Gaucher's Disease: A Case Of Huge Hepatosplenomegaly Clinically Confused With Kala Azar: Case Report And Review Of The Literature

Md. Sirazul Islam¹, ABM Sarwar-Alam², Faruk Ahmad³

Abstract
This is the case report of a 25 year old young man who presented with low grade irregular fever, weight loss and huge hepatosplenomegaly. Although initially mislabeled as a case of kala azar and treated as such elsewhere, we could diagnose this case of Gaucher's disease after finding typical 'Gaucher cells' in his bone marrow smears. Palliative splenectomy was performed and the diagnosis was further confirmed by histopathological examination of the spleen. The case is discussed including a short review of the literature. This is probably the first reported case in Bangladesh.

Key words: Hepatosplenomegaly, kala azar and Gaucher's disease.

Introduction
Gaucher's disease (GD) is an autosomal recessive lipid storage disorder caused due to deficient or defective production of a naturally occurring lysosomal enzyme glucocerebrosidase (GD). Failing enzymatic degradation, there is accumulation of glucocerebroside (a glycolipid) in large quantities in lysosomes of reticuloendothelial (RE) cells i.e., macrophages of many organs, primarily liver, spleen and bone marrow but rarely the brain & nervous system, lungs, kidneys, skin and lymph nodes etc. Clinical manifestations are due to cellular and tissue damage consequent upon accumulation of abnormal RE cells in various organs and tissues. Glucocerebroside is a cellular breakdown product formed as a consequence of normal growth, development and senescence that requires further enzymatic degradation for elimination from the body. This condition was first described in 1882 by a French medical student Philippe Charles Ernest Gaucher who wrote a descriptive case report as a thesis for his degree of medicine. He considered large splenic cells that now bear his name as a manifestation of primary neoplasm of spleen¹. In 1906 Merchand proposed that the disease was caused by storage of some material in the reticuloendothelial cells and ultimately in 1934 Aghion showed that the material was glucocerebroside, a glucosyl ceramide². In 1965, the primary defect was detected as a deficiency in the enzyme glucocerebrosidase resulting in inability to degrade glucocerebroside³,⁴. Thus the diagnosis of GD by enzyme assay including heterozygote detection became available.

The glucocerebroside laden enlarged RE cells with eccentrically placed nuclei are called "Gaucher cells" which accumulate in many organs causing organomegaly with dysfunction and also marrow replacement with accompanying cytopenias. Gaucher cells in routinely stained preparations are variously described as having cytoplasm with wrinkled, striated, 'onion-skin' or 'crumpled-up paper' like appearance. The cytoplasm is stained by Periodic acid-Schiff (PAS) technique and also stains for acid phosphatase. While GD is almost always characterized by a deficiency of Beta-glucocerebrosidase⁵, in very rare instances a severe neuronopathic form of the disease occurs as a result of deficiency of the heat-stable glucocerebrosidase co-factor named saposin⁶.

GD is sporadic worldwide with an estimated incidence of 1:60-80000 individuals⁷ but it is most common in the Ashkenazi Jewish population in which the gene frequency is 0.034 resulting in a carrier (heterozygous) rate of 6.8 per cent and the expected birth frequency is 1:1000 in that population⁸. GD is also relatively common in a population isolate at Norrbottia in Northern

1. Dr. Md. Sirazul Islam, Professor and chief Scientific officer, Laboratory department of Clinical Pathology, Clinical Biochemistry & Haematoloty, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka
2. Dr AM Sarwar-e-Alam, Consultant Physician-Internal Medicine, Square Hospitals Ltd, Dhaka
3. Dr Faruq Ahmad, Professor of Surgery, Comilla Medical College, Comilla.

Correspondence to: Professor Md. Sirazul Islam, Laboratory BIRDEM.
Sweden. The GC gene is located on chromosome 1 at band q21 with a total length of seven kilobases. Both the active gene and a homologous (96%) pseudogene (downstream from the active gene) have been cloned and sequenced. This has facilitated molecular diagnosis of GD. More than 300 mutations causing GD have been described, most of these are point mutations.

Three major phenotypes of GD have been recognized clinically, determined in large part by the residual activity of the mutant enzyme. All three types are genetically similar progressive disorders. The residual activity of GC in type II is so low that abnormal cells accumulate in the central nervous system (CNS). This is the acute neuronopathic form of the disease which presents in early infancy with neurological complications, usually leading to death before the age of two years. This type II disease is rare and does not occur predominantly in Jewish families. Type I (adult) GD occurs in children as well as adults but is clearly differentiated from Type II (adult infantile neuronopathic) and Type III (Juvenile) disease by the absence of primary neurological symptoms. Hepatosplenomegaly, usually common to all three types, may be quite pronounced in type I. Type III is a less well-defined subacute neuronopathic disorder with later onset of neurological symptoms (from two to 20 years) and a better prognosis. Usually death ensues by the age of 30 years. This last one is a prototype of Norrbottian (Northern Sweden) disease.

The clinical manifestations of GD are produced by the accumulation of 'Gaucher cells' in various organs as mentioned earlier. There is great variability in the severity of all types of GD. Type I (adult type) disease may be entirely asymptomatic, discovered during population survey or during investigation for an unrelated haematological disorder. In the symptomatic patients, the spleen may be barely palpable or it may be massively enlarged producing pressure symptoms due to its great bulk and by sequestering formed elements of the blood resulting in variable cytopenias. Skeletal disorders and bone lesions that may cause pain are common in type I, occasionally present in type III and usually absent in type II disease. Patchy areas of bone demineralization and areas of necrosis may be present. Widening of the distal femur may give rise to a typical "Erlen-Mayer flask deformity". Brownish masses of Gaucher cells may appear at sclero-corneal limbus of the eyes. Since the disease is rare, in non-endemic population a case of huge splenomegaly or hepatospleno-megaly will obviously, not raise the suspicion of GD from the outset rather it may point to some other locally prevalent parasitic or infectious diseases like malaria, kala azar (visceral leishmaniasis), schistosomiasis, brucellosis etc. or other medical problems associated with organomegaly.

We report a case of type I GD in a Bangladeshi young man of 25 years who presented with huge hepatospleno-megaly and had been otherwise misdiagnosed as a case of kala azar (visceral leishmaniasis) in two local hospitals respectively and he was repeatedly treated as such with potentially toxic drugs without any benefit during five years time prior to presenting to us. We could diagnose the case easily by finding typical Gaucher cells in the bone marrow smears although the advice from the physician was "Bone marrow examination for LD (Leishman-Donovan) bodies"; LD bodies were not found. As the patient had mainly pressure symptoms due to huge spleen, he was treated palliatively by splenectomy with considerable relief of symptoms. Enzyme replacement therapy was not possible due to local unavailability and high cost of the drug. Since the patient could not produce previous bone marrow examination reports (lost) it is assumed that Kala azar was a (overenthusiastic) misdiagnosis or the treatment for leishmaniasis was given on empirical basis. Our diagnosis was mainly based on morphology including cytochemistry but confirmatory enzyme assay and genetic studies were not possible due to local unavailability of the tests. The case is discussed with emphasis on correct diagnosis particularly before instituting a costly or potentially toxic therapy. A short review of available literature is also included.

So far we know, this is the first reported case in Bangladesh.

Case History

Mr M H, a 25 years old unmarried Bangladeshi young man, salesman in a grocer's shop by profession, hailing from Daudkandi under district of Comilla presented on September 16,2005 with the complaints of low grade irregular fever, progressive weight loss and constipation for five years; gradually increasing abdominal fullness and discomfort with vague dragging pain for last three years; inability to take adequate food due to abdominal fullness in spite of good appetite for last two years. Initially, four years ago, he attended a postgraduate teaching hospital where he was admitted and bone marrow examination was done there along with other routine investigations. He was told that he had kala azar and was treated there as such by a thirty days'
course of intravenous injections (Problably Inj, Sodium Stibo-glucone). The Patient could not produce any document of his admission and treatment there which he confessed to be lost. Later on, after two years, noticing no improvements rather worsening of his symptoms he went to a private hospital of Dhaka city where he was admitted again under a medical consultant. Bone marrow examination was done again along with other investigations; treated similarly by a course of i.v. injections of Sodium stibogluconate followed by seven days' course of Inj. Amphotericin B (according to his discharge certificate). Unfortunately, he could not produce reports of laboratory investigations including that of bone marrow examination which he had lost and there was no mention as well of a positive finding of LD bodies in his discharge certificate. After waiting for further two years and noticing no improvements, the patient attended to one of us (ABMS) in the out patient clinic of 'Khidmah Hospital (Private) Ltd'. The patient had no history of previous blood transfusion or any significant illness in the past.

Parents of the patient were unrelated (no consanguinity); out of nine brothers and one sister, the patient was the fourth. His only sister died at the age of three years after three months' suffering from a severe undiagnosed illness. She developed distended abdomen during the course of her illness. Other eight brothers were so far normal.

On examination, the patient was found to be a short-stature man with a height of 151 cm, weight of 43 kg with protuberant abdomen; vital signs were normal but two enlarged lymph nodes were present-one in left posterior cervical triangle and another in left axilla, central group. All other findings of general examination including sexual development were normal. Abdominal examination revealed huge splenomegaly, spleen's tip touching symphysis pubis and moderate hepatomegaly (up to the level of umbilicus) sparing only a small abdominal space in the right lower quadrant laterally. Eye examination of the patient showed a yellow brown pingoecula at lateral corneo-scleral junction of left eye; right eye was normal. Both fundi were normal. All other systemic examination findings including nervous system were normal. Laboratory investigations showed-Haemoglobin 13.2 g/dl, Total WBC-81000/cm³, Differential count: Neutrophils- 50%, Lymphocytes- 41%, Monocytes- 07%, Eosinophils- 02%, MCV -85 fl, Platelet count- 182000/cm³; Serum total protein - 8g/dl, S. albumin-4.3 g/dl, S. total bilirubin- 1 mg/dl, S. ALT-23 U/L (Normal- up to 37 U/L), S. AST -27 U/L (Normal -up to 40 U/L), S. urea-28 mg/dl, S. creatinine- 1 mg/dl, S. acid phosphatase (total) 2.6 U/L (Normal: 0.4 to 2.4 g/L), Immunochromatographic Test (ICT) for Kaiza azan-negative, HIV test-negative, Blood group-B, Rh (D) positive. Fine Needle Aspiration Cytology (FNAC) of enlarged cervical lymph node was suggestive of chronic non-specific lymphadenitis; Gaucher cells were not seen. Bone narrow aspirate smears showed a moderately hypercellular, particulate marrow with normal M/E ratio (about 3:1). Erythropoiesis was normoblastic and active. Granulopoiesis was also normal with maturing to segmented forms; megakaryocytes were normal in number and morphology. Moderate number of typical Gaucher cells were seen scattered and in small groups on the smears with occasional bi- tri-, or multinucleate forms (Figure-1 a).

PAS (Periodic Acid Schiff) staining was done that showed positivity of the cells (Figure-1b). No LD bodies (Leishmanial parasites) were seen.

X-ray examination of the chest was normal. X-ray of both femora showed mild changes in the right characterized by inhomogenous medullary cavity of lower shaft with posterior cortical thickening and ill-definition of adjacent endoesteum but virtually normal left femur (Figure-2).

The diagnosis of type 1 Gaucher's disease was provisionally confirmed based mainly on bone marrow and other findings pending enzyme assay. Assay of enzyme glucocerebrosidase was not possible due to unavailability of the test in our country and the patient could not afford to get it done as well from abroad. Other family members of the patient including his brothers did not co-operate to get investigated as they had no obvious health problem.

As the patient had his main complaints (pressure symptoms) related to huge splenomegaly, it was decided to undertake splenectomy as a palhination. He was counselled and prepared for surgery. The patient was not considered as a member for enzyme replacement therapy due to unavailability of the drug in our country and its high cost if procured from abroad. Vaccination programme was started preoperatively against pneumococci and meningococci to be completed in due course. Splenectomy was performed in the 'Khidmah private hospital' on October 27, 2005 led by of one of us (FA), a small wedge biopsy of enlarged liver was also taken. The postoperative period was uneventful and the patient was discharged from the hospital on the ninth postoperative day with the advice of life
long prophylaxis of oral phenoxymethyl penicillin at 250 mg b.i.d dose. The spleen measured 25 cm x 12 cm x 10 cm and weighed 2500 gm with paler colour and smooth glistening capsule. A small piece of spleen was cut out and touch imprints were made on glass slides. The cut surface of spleen was paler grey and homogenous, no evidence of haemorrhage, degeneration or cystic changes were seen. The cut piece of spleen and wedge biopsy specimen of liver were preserved in 10% formalin and sent to BIRDEM (Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders) in separate containers respectively for histopathological examination. Touch imprint-smears of spleen were stained by both Leishman stain and PAS (Periodic Acid Schiff) method. Numerous morphologically typical and PAS-positive Gaucher cells were seen (Figure-3 and b).

Histopathological examination of splenic sections revealed massive infiltration by Gaucher cells characterized by presence of abundant eosinophilic fibrillary cytoplasm and eccentric nuclei (Figure-4a). The cells were PAS Positive (Figure-4b).

Figure-2: X-Ray of both femora showing mild changes in the lower end of the right (please see text for description).

Figure-1a: Gaucher cells in bone marrow smears-Leishman stain.

Figure-1b: Gaucher cells in the bone marrow smears-PAS stain.

Figure-3a: Imprint smear of cut surface of the spleen showing Gaucher cells-Leishman stain.

Figure-3b: Imprint smear of cut surface of the spleen showing PAS-Positive Gaucher cells.

Figure-4a: Gaucher cells in the histopathological section of the spleen (H&E stain).

Figure-4b: PAS-positive Gaucher cells in the splenic section.
Sections of liver biopsy showed well preserved hepatic architecture with virtually normal hepatocytes. The Kupffer cells were swollen and contained non-foamy fibrillary cytoplasm. There was no evidence of inflammation or malignancy.

Based on all above findings, the diagnosis was so far confirmed as Gaucher's disease, type 1 and the patient was advised for follow up initially after three months. After three months the patient was doing fine with stable normal blood counts and he was found very happy due to great relief from tense abdomen including relief from discomfort and dragging pain and above all, regaining ability to take considerable food. By three months he gained about two kilograms in spite of loss of two and a half kilograms’ spleen. He was further advised for subsequent follow up every six months but unfortunately he lost contact. We do not know his present fate but hope for the best.

Discussions

As mentioned earlier, GD is sporadic worldwide with a low incidence but common in Ashkenazi Jews and an isolated Norrbottian population in Northern Sweden. The disease may be very rare in some population. In Bangladesh, so far, there is no reported case and ours, probably is the first. This does not mean that the disease is extremely rare here rather it could be due to some reasons like under reporting, non-suspicious clinicians, unacquainted morphologists for detecting pathognomonic Gaucher cells, lack of population study, lack of or insufficient medical care facilities etc.

Since GD is an autosomal recessive disorder it is not gender specific and may affect both sexes equally. Of course, consanguinity is likely to play an important role in its causation but parents of our patient were unrelated. As mentioned earlier in the case history, the only sister of the patient died at an age of three years after three months’ suffering from a severe undiagnosed illness with a big tummy. Could it be due to similar genetic mutation, albeit severe, producing type II pher Notype or even type I with haematological crises of cytopenias, this is not certain. Type I disease is heterogeneous and may manifest at any age starting from childhood to the old age with variable presentations from entirely asymptomatic incidentally discovered disease during population survey with normal life expectancy to severely affected cases with organomegaly and cytopenias resulting in early death. Our patient presented at the age of about 20 years and although he had huge splenomegaly (resected spleen weighed 2500 gms) there were no cytopenias but pressure symptoms only.

Splenomegaly may occur as a result of various pathological factors like reactive increase of white pulp in inflammation and infection, congestive expansion of the red pulp compartment, increased blood pool, increased macrophage function, proliferative cellular infiltration, extramedullary haemopoiesis, storage disease, cysts and solid tumors etc. The relative incidence of the cause of splenomegaly is subject to geographical variations; in the western countries haematological disorders come first while in the tropics parasitic infections like malaria, leishmaniasis and schistosomiasis are of immediate concern. In Bangladesh, a case of huge splenomegaly brings in mind various differential diagnoses like visceral leishmaniasis, tropical splenomegaly syndrome (TSS), chronic myeloid leukaemia & chronic myelofibrosis, thalassaemias & haemoglobinopathies, cirrhosis of liver with portal hypertension, lymphoma, collagen diseases (e.g., SLE) and lastly, storage diseases etc. In our case, haematological disorders were excluded straightforward by normal blood counts and normal blood film findings. Absence of anaemia and lack of past history of malarial attacks excluded the possibility of TSS. Our patient was not a resident of kala azar endemic areas of Bangladesh. Moreover, negative immunological tests for leishmaniasis and history of failure of response to anti-kala azar drugs raised a big query about the validity of previous diagnosis of leishmaniasis; however, our findings of presence of typical Gaucher cells in the bone marrow smears in an otherwise unremarkable marrow made the diagnosis of Gaucher’s disease more or less straightforward.

Cells morphologically similar to typical Gaucher cells also may be found in patients with chronic myeloid leukaemia (CML), Hodgkin’s lymphoma, multiple myeloma, and AIDS. In these conditions enzymatic activity of GC is normal but the great inflow of glucocerebrosides into phagocytic cells far exceeds their normal capacity to degrade this glycolipid. We could exclude these conditions in our patient clinically by history, physical examination and routine laboratory investigations as mentioned earlier. 'Foam cells' of Niemann-Pick disease and engorged histiocytes of other storage disorders are morphologically quite different and usually not confused with Gaucher cells. Enzymatic assay of Beta-glucosidase activity in leucocytes or cultured fibroblasts is diagnostic of GD when a low value is detected. The test is not available in Bangladesh nor...
could our patient afford to get it done from abroad. However, enzymatic assay does not always identify heterozygote subjects since considerable overlap may be there between values in normal subjects and heterozygotes. Definitive diagnosis of the heterozygote state can only be established by DNA analysis.

Demonstrating the presence of known Gaucher mutations in the patient’s DNA can establish the diagnosis in index populations but its absence cannot exclude it. For example, if the DNA is examined for the most common five mutations, mutations will be detected on both alleles in approximately 97 percent of the Jewish patients but in only approximately 55 percent of the non-Jewish patients. We could not attempt for this diagnostic approach for limitations as mentioned as for enzymatic assay.

The serum levels of ferritin, angiotensin-converting enzyme (ACE) and acid phosphatase are typically elevated in GD. The enzyme chitotriosidase is derived from macrophages and is typically grossly elevated in untreated GD, and declines progressively with treatment. So, this can be used as a marker for monitoring enzyme replacement therapy (ERT) with few exceptions since up to 6% of the population are genetically deficient in this enzyme. Serum ferritin level and acid phosphatase levels were mildly elevated in our patient but ACE and chitotriosidase were not done due to local unavailability of the tests.

Liver enzymes may be elevated in GD if there is considerable hepatic parenchymal involvement but in our patient these were normal including serum bilirubin level. Skeletal involvement in our patient was minimal as mentioned in the case report and his left eye showed a pinguicula; although not specific these are supportive findings to the diagnosis of GD.

Rarely, renal, pulmonary and skin involvement may occur in type I GD. Increased incidence of malignancy including haematological malignancies, especially B-lymphocyte disorders (myeloma, monoclonal gamopathy of undetermined significance) and myelodysplasia are also noted in patients with this type. Our patient had no evidence of such involvement.

Prenatal diagnosis of GD may be established by examining amniocentesis cells for their beta-glucosidase activity or chorionic villus DNA for prevalent mutations.

Until 1990, treatment of GD consisted only of palliative measures such as splenectomy and hip replacement. Type I GD seems particularly suitable for enzyme replacement therapy (ERT) because of the lack of central nervous system involvement (visceral damage in GD is reversible whereas the brain damage usually is not). However, ERT has recently been licensed for patients which type III GD, who typically have milder CNS changes (e.g. ophthalmoplegia) with advanced systemic manifestations. ERT was tried by various workers since mid 1970s but its successful and regular clinical use started only in 1990s when a mannose terminated form of the enzyme extracted from human placenta was marketed commercially by the name algglucerase (Ceredase). Its has been replaced soon by imiglucerase (Cerezyme), the recombinant product. The presence of a mannose receptor on macrophages is exploited for internalization of the enzyme preparation hence its targeted action on lysosomes. The response to ERT is gratifying resulting in decrease in the size of liver and spleen and increase in the haemoglobin levels and the number of platelets of anaemic and thrombocytopenic patients respectively within six months of therapy. Response to bony lesions is much slower and improvement may be evident approximately after two years of treatment regardless of the dose that is used. ERT is administered as intravenous infusion typically at patient’s home. As because the enzyme preparation for ERT is extremely costly (about USL 4.00 per unit), a low dose regime (15 units/kg/ month) is preferred instead of earlier recommended higher dose (60 units/kg/1-2 wks) since excellent clinical response was achieved even with the low dose.

Besides ERT, an oral from of substrate reduction therapy (SRT) is targeted to inhibit synthesis of glucocerebrosidase. Among a number of potential inhibitors, only Miglustat (N-butyl deoxy nojirimycin, Zavesca, Vevesca) has been licensed for mild to moderate type I GD with reduced residual enzyme activity. SRT crosses the blood-brain barrier and is being evaluated recently in type III GD and other lysosomal storage diseases affecting the CNS (e.g. in Tay-Sach's disease, Niemann-Pick's disease type C). Supportive therapy for skeletal involvement (e.g. analgesics for bone pain, biphosphonates or analogs for osteopenia) and haematological manifestations (bone or platelet support) are given to the patients as may be necessary. Total hip replacement surgery is often successful in some severely incapacitated patients allowing them return to normal activity. Radiation therapy has been proved beneficial for relieving pain in some cases but failed to produce satisfactory response in other and therefore, is not recommended. Splenectomy may
improve cytopenias if evidence hypersplenism is present. Allogeneic bone marrow (stem cell)-transplantation is a curative form of therapy, and has a definite role in selected children with type III neutropathic GD\(^2,7\) but its limitation due to immediate risks and availability of effective ERT markedly limit the number of potential candidates for this therapeutic approach. Autologous transplantation after gene transfer into haemopoietic cells has been tried with some optimistic claims of success\(^47-51\) but it is no yet established as a successful modality of treatment of GD\(^52\). A new approach to the treatment of lysosomal storage disorders is the use of "chaperone therapy" in which an inhibitor (e.g. N-deoxynojirimycin) to the mutant enzyme is exploited to loosely bind (at lower concentration) thus stabilizing the enzyme (preventing early destruction) so that it can reach the lysosomes, the inhibitor then diffusing away from the enzyme\(^53\). Splenectomy was offered to our patient and it was performed as because ERT was not possible for reasons mentioned earlier. Splenectomy has some deleterious affects on the disease process of GD resulting in more accumulation of glucocerebrosides in liver and marrow thus worsening liver condition and rapid progression of bone lesions respectively\(^54-56\). However, no worsening of bone lesions after splenectomy could be documented in one study\(^67\). Our patient was quite well at three months follow up being symptom free and gaining weight but unfortunately he lost contact and did not reappear subsequently. This is not unusual in the perspective of his socioeconomic status. Splenectomy has its own accompanying hazards of susceptibility to infections particularly to capsulated bacteria for example, Haemophilus influenzae type b, pneumococci and meningococci etc. Our patient was vaccinated against pneumococci and meningococci and was advised for standard life long prophylaxis of oral penicillin at 250mg b.i.d dosage. Vaccination against H influenzae b is particularly important for infants and young children.

We would like to comment that although rare, Gaucher’s disease hence lysosomal storage disorders should be kept in mind as differential diagnosis when dealing with a case of unexplained hepatosplenomegaly as the proverb "your eyes cannot see what thy mind does not know" stands true on many occasions as possibly it had happened with our case. Many a time speculative diagnosis or empirical treatment is not helpful. Careful examination, repetitive if necessary, of morphology, is important to establish the diagnosis. Appropriate diagnosis spares the patient from undue expenditures and exposure to unnecessary interventions and potentially toxic drugs; our patient being a poor grocery salesman had to spend a sum of about ninety thousand taka during five years time of his illness before coming to us.

Acknowledgments

We would like to express our special thanks to Dr Nazma Afroz. Associate Professor and the technical staff of the department of Pathology, BIRDEM for their co-operation and help by providing us with the report and slides of sections of the spleen and liver specimens.

References


