Gaucher Disease: A First Reported Adult Case in Indonesia

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ABSTRACT

A 44-year-old female presented with a distended abdomen and fatigue. On physical examination, prominent splenomegaly was found. The laboratory investigations revealed pancytopenia and decreased albumin-globulin ratio. The abdominal ultrasonography revealed splenomegaly, cholelithiasis, and cystitis, and the bone survey showed osteopenia. Differential diagnoses included leukemia, multiple myeloma, and myelofibrosis therefore bone marrow puncture was performed. However, histopathologic examination found Gaucher-like cells in the bone marrow aspiration. The finding of CD68 positivity in Gaucher-like cells by using the immunohistochemistry staining supporting Gaucher disease. To confirm the diagnosis, an examination of glucocerebroside substrate from the patient's blood plasma was performed. Glucosylsphingosine, a deacylated form of glucosylceramide, was markedly elevated. Therefore, the diagnosis of Gaucher disease was confirmed. This is the first reported adult Gaucher case diagnosed in Indonesia.

***Keywords**: Gaucher Disease, Splenomegaly, Pancytopenia.*

INTRODUCTION

Gaucher disease (GD) is a lysosomal storage disease that is caused by autosomal recessive mutation in the gene glucocerebrosidase 1 (GBA1), located on chromosome 1q21.[1] This gene GBA1 mutation results in the absence or deficiency of β-glucocerebrosidase, thus leading to progressive accumulation of glucosylceramide within macrophage lysosome resulting cellular and tissue damage.[2]

Gaucher Disease (GD) is a rare genetic disorder with a prevalence is approximately 1 per 40,000-50,000 individuals in the general population.[3] The most common type of Gaucher disease is type I. It has variable onset and affects mainly visceral organs such as the liver, spleen, bone marrow, and occasionally the lung and central nervous system. There are also acute neuropathic (type II) and chronic neuropathic (type III) GD variants, with worse

clinical features and commonly manifested in early infancy or childhood.[4] The novelty of this case report is the first reported case in Indonesia with the finding of Gaucher-like cells in bone marrow biopsy and enzymatic analysis.

CASE ILLUSTRATION

A 44-year-old female came to the hematology medical oncology outpatient clinic with a chief complaint of abdominal distention for the past 3 years. The patient felt uncomfortable in the left upper abdomen and fatigued, despite still being able to perform daily activities. Other complaints were multiple rashes and bruising in her lower extremities. There was no fever, diarrhea, recurrent stomatitis, joint or bone pain. The patient also complained of weight loss of 3 kilograms during the past 3 years. The patient had no complaints about micturition and passing stool. The patient had no history of hypertension, diabetes, asthma, and allergy. There was no family history of hematology disease or similar symptoms. The patient has 3 children and works as a housewife.

The physical examination showed normal vital signs. The patient was 49 kg and 151 cm tall, with a body mass index of 21.49 kg/m^2. There was no jaundiced sclera, strabismus, or abnormal extraocular movement. Both lung and heart examinations showed no remarkable finding. The abdominal inspection showed a distended abdomen but no sign of abdominal varices or caput medusa. Liver palpation revealed an enlargement of 10 cm below the costal margin, and 6 cm below the xiphoid process. The spleen was Schuffner VII (**Figure 1**). There were no ascites. Another finding was multiple bruising in the lower extremities. There was no palpable lymph node in the neck, axilla, and inguinal.

The laboratory examination showed pancytopenia (Hb 9 g/dL, Hct 28%, WBC 3,010/µL, Platelet 20,000/µL). The reticulocyte count was 138%, and the corrected reticulocyte was 0.61. The lactate dehydrogenase was 219. There was no evidence of hepatitis B, Hepatitis C, and HIV infection. Peripheral blood smear showed normocytic normochromic, anisopoikilocytosis, fragmentocyte, and ovalocyte. In addition, white blood cell examination showed normal cell count and morphology. Platelet examination revealed normal morphology, but with decreased cell count. Other results were hyperferritinemia 1,904.6 ng/mL and increased globulin 3.9 g/dL, with low serum albumin level (3.6 g/dL).

Abdominal ultrasonography found cholelithiasis, cystitis, severe splenomegaly with craniocaudal diameter size was 28.9 cm and no sign of portal hypertension.

Differential diagnoses included chronic myeloid leukemia, multiple myeloma, and myelofibrosis. Then bone marrow biopsy was performed as there was pancytopenia, showing normocellular bone marrow tissue, normal maturation of the myeloid series, and

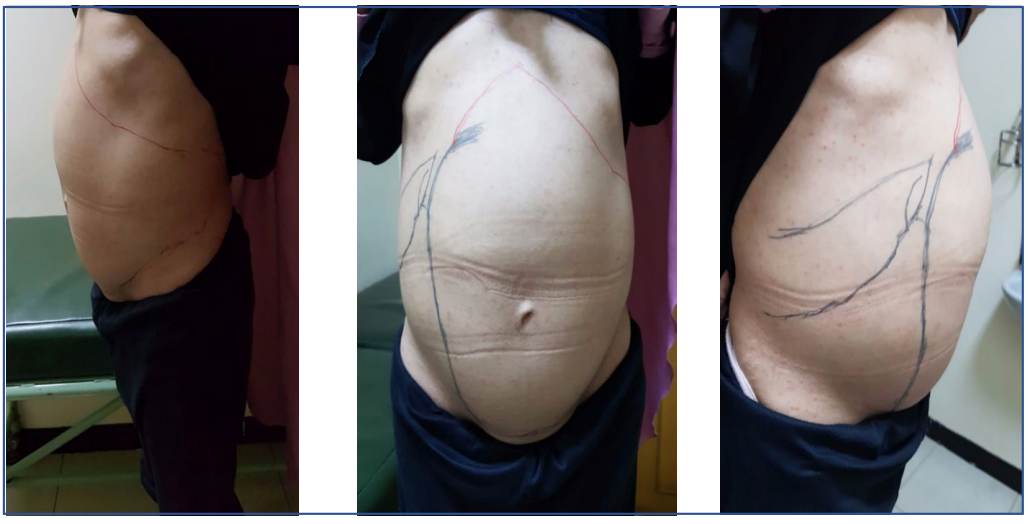

Figure 1. Splenomegaly Schaffner VII.

normal megakaryocyte morphology. Several clusters of histiocytes were found. The cells have small nuclei and the cytoplasms showed a "folded tissue paper" appearance, resembling Gaucher cells. No fibrosis was apparent (**Figure 2**). Based on bone marrow biopsy results, the diagnosis leads to Gaucher-like disease and can rule out other differential diagnosis such as leukemia, multiple myeloma, and primary myelofibrosis. For further diagnostic purposes, immunohistochemistry staining and JAK2 examination were proposed.

Immunostaining from the previous bone marrow biopsy specimen was performed. CD20 was found to be positive on small scattered lymphocytes and CD3 was positive on small scattered lymphocyte cells. Ki-67 was positive in 5% of cells and CD68 was positive in the resemblance of Gaucher cells. CD138 was positive on the scattered plasma cells and kappa--lambda ratio was normal (polyclonal). AE 1/AE 3 was negative. Glycophorin A was positive on erythroid lineage (**Figure 3**). The acid-fast bacilli staining was also performed, but the result was negative. Finally, the JAK2 molecular examination showed no V617F mutation in the JAK2 gene. The V617F mutation in the JAK2 gene was done to make sure there were no myeloproliferative neoplasms.

After the bone marrow biopsy was done, the bone survey examination revealed no Erlenmeyer flask deformity, signs of osteopenia, and decreased bone density with rough trabecula.

Diagnosis of GD could be confirmed with the absence or deficiency of β-glucosidase or excessive accumulation of glucosylceramide substrate. The enzyme analysis showed a slightly low β-glucosidase 1.05 uM/hr (normal >1.8 uM/hr; National Taiwan University). Thus, enzyme test was further evaluated and revealed markedly elevated glucosyl sphingosine (Lyso-GL1), 348.5 ng/mL (normal <3.0 ng/mL).

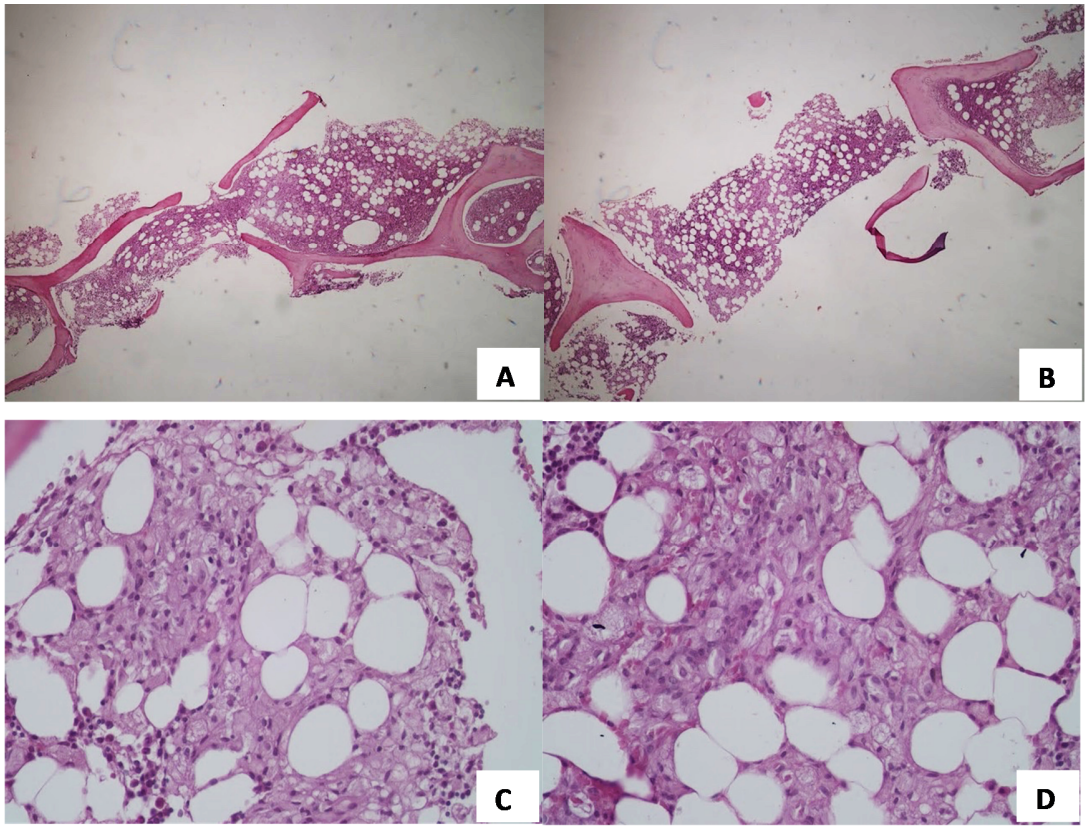

Figure 2. Histopathological features. (A, B) The bone marrow is normocellular, H&E 40x. (C, D) There are some clusters of histiocytes with small nuclei and the cytoplasms show a "folded tissue paper" appearance, resembling the Gaucher cells, H&E 400x.

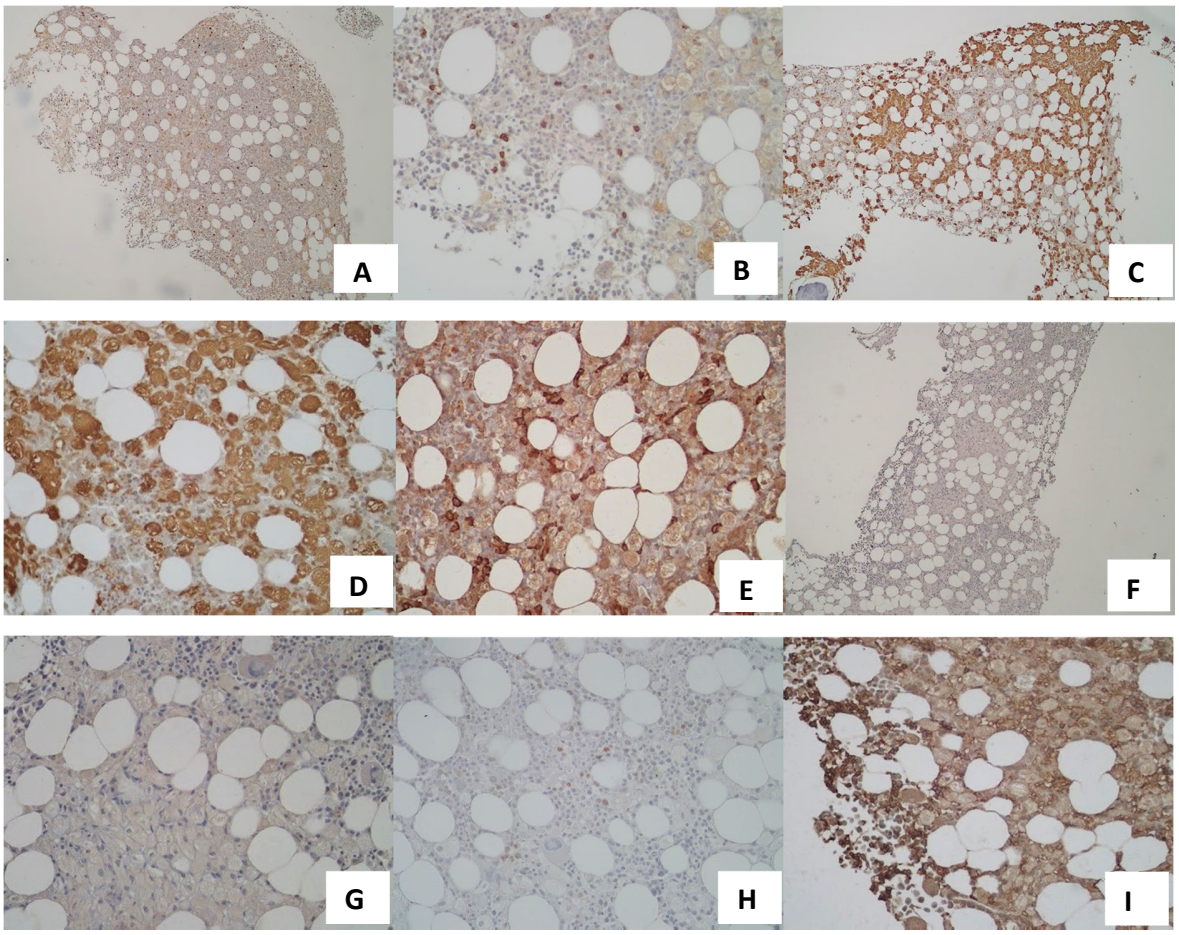

Figure 3. Immunohistochemistry profile. (A, B) Positive CD20 on small scattered lymphocytes, 100x and 400x. (C,D) Positive CD68 in the Gaucher-like cells, 100x and 400x. (E) Positive CD138 on scattered plasma cells, 400x. (F,G) Negative AE1/AE3, 100x and 400x. (H) Positive Ki67 in 5% of cells, 400x (I) Positive Glycophorin A on erythrocytes, 400x.

Other substrates level, globotriaosylceramide (Lyso-Gb3) and lysosphingomyelin (Lyso-SM) levels were slightly increased (1.2 ng/mL; normal <0.8 ng/mL and 15 ng/mL). Diagnosis of Gaucher Disease was established and the patient was submitted to an enzyme donation charity program.

DISCUSSION

Making the diagnosis of GD in this patient was challenging. GD in children is usually presented with delayed growth and development, splenomegaly, and hematologic abnormalities including thrombocytopenia and anemia. However, type I GD has variable age of onset. Thus, adults may also suffer from type I GD. The most common initial clinical presentations of type I GD are splenomegaly, pancytopenia, and hemorrhagic diathesis.[5] Other presentations may be acute or chronic osteopenia,[6] neurological involvement such as extrapyramidal signs, and Parkinsonism.[7] Imaging findings for bone involvement can be identified such as osteopenia/osteoporosis, pathological fractures, focal lytic or sclerotic bone lesions, or osteonecrosis. Erlenmeyer flask deformity at the level of the distal femur is a distinct characteristic (however not pathognomonic) finding.[6]

Lung involvement may occur in type I GD, usually presented as lung interstitial disease and pulmonary hypertension. This mostly occurred in female patients who underwent splenectomy.[8] Type I GD patients may also present with immunological alteration. Gaucher disease is characterized by increased gamma globulin titer and more susceptible to develop plasma cell disorders, such as monoclonal gammopathy of uncertain significance (MGUS)

and multiple myeloma.[9] Metabolic alteration may also occur due to chronic inflammation which induces a hypercatabolic state and reduced body mass. Low high-density lipoprotein and high ferritin with iron overload are frequent. Gaucher disease is also associated with an increased risk of cholesterol-derived gallstones.[10]

Histopathologic features in GD show Gaucher cells in the bone marrow. Gaucher cell is a histiocyte with an abundant granular and fibrillar cytoplasm resembling a crumpled tissue paper. Gaucher cells typically have a single eccentrically located nucleus. It should be distinguished from pseudo-Gaucher cells or Gaucher-like cells. Gaucher cells and pseudo-Gaucher cells are very similar under the light microscopy level on routine Hematoxylin-Eosin staining. Electron microscopical features may also help to distinguish pseudo-Gaucher cells from true Gaucher cells. On electron microscopy, Gaucher cells do not contain typical tubular cytoplasmic inclusions.[11]

These Gaucher-like or pseudo-Gaucher cells can be seen in a variety of conditions such as chronic myeloid leukemia, acute lymphoblastic leukemia, multiple myeloma, myelodysplastic syndrome, thalassemia, and disseminated mycobacterial infection.[12] Pseudo-Gaucher cells in a patient with multiple myeloma has a quite different ultrastructural pattern. They contain crystalloid inclusions that correlate with abnormal kappa light chain precipitations due to sequence mutation. On electron microscopy, they show cytoplasmic crystalline inclusions instead of tubular cytoplasmic inclusion present in Gaucher cells. On routine staining, there are many plasma cells scattered. Patients with mycobacterial infection could also exhibit pseudo-Gaucher cells in bone marrow aspirates. They showed histiocytes with cytoplasms containing needle-like inclusion on electron microscopy.[11,13] These pseudo-Gaucher cells were smaller than typical Gaucher cells. They also showed granuloma on routine Hematoxylin-osin staining.

In a patient with mycobacterial infection, pseudo-Gaucher cells are formed due to inadequate digestion of mycobacterial bacilli by histiocytes and are usually found in a patient with immunodeficiency.[14] In a patient with chronic myeloid leukemia, acute lymphoblastic leukemia, Hodgkin lymphoma, and thalassemia, pseudo-Gaucher cells can also be found in the bone marrow biopsy. Electron microscopy examination of these cells showed elongated lysosomes filled with fibrillary inclusion. Occasional dense rounded structures may also be present. Typical tubular inclusion that presents in the true Gaucher cells cannot be found. These arise under high cell turnover conditions, reflecting an increased load of leucocyte membrane-derived glucosylceramide presented to macrophages.[15-17]

The confirmation of GD requires analysis of β-glucosidase activity or accumulation of glucosylceramide in tissues. In this case, we examined the accumulation of glucosylceramide substrate and the result showed markedly increased glucosyl sphingosine (also-GL1) and slightly increased globotriaosylceramide (lyso-Gb3) and lysosphingomyelin (lyso-SM) levels. Also-GL1 as a relevant biomarker, had been approved with sensitivity and specificity also-GL1 to distinguish GD patients and healthy controls were 100% with cut-off 4 nmol/l.[18] The mechanism of also-GL1 level increasing in GD has also been investigated. Dekker et al and Yamaguchi et al proposed that the major pathway formation of glycol-GL1 was the de-acylation of accumulating glucosylceramide that involves acid ceramidase enzyme.

Lyso-Gb3 and lyso-SM in this patient were slightly increased (1.2 ng/ml and 15 ng/ml).

Lyso-Gb3 was initially used to determine Fabry disease diagnosis. However, the cut-off of less-Gb3 for diagnosis of Fabry disease is >1.3 ng/ml,[19] Also-SM was also used to determine the diagnoses of Niemann-pick disease with a value of 3.3 fold to 100 fold increment in the disease (cut off 16.8 nM).[19,20] Similarly, Polo G et al also stated that Lyso-Gb3 and also-SM levels in plasma GD patients could be normal or slightly increased.[21]

In adults, splenomegaly can be caused by portal hypertension, one of the cirrhosis complications. On the other side, splenomegaly also can be caused by nonportal hypertension,

which one of the causes is Gaucher disease. Bone marrow biopsy to show the Gaucher-like cell and enzyme activity test for confirmation. The therapy of the Gaucher disease is enzyme replacement therapy. One of the enzyme replacement therapy is imiglucerase with an initial dose of 30-60 U/kg intravenous every 2 weeks.[22-24]

CONCLUSION

The finding of CD68-positive in Gaucher-like cells by using the immunohistochemistry staining supporting Gaucher disease. To confirm the diagnosis, an examination of glucocerebroside substrate from the patient's blood plasma was performed. Glucosylsphingosine, a deacylated form of glucosylceramide, was markedly elevated. Therefore, the diagnosis of Gaucher disease in this adult patient in Indonesia was confirmed.

DATA AVAILABILITY

All data generated or analyzed during this study are included within this article.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

1. Cormand B, Montfort M, Chabas A, Vilageliu L, Grinberg D. Genetic fine localization of the beta-glucocerebrosidase (GBA) and prosaposin (PSAP) genes; implication for Gaucher diseases. Hum Genet. 1997;100(1):75.
2. Beutler E, Grabowski GA. Gaucher diseases. New York: McGraw-Hill; 2001.
3. Dionisi-Vici C, Rizzo C, Burlina AB, et al. Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J Pediatr. 2002;140:321-7.
4. Nascimbeni F, Vici CD, Gentilucci UV, et al. AISF update on the diagnosis and management of adult-onset lysosomal storage diseases with hepatic involvement. Digestive and Liver Disease. 2020;52:359-67.
5. Linari S, Castaman G. Hematological manifestations and complications of Gaucher disease. Expert Rev Hematol. 2015;9(1):51-8.
6. Giuffrida G, Cappelini MD, Carubbi F, Di Rocco M, G L. Management of bone disease in Gaucher disease type I: Clinical Practice. Adv Ther. 2014:1-16.
7. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutation in Parkinson's disease. N Eng J Med. 2009;361:1651-61.
8. Lo MS, Liu J, Chen F, et al. Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. J Inherit Metab Dis. 2011;34(3):643-50.
9. Weinreb NJ, Mistry PK, Rosenbloom BE, MV D. MGUS, lymphoplasmacytic malignancies, and Gaucher disease: the significance of the clinical association. Blood. 2018;131(22):2500-1.
10. Taddei TH, Dziura J, Chen S, et al. High incidence of cholesterol gallstone disease in type I Gaucher disease: characterizing the biliary phenotype of type I Gaucher disease. J Inherit Metab Dis. 2010;33:291-300.
11. Shenjere P, Roy A, Eyden B, Banerjee SS. Pseudo-Gaucher cells in multiple myeloma. Int J Surg Pathol. 2008;16:176-9.
12. Bajaj P, Kasture J, BS S. Gaucher's disease - A case report. MVP J Med Sci. 2015;2:130-1.
13. Costello R OCT, Sébahoun G. Gaucher disease and multiple myeloma. Leuk Lymphoma. 2006;47:1365-8.
14. Dunn P. Pseudo-Gaucher cells in mycobacterial infection: a report of two cases. J Clin Pathol. 2005;58:1113-4.
15. Stewart AJ JR. Pseudo-Gaucher cells in myelodysplasia. J Clin Pathol. 1999;52:917-8.
16. Carrington PA SR, Lendon M. Pseudo-Gaucher cells. J Clin Pathol. 1992;45:360-1.
17. Büsche G MH, Schlué J, Delventhal S, et al. Frequency of pseudo-Gaucher cells in diagnostic bone marrow biopsies from patients with Ph-positive chronic myeloid leukemia. Virchow Arch. 1997;430:139-48.
18. Murugesan V, Chuang W-L, Liu J, et al. Glucosylsphingosine is a key biomarker of Gaucher disease: Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol. 2016;91:1082-9.
19. Smid BE, van der Tol L, Biegstraaten M, Linthorst GE, CEM H, BJHM P. Plasma lobotriaosylsphingosine about phenotypes of Fabry disease. J Med Genet. 15;52:262-8.
20. Polo G, Burlina AP, TB K, Zampieri M, et al. Diagnosis of sphingolipidoses: new simultaneous measurement of glycosphingolipids by LC-MS/MS: Clin Chem Lab Med CCLM; 017. Available from: https://www.degruyter.com/doi/10.1515/cclm-2016-0340.
21. Mashima R, Maekawa M, Narita A, Okuyama T, Mano N. Elevation of plasma

lysosphingomyelin-509 and urinary bile acid metabolite in Niemann-Pick disease type C-affected individuals. Mol Genet Metab Rep. 2018;15:90-5.
22. Phetthong T, Tim-Aroon T, Khongkraparn A, et al. Gaucher disease: clinical phenotypes and refining GBA mutational spectrum in Thai patients. Orphanet J Rare Dis. 2021;16:519.
23. Mistry PK, Cappellini MD, Lukina E, et al. A reappraisal of Gaucher disease-diagnosis and disease management algorithms. Am J Hematol. 2011;86(1):110-5.
24. Kaplan P, Baris H, De Meirleir L, et al. Revised recommendations for the management of Gaucher disease in children. Eur J Pediatr. 2013 Apr;172(4):447–58.