SKELETAL COMPLICATIONS IN GAUCHER'S DISEASE: A CASE REPORT

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ABSTRACT

Gaucher's disease is a rare inherited lysosomal storage disease due to a genetic deficiency of an enzyme acid-B-glucosidase. Onset and clinical course is very variable but main features are hepatosplenomegaly, anaemia, thrombocytopenia and many bone features including osteopenia, lytic lesions, pathological fractures, chronic bone pain, acute episodes of excruciating bone crisis, bone infarcts, osteonecrosis, septic arthritis and skeletal deformities. It should be considered in the differential diagnosis of patients who present with unexplained organomegaly, easy bruisability and/or bone pain.

INTRODUCTION

Gaucher's disease (Gaucher's splenomegaly) is a rare, inherited lysosomal storage disorder (1-8). It most often develops in children, adolescents and young adults and runs a protracted course (9-17). It is a pan-ethnic disorder found in every 40,000- 60,000 people in the general population, but more prevalent in the Ashkenazic Jews (2). It results from abnormal accumulation of glucocerebrosides in reticuloendothelial cells, the accumulation occuring because of deficiency of an enzyme, acid-*B* –glucosidase (glucocerebrosidase), necessary for the degradation of these glycolipids (3). The organs affected by Gaucher's disease include spleen, liver, lung, kidney, bone, bone marrow, lymph nodes, tonsils and thymus (4). The increasing proliferation and masses of the storage cells produce many symptoms and signs. The clinical manifestations that are quite striking and clearly related to the disease include hepato-splenomegaly, anaemia, thrombocytopenia, lymph node enlargement and bone lesions.

Bone involvement is perhaps the source of the most variable symptoms attributed to Gaucher's disease (14). The bone lesions include profound osteopenia, osteosclerosis, lytic lesions, pathological fractures, osteonecrosis, osteomyelitis, acute episodes of excruciating pain (bone crises), chronic bone pain and skeletal deformities which result from bone marrow replacement, compression of the intraosseous vasculature and erosion of osseous tissue (3,10). The skeletal manifestations are probably the most disabling aspect of the disease, with patients experiencing bone pain, some suffering bone crises and upto 20% getting impaired mobility while osteomyelitis and septic arthritis have also been reported (4,5,15). Vertebral compression has been noted to occur later in life while osteomyelitis has been observed to occur in the advanced stages of bone marrow infiltration, culminating in fracture. The impact on the patients quality of life is negative. The orthopaedic surgeon is concerned mainly with the skeletal manifestations of the disease, which usually begin in the femur, but have a greater impact on the patients quality of life than the haematological and visceral aspects (2,17). The purpose of this study is to present one patient that we consider to be a case of Gaucher's disease with distal femoral metaphyseal infarction.

CASE REPORT

In February 2008 a 14 year old boy presented to our unit with complaints of a protruding distal left thigh bone, a left thigh wound and inability to walk. These were of a duration of two months.

He had a remarkable past medical history of an abscess of the left thigh, multiple left knee swellings and multiple blood transfusions, the latest being 3 units in the preceding last one month in a medical facility elsewhere. No other history of allergies was obtained. Further enquiry to the medical history revealed a previous admission to the medical wards of the Kenyatta National Hospital in August 2006 and remained as an inpatient till January 2007, with recurrent left knee swellings, palpitations and severe anaemia (Hb 3.99). At this admission, splenomegaly was noted and a working diagnosis of Von Willibrands disease was embraced on the basis of a prolonged Activated Partial Thrombosplatin Time (APTT) (77 seconds versus 35 seconds for normal control). It was significantly noted that the patient did not have a family history of bleeding tendencies, which would have been the case if he was afflicted by Von Willibrands disease and further it would have been ideal to do Factor VIII:C, Factor VIII Ag and Factor VIIIR CoF to confirm the diagnosis of Von Willibrands disease. Patient received 5 units of blood, fresh frozen plasma, tranexamic acid, and desmopressin. Upon review, the left knee and distal thigh were found

to contain a tender fluctuant swelling and incision and drainage was undertaken. The pus drained grew *staphylococcus aureus* sensitive to almost all antibiotics and patient was treated with clindamycin, augmentin and metronidazole, in addition to 2 units of compatible fresh frozen plasma, tranexamic acid, novoseven and potent oral and injectable analgesics. Haemoglobin electrophoresis returned a result of AA, while the HIV test was negative.

His family history revealed that he was the 5th born in a family of 5 siblings. All other siblings were alive and well. Specifically, no family member had bleeding tendencies.

Physical examination revealed a young boy, looking small for age and very pale. The left knee was swolllen compared to the right, with the left lower limb held in external rotation. There was a wound on the medial aspect of the distal left thigh with the distal femoral bone protruding through the wound. Abdominal examination revealed a hepatosplenomegaly. X-rays done this time showed destroyed distal femoral metaphysis, osteosclerosis, irregular bone cortex and features of osteopenia in the left tibia and fibula.

Patient was worked up and prepared for surgery. Preoperative platelet count was $48.4x10^9$. Under vitamin K, cryoprecipitate, haematinics, antibiotics and whole blood, patient underwent two surgical procedures. First the patient was subjected to bone nibbling and debridement of all necrotic metaphyseal femoral bone. Culture grew *pseudomonas aeruginosa* and *proteus* which were sensitive to most antibiotics. Histopathological examination reported this as showing acute on chronic osteomyelitis. Later on he underwent a transarticular transfixing Kuntscher Nailing and bone grafting. Post operative haemorrhage was encountered and patient received 3 units of whole blood transfusion.

Figure 1: Destruction of distal femoral metaphysis. The distal epiphysis is spared.

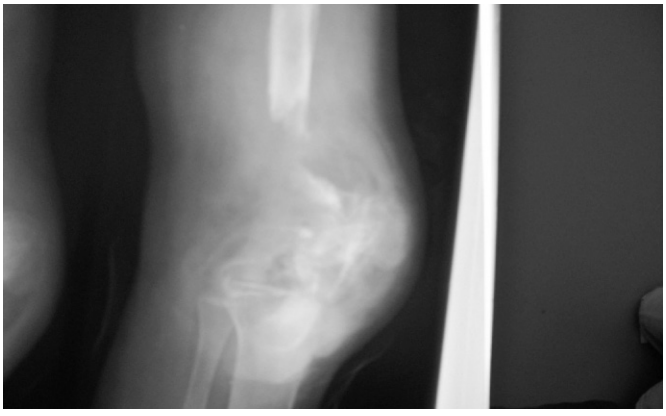


Figure 2: Further femoral destruction with marked tibial and fibula osteopenia

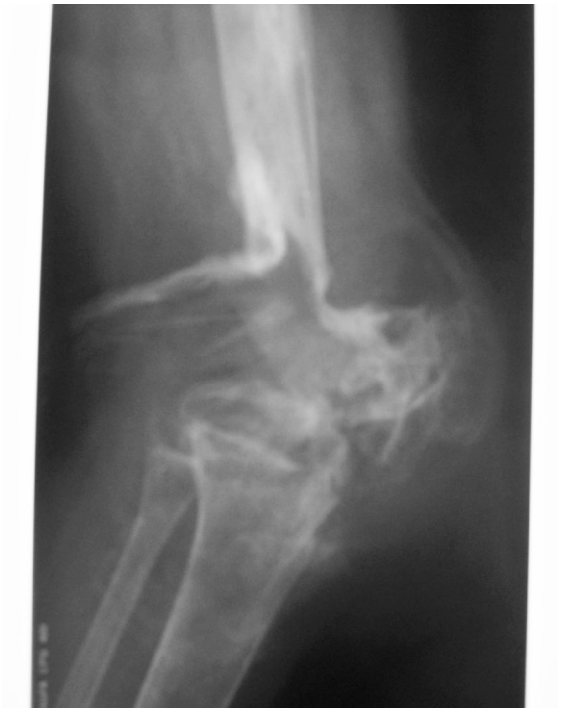


Figure 3: Splenic ultrasound scan showing splenomegaly

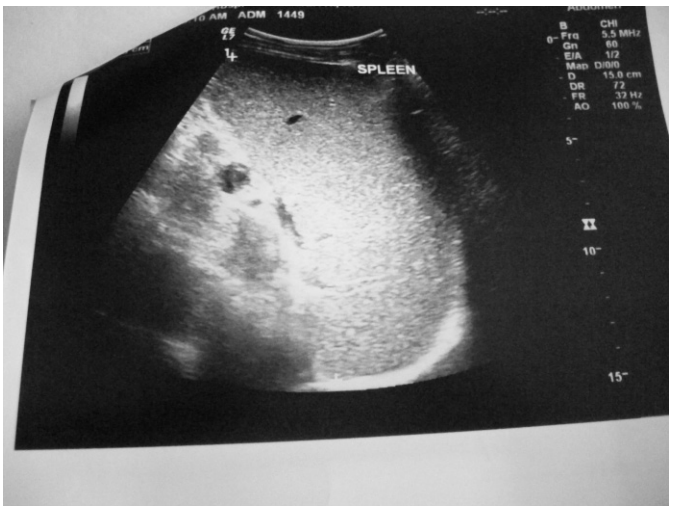


Figure 4: Liver ultrasound showing hepatomegaly and peri-portal fibrosis

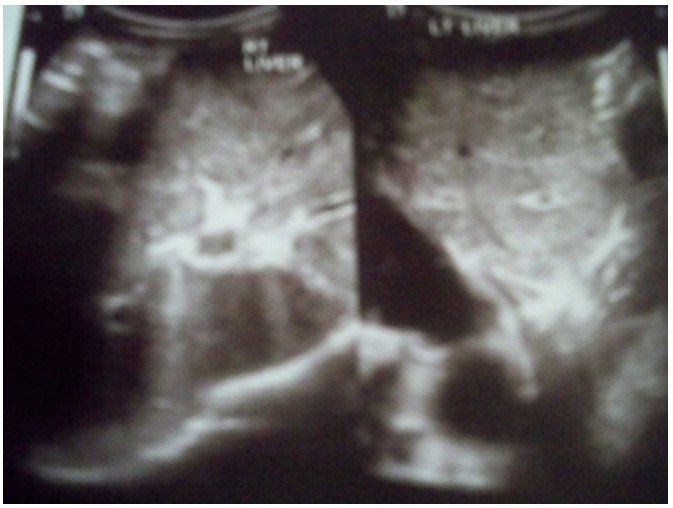
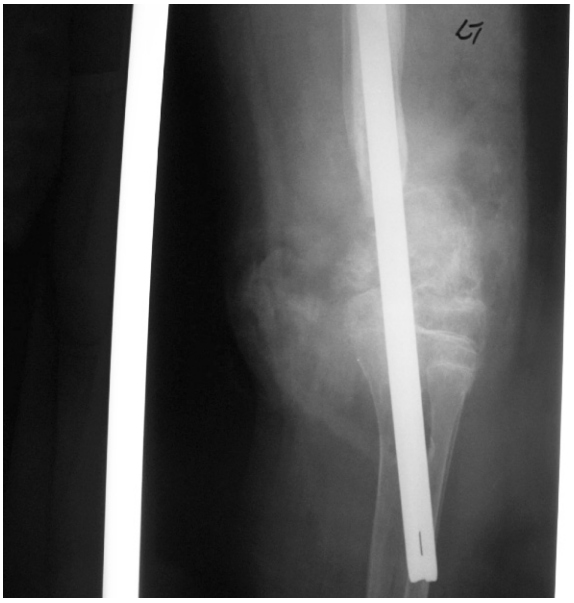


Figure 5: Fixation by a Transarticular Kuntscher Nail and bone grafting. Marked limb length discrepancy resulted



DISCUSSION

Its now 130 years since the description in 1882 by Phillipe Charles Ernest Gaucher of the condition now universally known as Gaucher's disease (3). Tremendous steps have been seen in the understanding of Gaucher's disease since then. First, the description of the abnormal biochemical defect, glucocerebroside accumulation in the cells by Epstein in 1924, including the description of the bone lesions. Next followed the description of the genetic transmission by Groen in 1948 and then the identification of the deficiency of the enzyme acid B-glucosidase by Brady in 1965 and lately the development of rhecombinant acid B-glucosidase in 1991. This is now in use as Enzyme Replacement Therapy (ERT) and recent progress is focusing on gene therapy as well as chaperone therapy. Confirmation of the diagnosis has also evolved from the traditional phase contrast microscopy demonstration of the glycolipid laden microphages in unstained smears of bone marrow obtained by bone marrow puncture or as specimens from surgical procedures such as splenectomy, liver biopsy, sequestrectomy or excisional biopsy of extraosseous soft tissues (11). Today, the diagnosis of Gaucher's disease is best established by measuring the acid B-glucosidase activity of peripheral blood leukocytes or in cultured skin fibroblasts from skin biopsy or other nucleated cells or by DNA analysis (10).

Despite these high technological advances, Gaucher's disease should be considered in the differential diagnosis of patients who present with unexplained organomegaly, easy bruisability and/or bone pain (17). All observers have noted the extreme clinical variability of Gaucher's disease, explained by the more than 200 mutations that have been identified in the glucocerebrosidase gene (4,6,9,14). Three major clinical variants of the disease are universally acknowledged but with wide phenotypic variation. Gaucher's disease is characterised by wide considerable variability in its clinical signs and symptoms, as well as its severity and course (13). This phenotypic variability is observed, even among siblings with the same genotype (3,10).

The patient presented above definitely fits into one of the clinical variants of Gaucher's disease. The attendant osteomyelitis and subsequent bone infarction of the distal femoral metaphysis following a superficial abscess fits into the category of little attention given to osteomyelitis as a complication of Gaucher's disease (12). Increased susceptibility to infection, by Gram positive cocci, *staphylococcus aureus*, was definitely demonstrated as was delayed surgical wound healing after draining of the superficial abscess.

The hepatosplenomegaly, recurrent bleeding tendencies, progressive osteomyelitis and ultimately distal metaphyseal femoral infarction as sequelae to a superficial thigh abscess add weight to a diagnosis of Gaucher's disease in a patient who also has growth retardation. This is in the clinical picture of Type 1 Gaucher's disease. Radiologically, the metaphyseal destruction with the attendant epiphyseal sparing in the femur are in keeping with the known pattern in Gaucher's disease (6). Further weight is lent by the remarkable osteopenia witnessed in the tibia and fibula. Further skeletal changes could be demonstrated but the imaging done for this patient was guided by the symptomatic areas .

The orthopaedic manifestations of this disease are no doubt important for the orthopaedic surgeon to recognize and understand (4). They are well exemplified in this case where the bone loss and protrusion through the thigh wound rendered the patient bedridden. With the currently available modalities of treatment available for Gaucher's disease, Enzyme Replacement Therapy (ERT), which has dramatically reduced the incidence of bone crises (14), it is important that an orthopaedic surgeon be able to make this diagnosis and get the patient to commence specific treatment and thus prevent the patient from developing skeletal complications. These skeletal complications, are considered to be the most disabling and irreversible and once they have set in osteonecrosis, osteosclerosis and vertebral compression cannot be reversed by ERT (10). Initiation of genetic counselling is also in the realm of the orthopaedic surgeon. Later orthopaedic intervention may be called upon to improve the quality of life of the patients by such procedures like Total Hip Replacement in the face of severe skeletal damage. For our patient the expected challenge will be to correct the large limb length discrepancy.

Instances of the diagnosis of Gaucher's disease not being made, despite later-recognized physical findings of a generalized sytemic disease or the syndrome of the "bone crises" not being appreciated in a known Gaucher's patient have been documented (12)."

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