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A CASE OF GAUCHER'S DISEASE IN AN ADULT.

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ABSTRACT
Gaucher disease, an autosomal recessive disorder, results from the defective activity of acid β-glucosidase. About 55–60% of patients are diagnosed at <20 years of age. The pattern of presentation is distinctly bimodal, with peaks at <10-15 years and ~25 years. All patients with Gaucher disease have nonuniform infiltration of bone marrow by lipid-laden macrophages termed Gaucher cells. This phenomenon can lead to marrow packing with subsequent infarction, ischemia, necrosis, and cortical bone destruction. It is an autosomal recessive disorder. This means that each parent must pass along an abnormal GBA gene for their child to get Gaucher. Parents may have only 1 GBA gene and, therefore, not show any signs of the disease, but be carriers of the disease. Gaucher disease type 1 is most commonly found among Ashkenazi Jews who have a high number of carriers of the defective GBA gene. There are 3 types of Gaucher's disease based on clinical manifestations and involvement of CNS.[1]

INTRODUCTION
Gaucher disease type 1 is a non neuronopathic disease (i.e., absence of early-onset or progressive CNS disease) presenting in childhood to adulthood as slowly to rapidly progressive visceral disease. Younger patients tend to have greater degrees of hepatosplenomegaly and accompanying blood cytopenias. In contrast, older patients have a greater tendency for chronic bone disease. Hepatosplenomegaly occurs in virtually all clinically identified patients.

In addition to bone marrow involvement, bone remodeling is defective, with loss of total bone calcium leading to osteopenia, osteonecrosis, avascular infarction, and vertebral compression fractures with spinal cord involvement. "Bone crises" are associated with localized excruciating pain and, on occasion, local erythema, fever, and leukocytosis. These crises represent acute infarctions of bone, as evidenced in nuclear scans by localized absent uptake of pyrophosphate agents. Decreased acid β-glucosidase activity (0–20% of normal) in nucleated cells establishes the diagnosis.[1]

Gaucher disease type 2 is a rare, severe, progressive CNS disease that leads to death by 2 years of age, depending on supportive care. Gaucher disease type 3 has highly variable

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manifestations in the CNS and viscera. It can present in early childhood with rapidly progressive, massive visceral disease and slowly progress to static CNS involvement that may not be evident by standard IQ evaluations; in adolescence with dementia; or in early adulthood with rapidly progressive, uncontrollable myoclonic seizures and mild visceral disease.

Regular intravenous ET (Enzyme therapy) has been the first-line treatment for significantly affected patients and is highly efficacious and safe in diminishing hepatosplenomegaly and improving hematologic values. An oral substrate reduction therapy (eliglustat tartrate), which inhibits glycolipid synthesis, is approved as a first-line therapy for adults. Bone disease is decreased and can be prevented, but irreversible damage cannot be reversed, by ET. [2]

CASE REPORT

A 35 year old female presented to Dr DY Patil Hospital and research centre with complaints of fever with chills since 3 days, abdominal distention since 1.5 year which was gradual on onset and progressive in nature associated with pain and nausea, breathlessness since 1.5 months which had increased since 4 days. No comorbidities were present. Routine investigations revealed pancytopenia, low serum albumin, increased inflammatory markers (CRP, ESR, Ferritin), low serum iron and deranged coagulation profile and deranged LFT. USG A/P was done which was suggestive of hepatomegaly, massive splenomegaly with multiple areas of dense moving internal echoes likely abscess formation and moderate ascites.

Bone marrow aspiration and biopsy was done in view of pancytopenia which was showed crumbled tissue paper appearance, positive PAS stain, high iron stores suggestive of storage disorder favouring Gaucher's disease

Ascitic tapping was done and it showed lymphocytic predominant picture and low glucose. CECT abdomen pelvis was done which was suggestive of hepatomegaly with heterogenous enhancement of the liver, massive splenomegaly with multiple well defined areas of low attenuation suggestive of liquefactive changes, few non enhancing calcified areas with intervening hypodense areas suggestive of old splenic infarcts and moderate ascitis

Beta glucosidase enzyme assay was done which showed deficiency of the enzyme (1.54 nmol/hr/min). GBA1 gene assay revealed pathogenic variant of the same. Patient was then planned for splenectomy and enzyme replacement therapy. Due to her financial constraints, recombinant enzyme treatment could not be initiated immediately. Efforts were made and pharmaceutical companies were approached.

The patient eventually had respiratory depression and drop in GCS. Later, she developed sepsis with septic shock and succumbed to death.

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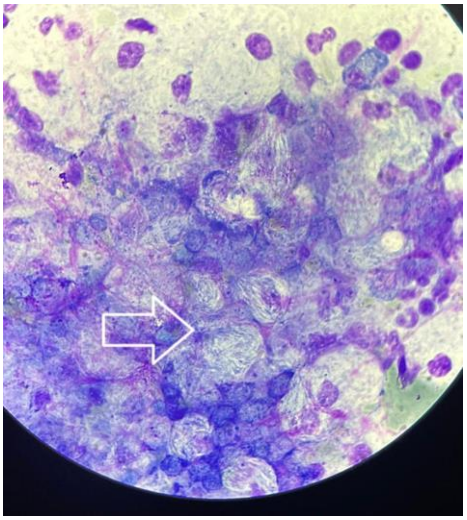
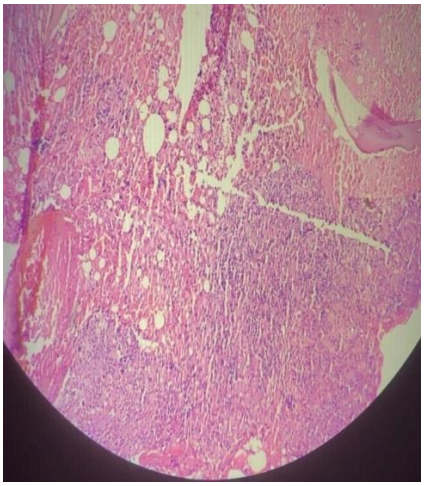


Bone Marrow Biopsy showing Crumpled tissue paper



Bone marrow biopsy showing hypercellular bone marrow with marked interstitial to diffuse infiltrates of large periodic acid-Schiff (PAS) stain positive cells

DISCUSSION

Gaucher disease is the result of a build up of certain fatty substances due to deficiency of enzyme glucocerebrosidase. This causes organs to enlarge and affect their function. The fatty substances also can build up in bone tissue, weakening the bone and increasing the risk of fractures. If the bone marrow is affected, it can interfere with blood's ability to clot. Gaucher disease symptoms vary widely from person to person. When they appear in adulthood, they usually cause unexplained bleeding and bruising, abdomen distention from an enlarged spleen and liver, bone fractures, and more. Type 1 Gaucher's disease, known as the chronic, non-neuropathic, adult-type accounts for more than 95% of the cases reported in the literature.[4]

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Diagnosis of Gauchers require multiple testings which include bone marrow biopsy, genetic testing along with other routine investigations. Decreased acid β-glucosidase activity (0–20% of normal) in nucleated cells establishes the diagnosis. The enzyme is not normally present in bodily fluids. [3]

Treatment of Gaucher's disease requires a multi-disciplinary approach involving internal medicine, pediatrics, radiology, pathology, molecular biology, etc. Modalities of treatment include enzyme replacement treatment (ERT), substrate reduction therapy (SRT), bone marrow transplantation, splenectomy, and if needed, blood transfusion. Oral drug therapy includes-

1) Miglustat (Zavesca) which appears to interfere with the production of fatty substances that build up in people with Gaucher disease.
2) Eliglustat (Cerdelga). This drug also seems to inhibit the production of fatty substances that build up in people with the most common form of Gaucher disease. Possible side effects include fatigue, headache, nausea and diarrhea

Adult patients may benefit from adjunctive treatment with bisphosphonates or other interventions to improve bone density. Adults who cannot be treated with enzyme, either because it is not effective or because they have developed an allergy or other hypersensitivities to the enzyme, may receive substrate reduction therapy with either Eliglustat tartrate or Miglustat; the latter is approved as a second-line oral therapy.[3]

CONCLUSION

Gaucher's disease, a lysosomal storage disorder with is autosomal recessive is more commonly seen in children than adults but due to its bimodal presentation, it must be considered in adults also if they present with the mentioned symptoms. Since, it is a genetically acquired condition, genetic counselling must be done and other family members should be screened so treatment can be given timely to avoid complications.

Timely intervention and initiation of enzyme replacement therapy can help prevent further consequences of the disease. The management of the disease requires multi-disciplinary approach including general medicine, paediatrics, pathology, surgery etc.

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