

Case Report

A rare case of inherited disorder with atypical imaging findings – A case report

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ABSTRACT

Gaucher's disease (GD) is one of the most commonly known which is a progressive, rare hereditary disease, with an autosomal recessive inheritance pattern. It produces a deficiency in the activity of the enzyme beta-glucosidase provoking an accumulation of glucosylceramide in the lysosomes of different cells causing cytopenias, hepatosplenomegaly, changes in the central nervous system, and skeletal manifestations. The viscera most commonly involved with accumulation of Gaucher cells is the liver and spleen. Current recommendation for evaluating and monitoring visceral involvement is volumetric magnetic resonance imaging (preferred due to lack of ionizing radiation) or computed tomography every 12–24 months. Here, we report a case of GD presented with abdominal distension since past 3 months, decreased appetite since past 1 month, and breathlessness since past 1 month.

Keywords: Gaucher's disease, Hepatosplenomegaly, Beta-glucosidase, Enzyme replacement therapy

INTRODUCTION

Lysosomal storage disorders (LSDs) are a collection of several genetic disorders occurred due to the mutation in genes that encode for enzymes involved in the degradation of complex macromolecules.^[1] Deficiency of these enzymes results in cellular dysfunction and various clinical manifestations. Of the several known LSDs, Gaucher's disease (GD) is one of the most commonly known worldwide. It is a progressive, rare hereditary disease, with an autosomal recessive inheritance pattern described in 1882 by Philippe Charles Ernest Gaucher.^[2] It produces a deficiency in the activity of the enzyme acid beta-glucosidase (GBA) located on chromosome 1, provoking an accumulation of glucocerebroside in the lysosomes of different cells,^[3] causing cytopenias, hepatosplenomegaly, changes in the central nervous system (CNS), and skeletal manifestations, the latter being one of the most disabling aspects.

Depending on the clinical expression, different types can be distinguished: Type 1 (adult non-neuronopathic), the most common form with variable manifestations such as spleen and liver enlargement, bone problems, and fatigue, but not involving the CNS; Type 2 (acute neuronopathic), infrequent, fatal after birth and involvement of the CNS; and Type 3 (subacute or chronic neuronopathic),^[3] beginning during childhood, adolescence, or adulthood, with involvement of the CNS.

Type 1 GD has a prevalence of 90–95%, with an invariable clinical presentation that ranges from being asymptomatic throughout the life to early-onset of symptoms in the childhood. Although

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type 1 GD is not life-threatening, it decreases the quality of life and increases morbidity. Fatigue is very common in children; other symptoms include retarded growth, delayed puberty, splenomegaly, hepatomegaly, and mucocutaneous bleeding.^[4-7] Type I GD is more prevalent in Ashkenazi Jewish population. Of all mutations of the GBA, 84 GG insertion particularly occurs in Ashkenazi Jewish and N370S mutation is frequent in these population.^[8]

Type 2 GD occurs in less than 2% of cases. The disease manifests itself at a very early stage in the infancy and is associated with severe neurological impairment.^[9] Splenomegaly has always been reported, along with thrombocytopenia, growth retardation, lung lesions, and pulmonary infiltration by Gaucher cells. Death is usually reported before the 3rd year of life.^[10,11]

Type 3 GD occurs in 5% of cases, with heterogenous phenotypes, ranging from moderate systemic involvement to more severe neurological symptoms such as progressive myoclonus epilepsy, cerebellar ataxia or spasticity, and dementia.^[9,12,13] This type has been reported to be more common in young children, with behavioral changes and death reported in few patients.^[12,14]

Diagnosis of GD is made on the basis of clinical history, physical examination, laboratory test, and imaging results and confirmed by a blood test showing deficient glucocerebrosidase enzyme and genetic mutation studies when the diagnosis is doubtful. History of consanguinity and family history of suspected or proven GD will support the diagnosis.^[3] Here, we report a case of GD presented with massive splenomegaly as the prodromal symptom. The present case is of relevant interest to the scientific community due to its low incidence, which makes it a rarely-suspected diagnostic possibility, leading, not infrequently, to a diagnostic delay, which makes it important for medical personnel in charge of its diagnosis and monitoring.

CASE REPORT

A 35-year-old female patient came to the department of internal medicine with the complaint of abdominal distension since past 3 months, decreased appetite since past 1 month, and breathlessness since past 1 month. There was no history of hematuria, lithuria, pyuria, frequency, urgency, hesitancy, burning micturition, bowel disturbances, weight loss, loss of appetite, and trauma. No history of IHD or relevant surgeries and addictions was there.

In the department of radiodiagnosis, ultrasound was done, which revealed hepatosplenomegaly and computed tomography (CT) scan was done. CT scan was done in Ingenuity elite 128 slice Philips CT scan machine. Plain and post-contrast contiguous axial CT sections were taken for abdomen and pelvis with oral and intravenous contrast.

Routine blood investigations were performed and random blood glucose was 95 mg/dL.

In CT scan, hepatomegaly noted with maximum craniocaudal dimension of 21 cm. There was heterogeneous enhancement of the liver with multiple non-enhancing areas measuring around 8–10 mm in venous and arterial phases with isodense on delayed images in both lobes of liver; some of them were subcapsular in location.

Massive splenomegaly noted with maximum craniocaudal dimension of 32 cm [Figure 1a]. Multiple well-defined areas of low attenuation were noted in the spleen, showing no contrast enhancement. The main splenic vein appeared dilated with normal contrast opacification and splenic artery spears normal at splenic hilum. Few of the areas showed well-defined enhancing wall formation with large central non-enhancing necrotic area [Figure 1b]. It was causing displacement of bowel loops to the right [Figure 1c], stomach anteriorly, and left kidney more posteriorly and inferiorly. Surrounding splenic parenchyma showed few non-enhancing calcified areas with intervening hypodense areas-likely suggestive of old splenic infarcts or Gaucheromas [Figure 1b and c]. Moderate ascites was noted.

The patient underwent spleen biopsy. The histopathology report showed enlarged macrophages in the spleen [Figure 1d]. Magnetic resonance imaging (MRI) could not be performed as patient had metallic implant for the tibia fracture. Chest radiograph was performed and is normal [Figure 2].

DISCUSSION

Gaucher's disease results from deficiency of a lysosomal enzyme glucocerebrosidase (also known as acid GBA). The enzyme acts on the substrate glucocerebroside which is a component of the cell membrane. In the normal lysosome, protein saposin C presents glucocerebroside to GBA which activates the enzyme. This enzyme is responsible for hydrolytic breakdown of glucosylceramide to glucose and ceramide. Deficiency of the enzyme leads to accumulation of glucosylceramide and other glycolipids in the lysosomes of macrophages, primarily in the spleen, liver, bone marrow, brain, osteoclasts and less often the lungs, skin, kidneys, conjunctivae, and heart.^[15]

The most common signs and symptoms noted in GD are splenomegaly (95%), hepatomegaly (87%), radiological bone disease (81%), thrombocytopenia (50%), anemia (40%), growth retardation (34%), bone pain (27%), and bone crisis (9%). A skeletal manifestation is found more often in older children.^[4] Skeletal manifestations include bone infarcts, osteopenia, avascular necrosis particularly of the femoral head, Erlenmeyer flask deformity, and vertebra plana.^[16] The viscera most commonly involved with accumulation of Gaucher cells are the liver and spleen. The pulmonary system

can be involved as well, although it is very rare. The current recommendation for evaluating and monitoring visceral involvement is volumetric MRI (preferred due to lack of ionizing radiation) or CT every 12–24 months.^[17]

Gaucher cells accumulate in the Kupfer cells of the liver, leading to hepatomegaly. Liver volumes in type 1 patients are typically approximately 2 times normal.^[18] It is notable that glycolipid does not accumulate in the hepatocytes.^[18,19] The Gaucher cells can conglomerate into nodules that can be seen with sonography or MRI. These nodules may be hypoechoic, hyperechoic, or mixed on sonography.^[20,21] On MRI, the nodules typically appear isointense or low signal intensity (SI) on T1-weighted imaging (WI) and high SI on T2 WI. Focal areas of extramedullary hematopoiesis can have a similar appearance and can also be seen due the accompanying anemia. Hepatic infiltration can also lead to fibrosis and cirrhosis.^[22]

Splenomegaly results from accumulation of Gaucher cells within the spleen. Spleen volumes in type 1 GD are typically 5–15 times normal, but the spleen size can be significantly enlarged in some cases and may be over 50 times normal.^[23] Focal splenic masses are common and may represent clusters of Gaucher cells or extramedullary hematopoiesis. They may be detected with sonography, CT, or MRI. Similar to the liver, Gaucher masses in the spleen may be hypoechoic, hyperechoic, or mixed echogenicity.^[21,24] On CT, the masses are low density.^[25] and occasionally peripherally calcified. These masses are most commonly imaged with MRI. They typically are low SI or isointense on T1WI and high SI on T2WI.^[26] Low SI on gradient recalled echo imaging in these masses is thought to be secondary to iron contained in the Gaucher cells.^[27] Splenic infarcts can occur as well due to massive splenomegaly and can be detected with imaging as well.

The differential diagnosis of GD is mainly of disease associated with splenomegaly and cytopenia. These would include hematological malignancies and storage disorders like Niemann-Pick. Most of these disorders have characteristic clinical, radiographic, or laboratory features that distinguish them from GD.^[28] The manifestations are highlighted in Table 1.^[29]

Table 1: Radiological manifestations of Gaucher's disease

Skeletal manifestations	Bone infarcts, osteopenia, avascular necrosis particularly of the femoral head, Erlenmeyer flask deformity and vertebra plana ^[16]
Visceral manifestations	Hepatomegaly, splenomegaly, splenic infarcts
Pulmonary manifestations	Bilateral reticulonodular interstitial pattern ^[29]

Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are the backbone of the management.

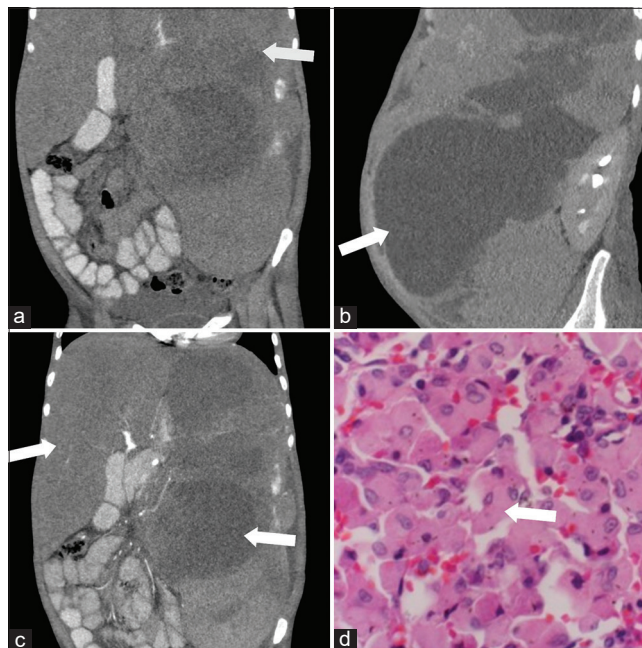


Figure 1: (a) Coronal computed tomography (CT) section showing massive splenomegaly (white arrow) with maximum craniocaudal dimension of 32 cm, (b) sagittal CT section shows a large central non-enhancing necrotic (white arrow) area likely representing Gaucheroma, and (c) coronal CT section showing massive hepatomegaly (right arrow) and splenomegaly (left arrow) with areas of low attenuation in the spleen showing no contrast enhancement. The massive spleen is displacing the bowel loops toward the left (d) histopathology of the spleen at higher magnification shows enlarged macrophages in the spleen with wrinkled tissue paper cytoplasmic appearance (white arrow) – typical of Gaucher's cells.

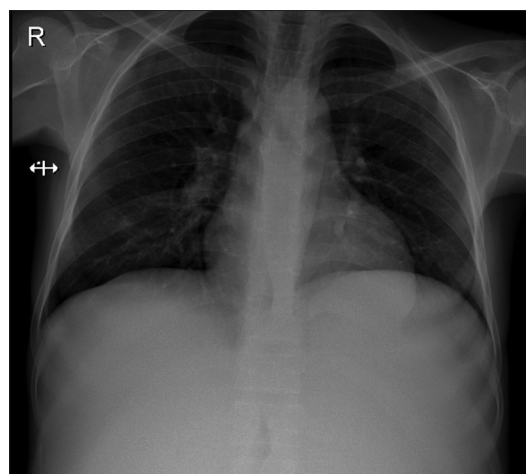


Figure 2: Chest radiograph shows no obvious abnormality.

ERT causes a dramatic effect on organomegaly with a 25% of decrease in liver and spleen volume in first 6 months.^[30] Hemoglobin rises by 1.5 g% in the first 4–6 months and platelet counts will double in the 1st year

of treatment. However, many patients would still require surgical treatment in the form of splenectomy to correct their pancytopenia.^[31] SRT is a newer form of therapy uses agents that will inhibit the enzyme glucosylceramide synthetase and thus decrease the biosynthesis of glucocerebrosidase. One of the major advantages of SRT is its ability to cross the blood–brain barrier and thus improve the neurological symptoms of GD. Advances in the management of this neglected, rare disorder, continue to be hindered by high cost of therapy.^[32]

CONCLUSION

In this case report, hepatomegaly with heterogeneous enhancement of the liver with multiple non-enhancing areas in venous and arterial phases with isodense on delayed images in both lobes of liver, massive splenomegaly with multiple well-defined areas of low attenuation in the spleen with few of the areas, showed well-defined enhancing wall formation with large central non-enhancing necrotic area, surrounding splenic parenchyma showed few non-enhancing calcified areas with intervening hypodense areas likely suggestive of old splenic infarcts/Gaucheromas. The confirmation was done by spleen biopsy. The visceral manifestations in GD respond more quickly usually within a few months or years. Imaging plays a key role in both initial diagnosis and routine monitoring of patient on treatment.

TEACHING POINTS

1. Gaucher's disease is a rare genetic disorder caused due to deficiency of enzyme beta glucosidase.
2. Manifestations include hepatomegaly, splenomegaly, bone infarcts, avascular necrosis particularly of femoral head, Erlenmeyer flask deformity and vertebra plana.

MCQs:

1. GD occurs due to the deficiency of
 - a. Glucocerebrosidase
 - b. Streptokinase
 - c. Hexokinase
 - d. Serratiopeptidase

Answer Key: a

2. Which is the non-neuronopathic type of GD ?
 - a. Type 1
 - b. Type 2
 - c. Type 3
 - d. None of the above

Answer Key: a

Ethical approval

Institutional Review Board approval is not required/waived-off.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Ginzburg L, Kacher Y, Futerman AH. The pathogenesis of glycosphingolipid storage disorders. *Semin Cell Dev Biol* 2004;15:417-31.
2. Dandana A, Ben Khelifa S, Chahed H, Miled A, Ferchichi S. Gaucher disease: Clinical, biological and therapeutic aspects. *Pathobiology* 2016;83:13-23.
3. Elstein D, Abrahamov A, Hadas-Halpem I, Zimran A. Gaucher's disease. *Lancet* 2001;358:324-7.
4. Kaplan P, Andersson HC, Kacena KA, Yee YD. The clinical and demographic characteristics of nonneuronopathic Gaucher disease in 887 children at diagnosis. *Arch Pediatr Adolesc Med* 2006;160:603-8.
5. Stirnemann J, Vigan M, Hamroun D, Heraoui D, Rossi-Semerano L, Berger MG, *et al.* The French Gaucher's disease registry: Clinical characteristics, complications and treatment of 562 patients. *Orphanet J Rare Dis* 2012;7:77.
6. Grabowski GA, Zimran A, Ida H. Gaucher disease Types 1 and 3: Phenotypic characterization of large populations from the ICGG Gaucher Registry. *Am J Hematol* 2015;90:S12-8.
7. Gillis S, Hyam E, Abrahamov A, Elstein D, Zimran A. Platelet function abnormalities in Gaucher disease patients. *Am J Hematol* 1999;61:103-6.
8. Diaz GA, Gelb BD, Risch N, Nygaard TG, Frisch A, Cohen IJ, *et al.* Gaucher disease: The origins of the Ashkenazi Jewish N370S and 84GG acid beta-glucosidase mutations. *Am J Hum Genet* 2000;66:1821-32.
9. Tajima A, Yokoi T, Ariga M, Ito T, Kaneshiro E, Eto Y, *et al.* Clinical and genetic study of Japanese patients with Type 3 Gaucher disease. *Mol Genet Metab* 2009;97:272-7.
10. Mignot C, Doummar D, Maire I, De Villemeur TB. French Type 2 Gaucher Disease Study Group. Type 2 Gaucher disease: 15 new cases and review of the literature. *Brain Dev* 2006;28:39-48.
11. Mignot C, Gelot A, De Villemeur TB. Gaucher disease. *Handb*

- Clin Neurol 2013;113:1709-15.
12. Tylki-Szymańska A, Vellodi A, El-Beshlawy A, Cole JA, Kolodny E. Neuronopathic Gaucher disease: Demographic and clinical features of 131 patients enrolled in the International Collaborative Gaucher Group Neurological Outcomes Subregistry. *J Inherit Metab Dis* 2010;33:339-46.
 13. Kraoua I, Sedel F, Caillaud C, Froissart R, Stirnemann J, Chaurand G, *et al.* A French experience of Type 3 Gaucher disease: Phenotypic diversity and neurological outcome of 10 patients. *Brain Dev* 2011;33:131-9.
 14. Abdelwahab M, Blankenship D, Schiffmann R. Long-term follow-up and sudden unexpected death in Gaucher disease Type 3 in Egypt. *Neurol Genet* 2016;2:e55.
 15. Nagral A. Gaucher disease. *J Clin Exp Hepatol* 2014;4:37-50.
 16. Grainger & Allison's Diagnostic Radiology Essentials/Lee A. Grant, Nyree Griffin 2nd Edition, 2018
 17. Weinreb NJ, Aggio MC, Andersson HC, Andria G, Charrow J, Clarke JT, *et al.* Gaucher disease Type 1: Revised recommendations on evaluations and monitoring for adult patients. *Semin Hematol* 2004;41:15-22.
 18. James SP, Stromeyer FW, Chang C, Barranger JA. Liver abnormalities in patients with Gaucher's disease. *Gastroenterology* 1981;80:126-33.
 19. James SP, Stromeyer FW, Stowens DW, Barranger JA. Gaucher disease: Hepatic abnormalities in 25 patients. *Prog Clin Biol Res* 1982;95:131-42.
 20. Patlas M, Hadas-Halpern I, Abrahamov A, Elstein D, Zimran A. Spectrum of abdominal sonographic findings in 103 pediatric patients with Gaucher disease. *Eur Radiol* 2002;12:397-400.
 21. Neudorfer O, Hadas-Halpern I, Elstein D, Abrahamov A, Zimran A. Abdominal ultrasound findings mimicking hematological malignancies in a study of 218 Gaucher patients. *Am J Hematol* 1997;55:28-34.
 22. Lee RE. The pathology of Gaucher disease. *Prog Clin Biol Res* 1982;95:177-217.
 23. Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, *et al.*, editors. *The Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New-York: McGraw-Hill; 2001.
 24. Hill SC, Reinig JW, Barranger JA, Fink J, Shawker TH. Gaucher disease: Sonographic appearance of the spleen. *Radiology* 1986;160:631-4.
 25. Poll LW, Koch JA, vom Dahl S, Sarbia M, Häussinger D, Mödder U. Gaucher disease of the spleen: CT and MR findings. *Abdom Imaging* 2000;25:286-9.
 26. Hill SC, Damaska BM, Ling A, Patterson K, Di Bisceglie AM, Brady RO, *et al.* Gaucher disease: Abdominal MR imaging findings in 46 patients. *Radiology* 1992;184:561-6.
 27. Terk MR, Esplin J, Lee K, Magre G, Colletti PM. MR imaging of patients with Type 1 Gaucher's disease: Relationship between bone and visceral changes. *AJR Am J Roentgenol* 1995;165:599-604.
 28. Lo SM, McNamara J, Seashore MR, Mistry PK. Misdiagnosis of Niemann-Pick disease Type C as Gaucher disease. *J Inherit Metab Dis* 2010;33:S429-33.
 29. De Farias LP, Padilha IG, Dos Santos CJ, Miranda Maranhão CP, de Miranda CM. Pulmonary involvement in Gaucher disease. *Radiol Bras* 2017;50:408-9.
 30. Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppelt SH, Hill SC, *et al.* Replacement therapy for inherited enzyme deficiency--macrophage-targeted Glucocerebrosidase for Gaucher's disease. *N Engl J Med* 1991;324:1464-70.
 31. Rubin M, Yompolski I, Lambrozo R, Zaizov R, Dintsman M. Partial splenectomy in Gaucher's disease. *J Pediatr Surg* 1986;21:125-8.
 32. Singla S, Ninama R, Jain B, Goyal S. Gaucher's disease: A case report. *Int J Res Med Sci* 2017;5:1712-4.

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