follow up of the patient after treatment can be done by estimating the bio marker (Chititriosidase and CCL18) which is secreted by the gaucher cells.[2] In the recent times glucosylsphingosine has been validated as a biomarker of Gaucher's disease.[3]

Disease specific management for Gaucher's disease is enzyme replacement therapy (Imiglucerase), substrate reduction therapy (Miglustat), pharmacologic chaperones (Isofagomine, Ambroxol) and Allogenic bone marrow transplantation.[3]

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