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Case Report

Gaucher Disease in a Two-Year-Old Girl with Hyperferritinemia: A Case Report

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Abstract: Gaucher Disease (GD) is the most prevalent inherited lysosomal storage disorder characterized by a glucocerebroside enzyme deficiency. This enzyme is a lysosomal hydrolase that plays a role in the breakdown of the glycosphingolipid complex. In general population, this disease is rare, with an incidence of about 0.39 to 5.80 per 100.000 birth and a prevalence of about 0.70 to 1.75 per 100.000 birth. We reported a two-year-old female patient who presented with a gradual increase of abdominal circumference and gum bleeding. There is a family history of third-degree consanguinity. Physical examination showed hepatosplenomegaly, and the laboratory results revealed the presence of hyperferritinemia and pancytopenia. Bone marrow biopsy revealed Gaucher cells. The diagnosis of GD was confirmed by a low level of glucocerebrosidase activity (0.27 uM/hr) and the presence of a homozygous mutation in exon 11 (c.1448T>C) of GBA gene, indicating an autosomal recessive GD. Conclusion: Early identification through clinical and histological findings in GD is critical. Children with unexplained hyperferritinemia and hepatosplenomegaly should be suspected of GD as one of the differential diagnosis. The early diagnosis of GD is the key to effective management, such as enzyme replacement, which may decrease its morbidity.

Keywords: Gaucher Disease, Hyperferritinemia, Hepatosplenomegaly

1. Introduction

Gaucher Disease (GD) is a rare disease caused by the deficiency of an enzyme called Glucocerebrosidase (GBA) needed to break down the glycosphingolipid complex. Gaucher Disease (GD) is the most common inherited lysosomal storage disorder, especially in children [1, 2]. The prevalence of GD ranged from 0.70 to 1.75 per 100.000 and the incidence varies from 0.39 to 5.80 per 100.000 birth in the general population [3]. GD is an autosomal recessive disorder. The recessive autosomal gene's phenotypic manifestation may emerge as a consequence of marital consanguinity over generations [4]. GD is a multiple organ chronic disorder. Due to the lack of GBA enzyme synthesis, there is a pathological accumulation of glucosylceramide in the monocytes and macrophages of the organ-like bone marrow, liver, lungs, and bone. Chromosome 1 (1q21-1q31) is the storage of defective human gene (GBA1 gene) and the pseudogene [2].

There are three types of GD, type 1 is the most common group and different from type 2 and 3 which is characterized by hepatosplenomegaly, lung and skeletal disorders, and hematological disturbance [5]. GD type 2 and 3 have neurological involvement, type 2 is an acute neuronopathic GD and type 3 is also known as chronic neuronopathic GD [6].

Bone marrow aspiration is not a routine examination to confirm diagnosis of GD, in patient isolated thrombocytopenia and/or splenomegaly without another causal might conducted this examination [7].

Hyperferritinemia is a frequent finding in practice. There is a low grade chronic inflammatory state and macrophage inflammatory protein in GD that can lead to increasing ferritin levels and increasing hepcidin in circulation [12].

We report a GD patient with the clinical manifestation of recurrent gum bleeding, pancytopenia, hepatosplenomegaly and hyperferritinemia. The aim of this case report is to

increase the awareness and knowledge of the physicians regarding GD as a rare disease, which might increase our ability to recognize the disease.

2. Case Illustration

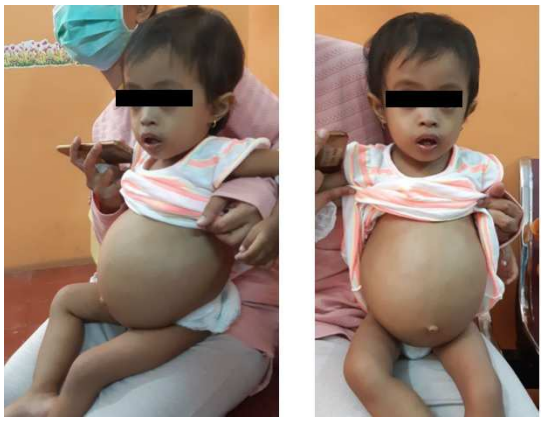

Figure 1. *Female, 2 years old with organomegaly.*

A female two-year-old female patient with a history of recurrent gum bleeding, pancytopenia, and hepatosplenomegaly since 20 months old was admitted to a tertiary care hospital (Figure 1). The patient complained of an enlarged abdomen since the age of 17 months old, and the enlarged abdomen was hard on palpation and was not accompanied by pain. The patient was previously admitted to the hospital and was diagnosed with alpha thalassemia since one year old. She underwent regular blood transfusion every 3-4 weeks for six months and received iron-chelating treatment with Ferriprox® 200 mg every 24 hours orally. Ferritin level was very high and not in accordance with the number of blood transfusions received.

The patient is the second child of two siblings from consanguineous marriage parents, and her father and mother were cousins. The patient's aunties were twins and had similar features with the patient and had already passed away. The patient had a distant relative from her great-great-grandfather who had already been diagnosed with Gaucher Disease [5] (Figure 2). She had no history of genetic, hormonal, or mental disease in her family, and her developmental history was also normal.

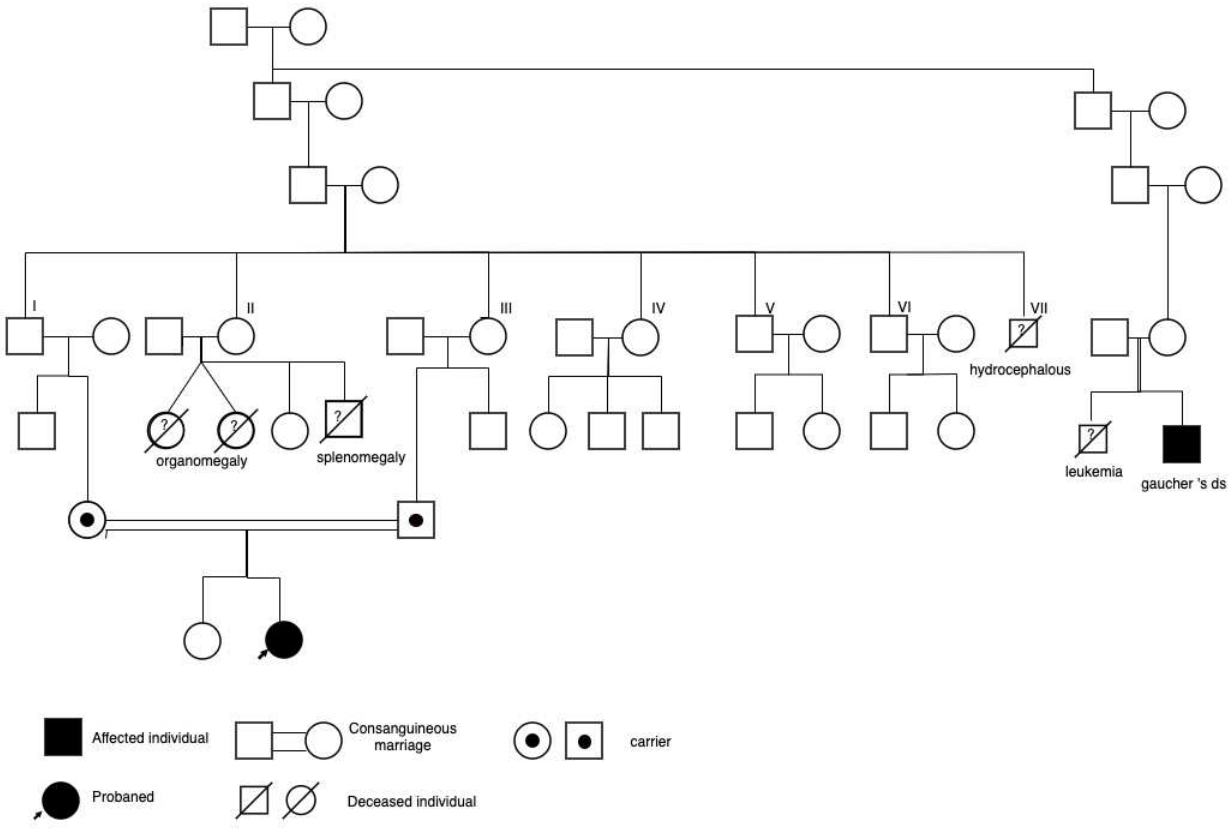

Figure 2. *Pedigree.*

The patient was previously diagnosed with alpha thalassemia since one year old. Her physical examination showed pale and hepatosplenomegaly. Her laboratory examination showed pancytopenia and high-performance liquid chromatography revealed HbA2 of 2.4% and HbF of 1%. Then, bone marrow aspiration was planned to the patient.

The developmental status of the patient was normal even though the examination concluded a severe malnutrition and stunting in this patient. The child appeared anemic based on examination. There was no spontaneous bleeding, no prolonged fever, no lymph node enlargement, and no bone pain.

Upon physical examination, the liver was palpable about 3 cm below the right costal arch and spleen around schuffner 7. Ultrasonography results also show an enlargement of the hepatosplenomegaly. Neurological examination was normal. The laboratory result showed the leukocyte level of $3.82x10^3/\mu L$ (neutrophile 27.39%, lymphocyte of 62.82%, monocyte of 6.97%, eosinophil of 0.84%, basophil 1.97%), hemoglobin level of 9.91 g/dl (MCV 84.87 and MCH 26.29) and platelet count of $31.44x10^3/\mu L$. Peripheral blood smear revealed pancytopenia. Reticulocyte percentage was 3.3%, and absolute reticulocyte count was 77.3x103/µL. The liver enzyme slightly increased for aspartate aminotransferase (65.9 U/L), and alanine aminotransferase (26.6 U/L) was normal. The examination of kidney function was normal with the ureum level of 8.5 mg/dl dan creatinine level of 0.16 mg/dl. Serum protein, albumin, and thyroid hormone were unremarkable.

Iron profile revealed serum iron of 22.92 g/dL, TIBC of 417 g/dL, and ferritin of 1294 ng/ml. Bone marrow biopsy results show Gaucher cells (Figure 3) seen as cells with a small eccentrical round nucleus surrounded by cytoplasmic inclusions that consist of tubule-like structures. The Gaucher cells are often described as crumpled tissue paper appearance. The bone survey revealed Erlenmeyer flask femur deformity on both sides. Measurement of GBA level revealed that the level of β-Glucosidase was 0.27 uM/hr (normal level >1.8 uM/hr), confirming Gaucher disease diagnosisMutation analysis was performed by Restriction Fragment Length Polymorphisms (RFLP) targeting two common pathogenic variants N370S and L444P in GBA gene.

The segment of exon 9-11 of GBA gene was first amplified by a pair of primers before the samples were digested using restricted enzyme. The analysis was continued by Agarose Gel Electrophoresis (AGE) and visualization of DNA band under UV light in gel documentation system. In this patient, we found a homozygous mutation in exon 11 (c.1448T>C) of GBA gen, and this finding is consistent with autosomal recessive GD.

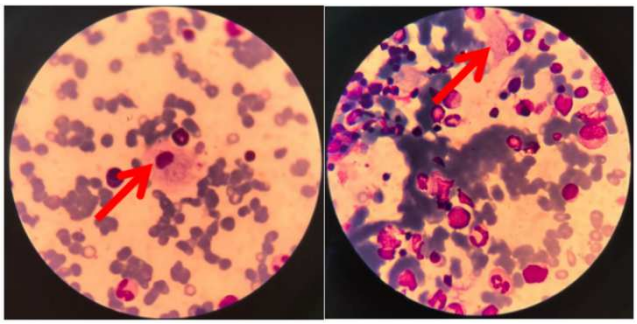

Figure 3. *Bone marrow biopsy with H&E staining: consist of histiocytes sheet, with a lot of granular and fibrillar cytoplasm that form like crumpled tissue paper - consistent with Gaucher cells.*

Heterozygous variation of GBA gene in exon 11 (c.1448T>C) were found in her mother and father but was absent in her sister.

3. Discussion

Lysosomal Storage Diseases (LSD) are one of the most common inherited metabolic disorders. Due to the defective functioning of lysosomes, there is accumulation of undegraded substrate in various organs cells. The clinical manifestation of this process depends on the certain substrate and the location of accumulation. In general, LSD is a progressive disease with variable rate of progression. In some cases, the advent of novel therapies has changed the natural history of LSD [6].

One of the most frequent type of LSD is GD, and the prevalence of GD is estimated to be about 1/40.000. This disorder occurs more often in Ashkenazi Jewish population, with the incidence increased as high as 1/1000. The recessive autosomal gene's phenotypic manifestation may emerge as a consequence of marital consanguinity over generations [4]. GD is a chronic progressive autosomal recessive genetic disease. Mutation in the GBA1 gene, located in chromosome 1 (1q21-1q31), has a major role in GBA development [2]. This mutation leads to decreased activity of the GBA (lysosomal enzyme), which hydrolyzes glucosylceramide (GlcCer) into ceramide and glucose [7].

The undegraded glucosylceramide (glycolipid substrates) accumulates in the body and can be found in reticuloendothelial system (RES) cells. It leads to several manifestations, such as splenomegaly, hepatomegaly, abdominal discomfort, spontaneous bruising or bleeding (associated with thrombocytopenia and/or coagulopathy), anemia, chronic fatigue, abnormal liver function, and varied bone disease manifestations (bone pain, defective bone mineralization, osteolysis, infarction, osteonecrosis, and pathological fractures). More than 80% of patients with Gaucher disease had a manifestation of skeletal disease, and this condition had a big impact on quality of life [8, 9]. Based on the clinical features, GD is divided into three types. GD type 1 is known as a non-neuronopathic type. GD type 1 is the most common group and different from type 2 and 3 as it does not have neurological involvement. GD type 2 and 3 have neurological involvement, type 2 is an acute neuronopathic GD and type 3 is also known as chronic neuronopathic GD. About 95% of GD cases are type 1 characterized by hepatosplenomegaly, lung and skeletal disorders, and hematological disturbance such as anemia, thrombocytopenia, and coagulation abnormalities. GD type 2 is scarce, develops rapidly, and has a severe progression. The manifestation of type 2 GD also similar to type 1 which also attacks organs and the central nervous system. The onset before 2 years and death usually occurs between 2 and 4 years old due to severe central nervous system disorder and lung failure. Patients with type 3 may have onset prior to 2 years of age, but the progression is not as severe. These patients may have three to four-decade of survival. GD may also manifest as a cardiovascular disorder and result in perinatal mortality [6].

GD type I had a highly aggressive phenotype with splenohepatomegaly, cytopenia, irritability, bone disorder, failure to thrive. Without treatment, it results in early mortality [10, 11]. In this case, a patient came with complaint of enlarged

abdomen and decrease of hematology parameter. The patient was diagnosed by pancytopenia, organomegaly and hyperferritinemia. Patient's parents had history of consanguinity marriage and history of similar symptoms in family. Therefore, bone marrow and metabolic examination was performed. X-ray revealed that our patient had Erlenmeyer flask deformity in both femurs (Figure 4). At first, the patient was suspected with metabolic disorder because of unexplained hyperferritinemia and organomegaly. One possible factor that associated with GD is the overload of iron that gradually form a redox-active iron, ferritin is essential to binding redox-active iron that can cause cellular damage by free iron and this mechanism can cause high level of ferritin [12]. Gaucher cells infiltrating the bone marrow, spleen, and liver are associated with the cause of organomegaly, cytopenia and bone lession [5].

Hyperferritinemia is a frequent finding in practice and is generally associated with increased Transferrin saturation. In GD, there is a low-grade chronic inflammatory state and macrophage inflammatory protein that can increase ferritin levels and increase hepcidin in circulation. Increased hepcidin level causes decreased availability of ferroportin exporters to export iron out of the cells, resulting in increased intracellular iron levels. In this situation, iron release from macrophages is blocked and transferrin saturation is normal [12]. In this case, there was normal transferrin saturation with hyperferritinemia, organomegaly and thrombocytopenia, suggesting the diagnosis of Gaucher Disease. Delayed diagnosis of GD still becomes our main problem. It need several since the onset of signs and symptoms have complained. Rare diseases had a common problem characterized by a progressive onset of symptoms. Bone marrow aspiration is not a routine examination to confirm a diagnosis of GD. Patients with isolated thrombocytopenia and/or splenomegaly without another causal might conduct this examination. It may help to reveal the presence of Gaucher cells. As a cause of Gaucher disease, deficiency in GBA predisposes glucosylceramide accumulation, which leads to aggregation of fibrillar. Accumulation of fibrillar aggregates in macrophages makes an appearance of "crumpled tissue paper" in cell cytoplasm [7].

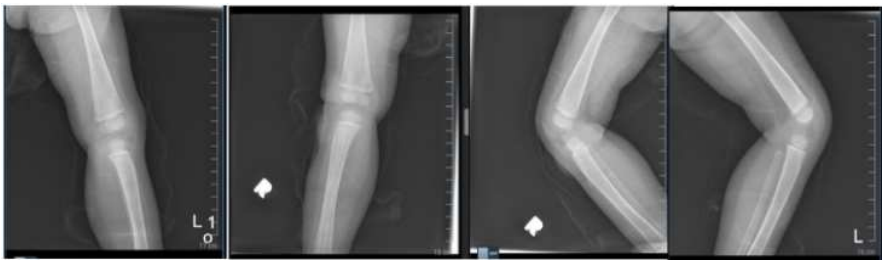

Figure 4. *Diaphyseal constriction with metaphyseal flaring on left and right bone femur.*

Gaucher disease may also can be found during examination for organomegaly. Tissue, especially bone marrow or liver, biopsy specimens may reveal Gaucher cells. This examination had often conducted during the investigations for hepatomegaly or abnormal liver function tests. Measurement of acid β-glucosidase activity in leukocytes from peripheral blood or enzymatic analysis of fibroblast cultured from skin biopsy specimens may result in a specific diagnosis. Molecular analysis of GBA gene, which encodes lysosomal GBA, has a role in confirmation and characterization of the disease [1].

In recent years, enzyme estimation on Dried Blood Spots (DBS) has been studied and initially was used for screening the newborn. DBS technique is an accessible modality to apply, and it requires a few drops of blood with easy mobility without special storage requirements. Therefore, it is highly recommended in a remote areas. These advantages make DBS adopted to help an early diagnosis of LSD [13].

This day, DNA analysis is a popular method for population screening. Ashkenazi Jewish population is higher-risk population of GD, therefor it is usually included in a panel of analysis. This screening method is quite effective. Up to 95% of mutant alleles could be identified by screening for 4–8 common GBA1 mutations. Prenatal screening could be performed to identify specific mutations in carriers, especially in families with a history of affected families [14].

In this case, the patient was found with low level of β-glucocerebrosidase (0.27 uM/hr) using DBS enzyme assay method and we found homozygous mutation in exon 11 (c.1448T>C) of GBA gen. This finding is consistent with autosomal recessive GD and heterozygous variations in exon 11 (c.1448T>C) of GBA gene were found in the patient's mother and father.

Accumulation of glucocerebroside in the reticuloendothelial system especially Gaucher cells in the spleen and Kupffer cells in the liver, may predispose organomegaly [15]. GD characterize by hepatosplenomegaly, which is presented in early childhood. Majority of GD-related mortality is contributed by liver disease. The mechanism of hepatic fibrosis in GD is not fully understood yet. It is related to a lack understanding of role Gaucher cell and the onset of hepatic fibrosis. Chroming low-grade inflammation may establish a fibrogenic microenvironment in condition of Gaucher cell deposition. Conventionally, an ultrasound examination has been used to evaluate the development of cirrhotic morphology. Meanwhile, ultrasound has low sensitivity in detecting earlier fibrotic changes. Several noninvasive examinations of hepatic fibrosis include Magnetic Resonance Elastography (MRE), ultrasound Shear Wave Elastography (SWE), and Transient Elastography (TE). Recent evidence revealed organ enlargement is contributed by pro-inflammatory chemotaxis factor and partially by Gaucher cell [16]. In this case, patient had liver enlargement and can lead to liver fibrosis. With the condition of hepatomegaly and the severity of the disease, it is necessary to evaluate by using

elastography. MRE is not yet available at our center but ultrasound elastography is available to follow up on the progression of liver fibrosis.

Enzyme Replacement Therapy (ERT) and Substrate Reduction Therapy (SRT) are GD-specific therapy. ERT improves organomegaly and hematological manifestations significantly, as well as skeletal disorders. In GD type 1, it reverses growth failure and prevents avascular necrosis development [17].

ERT should be given a long-life. ERT is administered once every 14 days as an intravenous infusion. Using glucosylceramide synthase inhibitor, which has a role in glucosylceramide synthesis as a limiting enzyme is an approach in substrate reduction therapy of GD. This principle may balance the residual activity of β-glucosidase due to GBA mutations. The advantage of SRT is its oral administration which is less invasive than other therapy. Initially, most newly diagnosed patients are treated by ERT and replaced to SRT at a later age. ERT should be administered as soon as children with GD have symptoms to avoid irreversible bone and visceral damage and development restriction [6]. Limgala, et al. found a positive correlation between delay in starting therapy and symptoms severity with r value of 0.55 (P = 0.0018). This result mean that greater the delay in therapy is associated with more severe symptoms [18]. In our case, patients had not received ERT therapy. Medical costs of the therapy still constrained the patient. Six months after the diagnosis was confirmed, the patient had been deceased.

4. Conclusion

Gaucher disease is a rare genetic disorder that may affect several organs of the body. It is characterized by varying manifestations and severity of the symptoms depending on GD type. Early diagnosis based on clinical manifestation and histological findings is important to provide safe and effective treatment for the patient. Unexplained hepatosplenomegaly and hyperferritinemia in pediatrics should be suspected of GD as one of the differential diagnosis. Treating patients with rare diseases is a persistent challenge, especially in a pediatric population. Spreading the knowledge to a broader scope helps the physicians and pediatricians recognize the disease and make earlier decisions in managing the patients.

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