A 31-Year-Old Woman with Abdominal Pain

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CASE

A 31-year-old woman with no significant past medical history presented to the hospital with complaints of dull, achy, diffuse, non-radiating abdominal pain, abdominal distention, loss of appetite, and constipation which were progressively worsening over the past one year. On physical exam, her vital signs were within the normal range, she weighed 57 kilogram (kg) and had abdominal distention with marked palpable hepatosplenomegaly. Abdominal tenderness, shifting dullness and a fluid wave were absent.

Her metabolic panel revealed no abnormalities. A complete blood count revealed a white blood cell count of 4,100/μl (normal range 4,000-11,000/μl), a platelet count of 87,000/μl (normal range 150,000 - 450,000/μl), and hemoglobin and hematocrit of 11.7 g/dl (normal range 12.0 to 15.5 g/dl) and 34.8% (normal range 37-48%), respectively. Computerized Tomography (CT) of the abdomen showed marked hepatosplenomegaly and no pelvic or abdominal lymphadenopathy (Figure 1). The peripheral smear showed myeloid cells with no dysplasia, small lymphocytes with minimal cytoplasm and dense chromatin, no leukemia and no immunophenotypic evidence of lymphoma by flow cytometry. A bone marrow biopsy was performed which revealed normal cellular bone marrow with trilineage hematopoiesis and abnormal histiocytosis, suspicious for a storage disorder (Figures 2 and 3). The glucocerebrosidase enzyme activity was found to be depressed at 1.539 nanomoles/hr/mg protein [normal range 7.5-14.5]. She was subsequently treated with recombinant glucocerebrosidase, and her symptoms gradually improved. A repeat CT scan of the abdomen at 6 months showed marked decrease in the hepatosplenomegaly (Figure 1). At her one year follow up, the hepatosplenomegaly was significantly reduced on physical exam, her pancytopenia had resolved, and her appetite had improved. After 15 months of follow up, the frequency of recombinant glucocerebrosidase administration was reduced. After 18 months follow up, her appetite was normal, her weight had improved to 72 kg and the hepatosplenomegaly was no longer present on physical exam. Labs revealed improvement of the white blood cell count to 6,200/μl, platelet count count to 216,000/μl, hemoglobin to 12.7 g/dl and hematocrit to 36.5%.

Gaucher disease is one the most common lysosomal storage disorders. It is acquired in an autosomal recessive pattern and is an inborn error of metabolism that affects the processing of cellular glycolipids. At its pathophysiologic core is a deficiency of the enzyme, β-glucocerebrosidase, which leads to the intracellular accumulation of its substrate, glucocerebroside, in cells of mononuclear phagocytic origin.
INTRODUCTION

Gaucher disease is an autosomal recessive-associated lysosomal storage disorder characterized by deficiency of β-glucocerebrosidase enzyme, leading to intracellular accumulation of its substrate, glucocerebroside, in cells of mononuclear phagocytic origin. The cells involved include histiocytes in the spleen, lymph nodes, and bone marrow, Kupffer cells in the liver, osteoclasts in the bone, microglial cells in the central nervous system, alveolar macrophages in the lungs and histiocytes in the gastrointestinal tracts, genitourinary tracts, and the peritoneum. The manifestations of the disease are varied based on the type and extent of the organ involvement.¹

HISTORY

Gaucher disease was first described in 1882 by Philippe Gaucher as “primary idiopathic hypertrophy of the spleen” and he presumed it to be a splenic neoplasm.² The accumulation of glucocerebroside as a result of the enzyme deficiency was first recognized in 1924 by Epstein.³ The metabolic defect, which is the deficiency of the lysosomal β-glucocerebrosidase, was identified by Roscoe Brady in 1965.⁴

EPIDEMIOLOGY

Gaucher disease (GD) is the most common lysosomal storage disorder affecting humans.⁵ It affects all racial and ethnic groups with an overall incidence of 1-in-40,000 to 1-in-60,000 births worldwide. Ashkenazi Jews have the highest incidence (i.e., 1 in 800 births). Type 1 is the most common variant of the disease worldwide accounting for more than 90% of the cases followed by type 3 and type 2.⁶

TYPES AND CLINICAL PRESENTATION

There are three types of GD based on clinical features and symptoms. Type 1, the adult non-neuronopathic form, is the most common type affecting young adults. Patients usually present with abdominal pain secondary to hepatosplenomegaly, as well as anemia, leukocytopenia and thrombocytopenia due to infiltration of bone marrow. The skeletal system may be affected leading to pathological fractures with minor injury or classic Erlenmeyer flask deformity of the distal femur.⁷

Type 2, the acute neuronopathic infantile form, is very rare and develops in infancy. Early nervous system and brainstem abnormalities occur and death occurs before the age of five years.⁸

Type 3, the subacute neuronopathic form, is seen in children and young adults. It is characterized by slow progressive involvement of the nervous system. It is subdivided into three types. Type 3a has predominant involvement of the nervous system with progressive dementia, ataxia, and myoclonus with associated mild hepatosplenomegaly.⁹ Type 3b is characterized by massive splenomegaly with extensive visceral and skeletal involvement and nervous system involvement limited to supranuclear gaze palsy or late onset of myoclonic seizures.¹⁰ Type 3c is the cardiovascular form which is characterized by cardiovascular calcification, corneal opacities, supranuclear gaze palsy, and minimal visceral and bone disease.¹¹

DIAGNOSTIC TESTING
The initial laboratory evaluation should include measurement of hemoglobin concentration, platelet count, and a peripheral smear. Measurement of the glucocerebrosidase enzyme activity in total leukocytes or mononuclear cells or cultured fibroblasts is the definitive test for diagnosis of GD. Type 1 patients generally have 10-15% of residual enzyme activity.²¹

Bone marrow aspiration aids in the diagnosis of GD, but is not mandatory and should not be done routinely.¹⁷ The classic bone marrow finding associated with GD is the presence of large cells with abundant granular or fibrillary blue-gray cytoplasm and a wrinkled tissue paper–like appearance with abundant lightly periodic acid-Schiff–positive fibrillary material in the cytoplasm called Gaucher cells. Gaucher cells may sometimes be difficult to distinguish from pseudo-Gaucher cells that are seen in multiple myeloma and are associated with histiocytic accumulation of immunoglobulin crystals.¹³

Mutation analysis is another diagnostic test which aids in additional confirmation of the diagnosis, prediction of the clinical manifestations and carrier identification among undiagnosed family members. The glucocerebrosidase gene is located on the long arm of chromosome 1 (1q21) and more than 400 mutations have been described so far.¹⁴,¹⁵

Magnetic resonance imaging is a sensitive method for detecting bone involvement such as osteonecrosis in Gaucher disease.¹⁶

**TREATMENT**

In the pre-enzyme replacement era, management of GD was primarily palliative in nature, mainly involving blood transfusion and splenectomy. But, it was observed that the incidence of bone involvement with lytic lesions increased within a few months of splenectomy. So, partial splenectomy was advocated to balance the deleterious effects of splenomegaly and bone involvement.¹⁷,¹⁸

The use of enzyme replacement therapy (ERT) was first reported by Barton et al. in 1990.¹⁹ They noted improvement of hemoglobin, platelet count and radiological skeletal lesions after 20 weeks of therapy in one Type 1 GD patient.¹⁹ Later, Barton et al. demonstrated the benefit of ERT in another study involving 12 patients.²⁰ They reported improvement in hemoglobin, platelet count, splenic volume, and hepatic volume as well as reduction in acid phosphatase and plasma glucocerebrosidase levels.²⁰ Currently imiglucerase, velaglucerase, and taliglucerase are approved ERTs for management of type 1 disease.²¹⁻²³ However, cost concerns are an obstacle for direct enzyme replacement therapy. It is estimated that the cost of ERT for a 70kg patient who receives 60 units/kg every two weeks is >400,000 USD.²⁴ Hence, ERT should only be used in patients who have indications. For type 1 disease, international expert consensus recommends use of ERT in symptomatic children and symptomatic adult patients with platelet count <60,000/microl, liver >2.5 times normal size, spleen >15 times normal size or radiologic evidence of skeletal disease.²⁵ The European Working Group on Gaucher Disease recommends use of ERT in type 3 GD patients with onset of severe systemic disease prior to 2 years of age, certain high-risk genotypes, or sibling of patients with chronic neuronopathic GD.²⁶ Treatment with ERT is usually given long term and sometimes for the lifetime of the individual.

Substrate reduction therapy is another modality of treatment which has been approved for patients who cannot tolerate or receive ERT. Reduction in the size of liver and spleen with the use of N-butyldeoxynojirimycin in GD was first reported by Pastores et al in 2005.²⁷ The potential of gene therapy in management of GD has been demonstrated in some animal studies and human studies but has not translated as well in clinical studies.²⁸⁻²⁹ Allogeneic bone marrow transplantation as a definitive therapy has been associated with the risk of multiple complications and significant mortality.³⁰

**REFERENCES**


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