

**Case Report**

# Gaucher Disease: A Rare Case in Children with Malignancy-Like Manifestation

**I Made Karma Setiyawan, I Gusti Lanang Sidiartha<sup>\*</sup>, I Gusti Ayu Putu Eka Pratiwi**

Department of Child Health, Udayana University, Denpasar, Indonesia

**Email address:**

lanangsidiartha@yahoo.com (I G. L. Sidiartha)

<sup>\*</sup>Corresponding author**To cite this article:**I Made Karma Setiyawan, I Gusti Lanang Sidiartha, I Gusti Ayu Putu Eka Pratiwi. Gaucher Disease: A Rare Case in Children with Malignancy-Like Manifestation. *International Journal of Genetics and Genomics*. Vol. 8, No. 4, 2020, pp. 133-137.

doi: 10.11648/j.ijgg.20200804.13

**Received:** October 15, 2020; **Accepted:** October 26, 2020; **Published:** November 4, 2020

---

**Abstract:** Gaucher Disease (GD) is an autosomal recessive systemic lysosomal storage disorder which is characterized by glucocerebroside deposition in cells of the macrophage-monocyte system as a result of a deficiency in lysosomal glycosidase (glucocerebrosidase). The high prevalence of symptomatic hepatosplenomegaly and thrombocytopenia in GD commonly lead patients to present to haematologists. The time period from onset of symptoms to diagnosis remains prolonged and patients are still predominately diagnosed by bone marrow biopsy. This is a case of a 4-years-old boy who presented with weakness, pallor, and gradually increasing abdominal girth. At first the patient was suspected as an abnormality in hematooncology field (acute leukemia) due to the results of the laboratories that revealed pancytopenia and the presence of organomegaly. After bone marrow aspiration examination conducted the result was not in accordance in the field of hematooncology. Final diagnosis of GD was established after reevaluating the bone marrow smears that find foam cells/Gaucher cells. Confirmation of diagnosis on Gaucher disease was performed by measurement of glucocerebrosidase activity, where is low in  $\beta$ -Glucosidase 0.07 uM/hr (reference range unit  $>1.8$  uM/hr). GD should be considered in the differential diagnosis of children with unexplained hepatosplenomegaly. Patients with acute leukemia suspicion should be examined for the possibility of having GD from bone marrow smears simultaneously. Moreover, the early recognition of GD would lead to safe and effective treatment with enzyme replacement which can decrease morbidity.

**Keywords:** Gaucher Disease, Hepatosplenomegaly, Pancytopenia

---

## 1. Introduction

Inborn errors of metabolism (IEMs) are rare genetic disorders that caused by defects of a single enzyme in a metabolic pathway. Gaucher disease (GD), one of the most prevalent lysosomal storage disorder, results from defective  $\beta$ -glucocerebrosidase production and subsequent accumulation of glucocerebroside (GCase) in macrophages [1]. Gaucher disease is autosomal recessive therefore marital consanguinity favors the emergence of phenotypic manifestations of recessive genes over several generations. The Gaucher cells are found in the splenic sinusoids, replace the Kupffer cells of the liver and alveolar macrophages of the lung, and infiltrate the bone marrow. Of all cell types, the

macrophages carry the greatest storage burden [2]. As a result of tissue macrophage distribution, splenomegaly is almost universal, with associated hypersplenism and thrombocytopenia. Anemia is less common, but when severe, it was associated with bone marrow failure caused by the infiltration and replacement of hematopoietic marrow. Gaucher disease has an insidious onset and patients may have extensive organ involvement with relatively minor overt symptomatology. Three clinical forms have been delineated, based on absence (type 1) or presence (types 2 and 3) of neurological signs and categorization of this course is useful when talking about management options and genetic counseling. The diagnosis may be established by the detection of Gaucher cells in tissues, by GCase activity in

leukocytes or cultured skin fibroblasts, or by molecular analysis [3]. Enzyme replacement therapy has been the gold standard for treatment of Gaucher disease with imiglucerase generally used as a first-line therapy.

Both GD type 1 and GD type 3 can present in childhood, though GD1 is more common. In childhood and adolescence, presenting symptoms of GD1 are primarily hematological, leading to frequent misdiagnosis of GD1 as a hematological/oncological disorder. The almost universal presence of concomitant thrombocytopenia or splenomegaly means that the majority of these patients eventually were reviewed by hematologists. Thrombocytopenia and splenomegaly, whether symptomatic or incidental findings, are reasons for referrals to hematologists and both have wide differential diagnoses including hematological malignancies, immune disorders and liver disease. An American study of over 2000 patients with splenomegaly found a hematological cause, most commonly leukemia or lymphoma, in 57%, infectious cause in 19% and liver disease in 11% [4]. Once GD was considered as the differential diagnosis, the next step is how to diagnose or exclude this disorder properly. A survey of hematologists was also reported that 62% would perform a bone marrow biopsy for the diagnosis of suspected GD [5].

## 2. Case Illustration

A four years old male was admitted to a tertiary care hospital with predominant clinical presentation of pancytopenia and hepatosplenomegaly (Figure 1). The patient complained of an enlarged stomach by age 9 months. The stomach size was said to increase without pain and hard when palpated. Patient was previously admitted to hospital at 9 months age with similar complaint of abdomen enlargement. Bone marrow aspiration examination had been carried out at that time for diagnostic and revealed normal result without malignancy suspected. Then patient didn't continue regular check up until 4 years of age due to no other complaint.

The patient is the fourth child of four siblings. He was born of consanguineous marriage. The patient's second sibling was said to had similar features and diagnosed with leukemia and passed away at the age of 5 years after following chemotherapy treatment for about 2 months. There were no history of any hormonal, genetic disease nor mental retardation in the patient's family. The patient's developmental history was said to be normal.

At the beginning of current hospitalization, patient was still suspected with acute leukemia malignancy (ALL differential diagnosis with AML) due to all the clinical symptom that showed pale and hepatosplenomegaly while pancytopenia was found from laboratory examination. Patient was planned to do bone marrow aspiration evaluation. Eventhough the patient had severe malnutrition and stunted as nutritional status, his developmental milestone was normal. On examination, the child was pale, no bleeding manifestation on the skin, no spontaneous bleeding, no prolonged fever and no bone pain. Liver enlargement was 7 cm palpable below the right

costochondral margin and 3 cm below processes xyploideus, the spleen enlargement was schuffner 8. Central neurological features and peripheral neuropathy examination was normal. From the laboratory result show leukocyte was  $4.06 \times 10^3/\mu\text{L}$  (neutrophil 51.19%, lymphocyte 41.21%, monocyte 3.72%, eosinophil 3.24%, basophil 0.64%), haemoglobin was 7.22 g/dl (MCV 75.92 and MCH 25.58) and platelet count was  $28.87 \times 10^3/\mu\text{L}$ . Peripheral blood smear revealed pancytopenia. Reticulocyte percentage 3.4% and reticulocyte absolute was  $122.8 \times 10^3/\mu\text{L}$ . Liver enzyme were slightly increase for aspartate aminotransferase (63.8 U/L) and alanine aminotransferase (12.2 U/L) was normal. Serum protein, albumin, kidney function and thyroid hormone were unremarkable. Iron profile revealed serum iron 54.17 g/dL, TIBC 344 g/dL, ferritin was not evaluated due to lack of reagent. Lipid profile showed low cholesterol level (total cholesterol 69 mg/dL, HDL cholesterol 9 mg/dL, and LDL cholesterol 30 mg/dL) and increase triglyceride level (186 mg/dL). Blood gas analysis showed pH 7.42,  $\text{pCO}_2$  31.2 mmHg,  $\text{HCO}_3^-$  19.9 mmol/L and base excess -4.5 mmol/L. Electrolyte serum results were sodium 134 mmol/L, potassium 3.97 mmol/L, chloride 94.2 mmol/L, and calcium 8.5 mmol/L. Ultrasound study of abdomen showed massive splenomegaly and hepatomegaly with coarse echotexture of liver. CT scan evaluation showed hepatomegaly and splenomegaly with multiple hypodense lesion on upper and lower spleen's pole. Initial bone marrow examination result not showed any abnormality in field of hematooncology therefore bone marrow result reevaluation was conducted to find unusual cells. Bone marrow biopsy showed sheets of Gaucher cells (Figure 2) seen as cell with small eccentric round nucleus surrounded by cytoplasmic inclusions which consists of tubule-like structures. The gaucher cells often describe as crumpled tissue paper appearance. Final diagnosis of GD was established after examining the bone marrow smears and find gaucher cells/foam cells. Confirmation of diagnosis on Gaucher disease was performed by measurement of glucocerebrosidase activity, where is low in  $\beta$ -Glucosidase 0.07 uM/hr (reference range  $>1.8$  uM/hr) are consistent with a diagnosis of Gaucher disease.

## 3. Discussion

Suspicion of IEM in clinical experience arise when we have difficult or peculiar cases that cannot be explained by known disease physiopathologies. Several clues suggesting an IEM include positive family history, consanguinity, loss of developmental milestones, siblings with unexplained infant/neonatal death, metabolic acidosis, neutropenia and/or thrombocytopenia, hepato and/ or splenomegaly, and unusual odor (urine or sweat) [6].

Gaucher disease (GD) is the most common lysosomal storage disease (LSD) with an estimated global incidence of 1:40.000-60.000 live births [7]. GD is a rare, autosomal, recessive genetic disease caused by mutations in the GBA1 gene, located on chromosome 1 (1q21) [8]. This leads to a markedly decreased activity of the lysosomal enzyme,

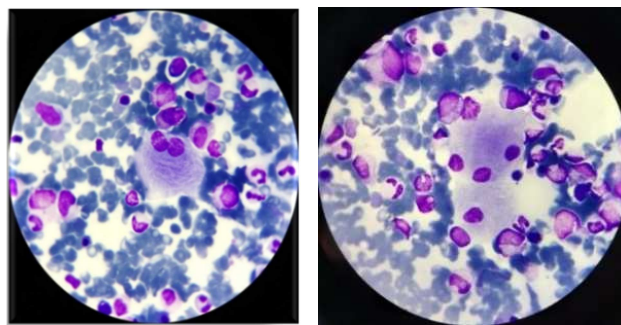
glucocerebrosidase (GCase, also called glucosylceramidase or acid  $\beta$ -glucosidase), which hydrolyzes glucosylceramide (GlcCer) into ceramide and glucose [1]. Gaucher disease is a genetic disorder, all close relatives of people with GD are at risk of having the disease or a potential carriers of the Gaucher gene. In each pregnancy, the chance of fetus to have two (affected) or no (unaffected) mutated genes is 25%. Moreover, there is a 50% chance with each pregnancy that the offspring have a mutation from one of parents (heterozygote carrier). Heterozygote carriers typically do not reveal clinical features of the condition [9]. Glucocerebrosidase accumulation, classically in tissue macrophages or other cells include immune cells, osteoblasts and hepatocytes contributes to fatigue, bleeding and easy bruising (due to pancytopenia from bone marrow and splenic sequestration), distended abdomen (due to hepatosplenomegaly), diffuse infiltrative pulmonary disease, and severe bone pain and pathologic fractures (due to bone marrow infiltration and macrophage produced cytokines). Nearly one-quarter of type 1 patients with Gaucher disease do not receive timely access to therapy, possibly due to the delays in obtaining a diagnosis after the onset of symptoms [10]. At the time the diagnostic process was started by pediatricians, family medicine or other specialists, the main manifestations included alterations in blood counts and spleen enlargement; this generally required a hematological consultation, that led to the diagnosis in approximately 75% of GD patients [5, 11]. Most patients will present or develop signs/symptoms that are commonly managed by hematologists for example anemia, thrombocytopenia, and splenomegaly thus bone marrow aspiration are indicated [12]. In this case, patient 4 years old came with complaint enlargement of abdomen followed by decrease of hematology parameter and at that moment was diagnosed by pancytopenia and organomegaly due to suspected acute leukemia (ALL differential diagnosed with AML). Patient had history of consanguinity marriage and sibling that have same symptoms and diagnosed with leukemia therefore bone marrow and metabolic examination was performed.

Despite advocating elimination of bone marrow aspiration for the sole purpose of GD diagnosis, there are valid indications for this examination in GD, all related to associated diseases [12]. Historically, patients with GD were diagnosed by bone marrow examination since the combination of anemia, thrombocytopenia, and/or splenomegaly suggested a hematological malignancy [13]. Gaucher disease is caused by a deficiency in glucocerebrosidase (GCase) (or  $\beta$ -glucosidase), which leads to an accumulation of glucosylceramide (GlcCer). Glucosylceramide forms fibrillar aggregates that accumulate in macrophages and result in the cell cytoplasm presenting a characteristic “crumpled tissue paper” appearance [1]. This phenomenon is believed to be due to the degradation of exogenous lipids derived from the renewal of blood cells. These glucosylceramide-laden macrophages are the typical Gaucher cells which can be seen in bone marrow aspiration with a May–Grünwald–Giemsa or Hematoxylin–Eosin staining [14]. These cells infiltrate various organs (spleen and

liver) and are responsible for the major signs of the disease. The monocyte/macrophage lineage is preferentially altered because of their role in eliminating erythroid and leukocytes, which contain large amounts of glycosphingolipids, a source of GlcCer. Gaucher cells finding during work-up of patients mandates enzyme activity measurement. In this case, bone marrow aspiration reevaluation find gaucher cell/foam cell.



**Figure 1.** Male, 4 years old with hepatosplenomegaly.



**Figure 2.** Bone marrow biopsy, high power view: sheets of histiocytes, with the abundant, granular and fibrillar cytoplasm resembling a crumpled tissue paper. Most of them had single nucleus with eccentrically placed nuclei-consistent with Gaucher cells.

Enzyme assays have been the gold standard for providing definitive diagnosis of lysosomal storage disorders (LSDs) by demonstrating deficient enzyme activity in leukocytes/plasma/cultured fibroblast. Dried blood spots technique has now been adopted for early diagnosis of LSDs due to the requirement of a few drops of blood, easy transportation especially from remote areas and simultaneous measurement of multiple analytes without special storage requirements [15]. Detection of low enzymatic activity of  $\beta$ -glucocerebrosidase in peripheral blood cells compared with normal controls is still the “gold standard” for diagnosis of GD. Residual levels of glucocerebrosidase in patients with GD have been variously estimated at 5-25% of normal activity [16]. Diagnostic test show decrease of acid  $\beta$ -glucosidase activity in peripheral blood leukocytes (normal range 2.1–2.5  $\mu\text{mol/l/hour}$ ) [3].

Originally, visceromegaly was attributed to simple accumulation glucocerebroside in the reticuloendothelial system with buildup of this material within Gaucher cells in the spleen as well as Kupffer cells in the liver. Hepatosplenomegaly is a hallmark of Gaucher disease and uniformly present beginning in childhood, and liver disease is a major contributor to Gaucher disease-related mortality. Currently, there is limited understanding of the mechanism

leading to development of hepatic fibrosis and Gaucher disease. This is largely due to the poorly understood link between the Gaucher cells and the onset of hepatic fibrosis. Gaucher cell deposition may establish a fibrogenic microenvironment due to chronic low-grade inflammation. An ultrasound examination has been traditionally used to monitor development of cirrhotic morphology but is relatively insensitive in detecting earlier fibrotic changes. Some means of noninvasively assessing hepatic fibrosis include non-imaging-based transient elastography (TE), ultrasound shear wave elastography (SWE), and magnetic resonance elastography (MRE) [17]. The disease specific management of GD includes enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). Therapy with ERT improve organomegaly and hematological manifestations significantly, and also skeletal manifestations, prevent avascular necrosis and reverse growth failure in GD type 1 [12]. However, less than 50% of patients with GD on therapy are expected to meet all these therapeutic goals [18]. Enzyme replacement therapy is a lifelong therapy and administered as an intravenous infusion once every 14 days. Substrate reduction therapy for GD is based on the principle of using inhibitor of glucosylceramide synthase, the rate limiting enzyme in synthesis of glucosylceramide to balance residual activity of acid  $\beta$ -glucosidase due to GBA mutations. One advantage of SRT is that it is administered orally rather than intravenously. Clinical practice varies widely, but most newly diagnosed patients are started on ERT initially. Some transition to SRT at a later age. Children with Gaucher disease should be started on ERT as soon as they are symptomatic to avoid irreversible bony and visceral damage as well as other long-term growth and development issues [19]. In this case, patients had not received ERT therapy due to still constrained in financing their plan to get therapy, where the ERT can only been administered in Jakarta. Patients had been deceased 8 months after diagnosis was confirmed.

## 4. Conclusions

Gaucher disease is a genetic disorder that affects different organs and tissues of the body. It is characterized by a spectrum of phenotypes that can present with varying degrees of severity. The presentation depends on the type of the disease. That is importance for early recognition by clinical manifestation and histological findings. GD should be considered in the differential diagnosis of children with unexplained hepatosplenomegaly. Patient with acute leukemia suspicion, parallel is examined for possible GD from bone marrow smears. Working with rare disease is a continual challenge, and more in a pediatric setting, the initial problem is, in our setting, to spread widely the knowledge to physicians to recognize the disease and to carry out an extensive baseline assessment to identified the patients in need of therapy and thus avoid complications. Moreover, the early recognition of GD would lead to safe and effective treatment with enzyme replacement which can decrease morbidity.

## Acknowledgements

None declared.

## References

- [1] Stirnemann J, Belmatoug N, Camou F, Serratrice C, Froissart R, Caillaud C, *et al.* A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci.* 2017; 18: 1-30.
- [2] Hughes D, Mikosch P, Belmatoug N, Carubbi F, Cox TM, Goker-Alpan O, *et al.* Gaucher disease in bone: from pathophysiology to practice. *Journal of Bone and Mineral Research.* 2019; 34: 996-1013.
- [3] Dandana A, Khelifa SB, Chahed H, Miled A, Ferchichi S. Gaucher disease: clinical, biological and therapeutic aspects. *Pathobiology.* 2016; 83: 13-23.
- [4] O'Reilly RA. Splenomegaly in 2,505 patients in a large university medical center from 1913 to 1995. 1913 to 1962: 2,056 patients. *West J Med.* 1998; 169: 78-87.
- [5] Mistry PK, Sadan S, Yang R, Yee J, Yang M. Consequences of diagnostic delays in type 1 Gaucher disease: The need for greater awareness among hematologists-oncologists and an opportunity for early diagnosis and intervention. *Am J Hematol.* 2007; 82: 697-701.
- [6] Martins AM. Inborn errors of metabolism: a clinical overview. *Sao Paulo Med J.* 1999; 117: 251-65.
- [7] Puri RD, Kapoor S, Kishnani PS, Dalal A, Gupta N, Muranjan M. Diagnosis and management of Gaucher disease Task Force of the Society for Indian Academy of Medical Genetics and the Indian Academy of Pediatrics. *Indian Pediatrics.* 2018; 55: 143-53.
- [8] Cox TM, Schofield JP. Gaucher's disease: clinical features and natural history. *Baillieres Clin Haematol.* 1997; 10: 657-89.
- [9] Tabrizi A, Jafari N, Mozafari H. Gaucher disease: new expanded classification emphasizing neurological features. *Iran J Child Neurol.* 2019; 13: 7-24.
- [10] Cappellini MD. A rare condition in haematological practice-Gaucher Disease. *European Oncology & Haematology.* 2015; 11: 15-20.
- [11] Thomas AS, Mehta A, Hughes DA. Gaucher disease: haematological presentations and complications. *Br J Haematol.* 2014; 165: 427-40.
- [12] Zimran A. How I treat Gaucher disease. *Blood.* 2011; 118: 1463-71.
- [13] Baris HN, Cohen IJ, Mistry PK. Gaucher disease: the metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr. Endocrinol* 2014; 12: 72-81.
- [14] Lobato JB, Hidalgo MJ, Jimenez LMJ. Biomarkers in lysosomal storage disease. *Diseases.* 2016; 4: 1-17.
- [15] Verma J, Thomas DC, Kasper DC, Sharma S, Puri RD, Bijarnia-Mahay S, *et al.* Inherited metabolic disorders: efficacy of enzyme assays on dried blood spots for the diagnosis of lysosomal storage disorders. *JIMD Reports.* 2015.
- [16] Linari S, Castaman G. Clinical manifestations and management of Gaucher Disease. *Clinical Cases in Mineral and Bone Metabolism.* 2015; 12: 157-64.

- [17] Degnan AJ, Ho-Fung VM, Ahrens-Nicklas RC, Barrera CA, Serai SD, Wang DJ, *et al.* Imaging of non-neuronopathic Gaucher disease: recent advances in quantitative imaging and comprehensive assessment of disease involvement. *Insights into Imaging*. 2019; 10: 1-19.
- [18] Grabowski GA, Leslie N, Wenstrup R. Enzyme replacement therapy for Gaucher disease: The first 5 years. *Blood Rev*. 1998; 12: 115–33.
- [19] Sun A. Lysosomal storage disease overview. *Annals of Translationa Medicine*. 2018; 6: 1-14.