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Case Report

Gaucher's Disease - A Rare Cause of Massive Splenomegaly

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Abstract:

Gaucher's disease (GD) is a lysosomal storage disorder due to glucocerebrosidase deficiency; it's one of the rare genetic diseases for which therapy is now available. Lysosomal storage of the substrate in cells of the reticuloendothelial system leads to multisystem manifestations, including involvement of the liver, spleen, bone marrow, lungs, and nervous system. Three different subtypes have been identified: Type 1, non-neuropathic form, adult onset; type 2, acute neuropathic form, infantile onset; type 3, neuropathic form, juvenile onset. The diagnosis is confirmed by presence of less than 15% activity of the enzyme Glucocerebrosidase in peripheral leucocyte with presence of Gaucher cells in macrophase monocyte system, is the pathological hallmark. Enzyme replacement therapy (ERT) is now available. We are reporting a case here which presented with cytopenia and massive splenomegaly. This case has been presented to focus on the importance of clinical examinations, differentiating from other diseases of similar manifestations, enzyme activity and bone marrow study for early diagnosis.

Key words: *Gaucher's disease, Splenomegaly, Enzymatic disorder*

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Introduction:

Most common lysosomal storage disorder is Gaucher disease expressed as autosomal recessive trait, resulting from a hereditary deficiency of the enzyme glucocerebrosidase (GBA) as a result of accumulation of the substrate of this enzyme there are many clinical manifestations.[1] After the discovery of the GBA gene, more than 200 mutations have been identified, but only a handful of mutations are recurrent (L444P, N370S, IVS2, D409H and 55Del).[1] The disorder produces a multisystem disease characterized by progressive visceral enlargement and gradual replacement of the bone marrow with lipid-laden macrophages. The symptoms includes anemia, coagulation abnormalities, visceral enlargement, and structural skeletal changes occur at some point during the course of the illness in most patients.[2] Three different subtypes have been identified delineated by presence or absence of neurological involvement. Type one, non-neuropathic form, adult onset; type two acute neuropathic form, infantile onset; type three, neuropathic form, juvenile onset.[2] The diagnosis is confirmed by presence of less than 15% activity of the enzyme Glucocerebrosidase in peripheral leucocyte.[3] It is highly sensitive, specific and less invasive. Also presence of Gaucher cells in macrophase monocyte system is the pathological hallmark in bone marrow, liver biopsy samples and genotype testing for detection of mutated alleles is also done.[3] Enzyme replacement therapy (ERT) is now available and includes imiglucerase (Cerezyme), velaglucerase alfa (VPRIV) and taliglucerase alfa (Elelyso);

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most patients receive the recombinant enzyme imiglucerase.[4] The response to this preparation differs according to: a) type of GD (type I or III); b) initial degree of involvement; and c) affected organs. In general, the best response is obtained in the hematological and visceral parameters. Prognosis of symptomatic patients with type one and type 3 disease on ERT is good, with life expectancy up to 68 years in type one if detected early.[5] We are reporting a case here which presented with cytopenia and massive splenomegaly. This case has been presented to focus on the importance of clinical examinations, differentiating from other diseases of similar manifestations, enzyme activity and bone marrow study for early diagnosis.

Case summary:

A 17-year-old female hailing from Tangail got admitted into Dhaka Medical College Hospital with abdominal distension, pallor and fatigue for one year. On query, she gave history of appearance of occasional black spot on different parts of the body for the last two months. There's no history of fever, weight loss, cough, abdominal pain, vomiting out blood, passage of black tarry stool, nasal bleeding or excessive menstrual flow. History of joint pain, oral ulceration and hair loss were absent. She is single, Muslim, born with parents with no consanguinity of marriage, her younger sister nor do her parents have any of those manifestations. She gave no history of blood transfusion. Her development corresponds with her age. On examination she was found anaemic, non-icteric, having few non blanching purpuric rashes on both legs. However, there was no palpable lymph node. Abdominal examination revealed massive non tender splenomegaly (about 14 cm from costal margin), firm in consistency, margin rounded, splenic notch present but no bruit or rub. Liver was just palpable, non-tender, having rounded margin; ascites was absent. Rest of the systemic examinations revealed no abnormality.

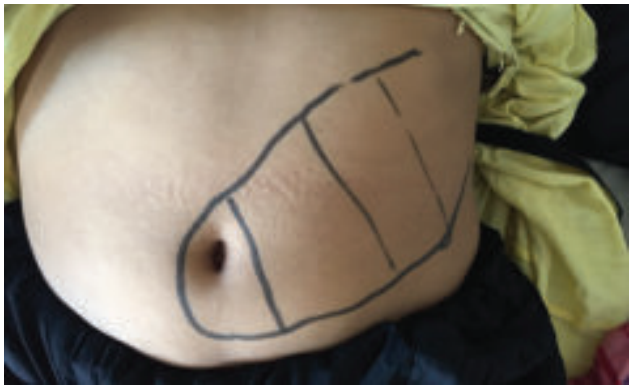

Figure 1: Massive splenomegaly

Laboratory investigations reveled Hb - 9.6 g/dl, ESR - 40 mm in 1st hour, Platelet 80,000/mm^3, WBC – 5600/mm^3. Absolute indices and reticulocyte count were within normal range. Peripheral blood film showed bicytopenia. Serum ferritin was normal (82.95 microgm/l). PT, APTT, SGPT, serum creatinine and random blood sugar within normal range. Serum ANA and Coomb's test and ICT for Kala-azar were found negative. USG revealed marked splenomegaly with mild hepatomegaly. Upper GI tract endoscopy was normal. HBsAg and Anti HCV were negative. X-rays of chest, both upper & lower limbs were found normal.

Bone Marrow study showed all cell lineage including erythrocytic, granulocytic and megakaryocytes normal in number and morphology. There were no plasma cells or LD body. However, there was increased number of histocytes which have crumbled tissue pattern/onion skin appearance. Features those were suggestive of Gaucher's disease. Serum beta glucocerebrosidase value very low (0.92) (Normal >4). The bone marrow study and the enzyme level confirm our case as Gaucher's disease.

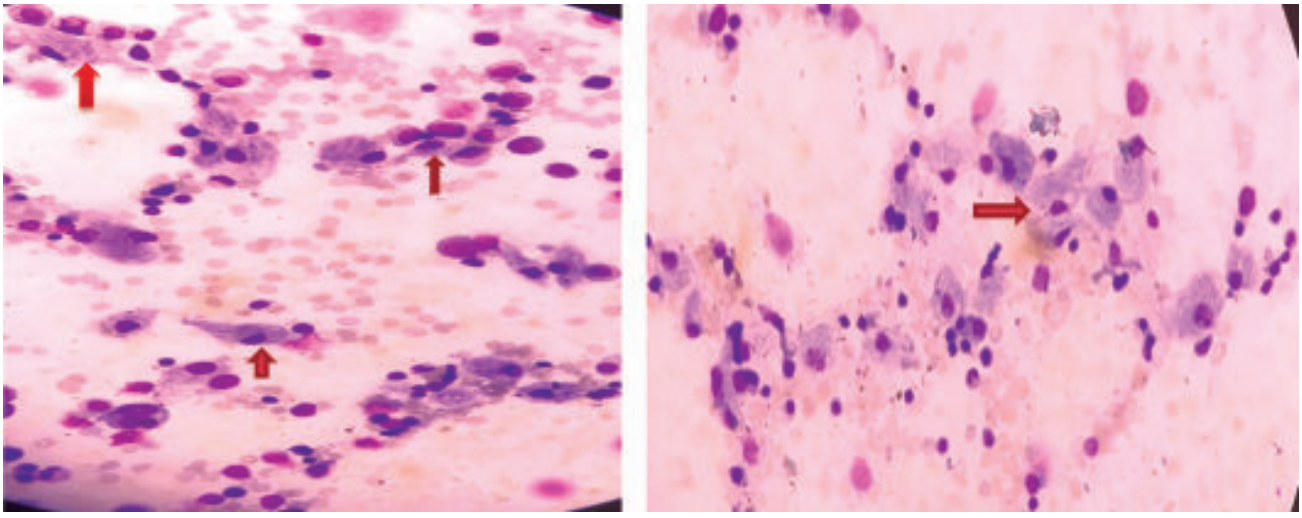

Figure 2: Typical Gaucher's Cell (arrow mark) in Bone Marrow smear - Leishman Stain

Discussion:

Gaucher's disease is an autosomal recessive disorder. Its overall incidence is approximately 1:40,000 individuals.[6] It can affects all racial and ethnic groups but prevalence is higher among Ashkenazi Jews. It is the most common lysosomal storage disorder.[7] Clinical research shows that Gaucher's disease manifests with broad phenotypic variation typical of many metabolic disorders, ranging from neonatal lethality to asymptomatic octogenarians. It has long been known that neither the amount of lipid stored, nor the residual enzymatic activity detected, correlates well with symptom severity.[8] Although Gaucher's disease is well known in adult patients but about two-thirds of the patients present before the age of 20 and onset in childhood is predictive of severe and progressive phenotype.[9] In Bangladesh, so far it will be the 2nd case to be reported; as 1st case was reported by Md. Sirazul Islam in 2009.[10] This does not mean GD is extremely rare in Bangladesh, rather it might be due to nonsuspicious clinicians, under reporting, unacquainted morphologist for detecting pathognomic Gaucher's cell and lack of population study. As GD is autosomal recessive so it's not gender specific. Certainly, consanguinity plays an important role for disease causation. The most common signs and symptoms noted in GD are splenomegaly (95%), hepatomegaly (87%), radiological bone disease (81 %), thrombocytopenia (50%), anemia (40%), growth retardation (34%), bone pain (27%), and bone crisis (9%). A skeletal manifestation is found more often in older children.[11] International Collaborative Gaucher's Group reported that 63% of patients have experience with bone pain and 26% develop bone crisis.[12] However, parents of our patient are unrelated. Our patient presented at the age of 20 with huge splenomegaly with cytopenia. The cause of splenomegaly varies according to disease etiology and geographical variations such as in western countries hematological disorder will be considered preferably but in tropical country like in Bangladesh parasitic infection (example Malaria, Kala-azar) are of immediate concern. In Bangladesh a case of huge splenomegaly brings various differentials in mind like visceral leishmaniasis, Malaria/ Tropical Splenomegaly Syndrome, Hereditary hemolytic disoreder, chronic myeloid leukaemia, Myelofibrosis, lymphoma, SLE and lastly storage or lysosomal diseases. In our case, we initially diagnosed her as a case of chronic ITP as there were ecchymosis, purpura, splenomegaly & bicytopenia (anaemia & thrombocytopenia) in her complete blood profile. Absence of previous history of malaria attack, negative ICT for malaria with absence of parasite in PBF exclude Malaria/TSS. In our patient hemoglobin electrophoresis was normal, coombs test & ANA were found negative so any hemolytic disorder (congenital or autoimmune) was virtually excluded. However, our patient was a resident of Kala-azar endemic zone[13] that's why we did ICT for kala-azar which was negative & bone marrow study to exclude leukaemia & kala-azar also. Some histiocytic disorders could explain the patient's symptoms, but these were ruled out as because she lacked other associated symptoms, such as rapid clinical deterioration, fever, wasting, skin rash and irritability. Among other histiocytic disorders, several metabolic storage disorders commonly present with hepatosplenomegaly. On bone marrow study we found typical Gaucher's cell where rest of the marrow showing normal erythrocyte, granulocyte & megakaryocyte lineage. These Bone marrow findings are suggestive of Gaucher's Disease but can also be found in CML, Hodgkin lymphoma, AIDS where enzyme glucocerebrocidase level is normal.[14] So we went for serum beta glucocerebrosidase level which found very low. That's make our diagnosis straight forward.

ERT is highly effective in improving the quality of life, growth velocity, weight gain and energy levels; other effects include a correction of both delayed puberty and hypermetabolic state.[15] Despite all the benefits of the ERT, our patient´s access to this therapy remained impossible due to its high cost, in fact, for a patient whose weight is 66 pounds the annual cost may reach 300.000 dollars. Therefore, the treatment in our study was always symptomatic (analgesics, transfusion).

Conclusion:

Gaucher's Disease, a rare lysosomal storage disease should be kept in mind as differential diagnosis when dealing a case of unexplained hepato-splenomegaly. Many a time speculative diagnosis or empirical treatment is not helpful. Moreover, the early recognition of GD would lead to safe and effective treatment with enzyme replacement which can decrease morbidity and reduce as far as possible the visceral and skeletal involvement.

Conflict of interest: None.

References:

1. Pastores GM, Weinreb NJ, Aerts H, Andria G, et al. Therapeutic Goals in the Treatment of Gaucher Disease. Seminars in Hematol.2004;41(5):4-14.

2. Beutler E, Grabowski GA. Gaucher disease. In: Scriver C, Beaudet AL, Sly WS, Valle D, eds.The Metabolic and Molecular Bases of Inherited Disease. 8th Ed. New York: McGraw-Hill.2001:3635-3668.

3. Germain DP, Mistry P. Phenotype variations in Gaucher disease. Rev de Med Int. 2006; 27(Suppl 1):7-10.

4. Sidransky E, Pastores GM, Mori M. Dosing enzyme replacement therapy for Gaucher disease: older, but are we wiser? Genet Med. 2009 Feb; 11(2):90–91.

5. Weinreb NJ, Deegan P, Kacena KA, Mistry P, Pastores GM, Velentgas P, et al. Life expectancy in Gaucher disease type 1. Am J Hematol. 2008; 83(12):896–900.

6. Mehta A, Epidemiology and natural history of Gaucher's disease Eur J Intern Med.2006;17 Suppl:S2-5.

7. Rajiv Singla, Abhishek Singla, Suresh Kumar, Anil Agarwal, Premashish Kar, Gaucher's disease with portal hypertension and hypersplenism. Tropical Gastroenterology 2011;32(1):66-68

8. Sidransky E. Gaucher disease: insights from a rare Mendelian disorder. Discov Med. 2012;14(77):273-81.

9. Levrat V, Forest I, Fouilhoux A, Guffon N. Gaucher disease in childhood. Rev Med Interne.2007;28(2):183-6.

10. Islam SM, Sarwar-e-Alam ABM, Ahmad F. Gauchers Disaease- A case of huge hepatosplenomegaly clinically confused with Kala-azar: Case report & literature review. Bangladesh J Pathol 2009;24(2):25-33. http://dx.doi.org/10.3329/bjpath.v24i2.4115

11. Kaplan P, Andersson HC, Kacena KA, Yee JD. The clinical and demographic characteristics of nonneuronopathic Gaucher disease in 887 children at diagnosis. Arch Pediatr Adolesc Med.2006;160(6):603-8.

12. Brisca G, Di Rocco M, Picco P, Damasio MB, Martini A. Cox arthritis as the presenting symptom of Gaucher disease type 1. Arthritis 2011;2011:361279.

13. Bern C and Chowdhury R. The epidemiology of visceral leishmaniasis in Bangladesh: prospects for improved control. Indian J Med Res 2006;123:275-288.

14. Ahin DG, Teke HU, Karagülle M, Andýç N, Gündüz E, Iþýksoy S et al. Gaucher Cells or Pseudo-Gaucher Cells: That's the Question. Turk J Haematol. 2014;31(4):428–429.

15. Mistry PK, Ayala A. A practical approach to diagnosis and management of Gaucher's disease. Bailliers Clin Haematol. 1997;10(4):817-838.