

Case Report

Gaucher Disease Type 1 Presenting with Unexplained Hepatosplenomegaly

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Abstract:

Gaucher disease (GD) is a rare autosomal recessive disease that the clinical symptoms may present early among infants (type 2) or appear among adolescents and young adults (type 1 and 3). The lack of the glucocerebrosidase (β -glucosidase) enzyme causes the accumulation of glucosylceramide in the liver, spleen, brain, bone, bone marrow and lungs. The clinical presentation varies depending on the type of GD. The neurological disorder is found in type 2 and type 3 GD. Other symptoms of GD include hepatomegaly, splenomegaly, cytopenia, bone pain or bone fracture. Glucocerebrosidase activity and mutation in the glucocerebrosidase (GBA) gene are the current diagnostic tools for GD. In this study, we illustrated the case of a 35-year-old man who had unexplained hepatosplenomegaly with pancytopenia related to Gaucher disease type 1. He had low β -glucosidase activity and GBA mutation (R120W and D409H).

Keywords : ● Hepatosplenomegaly ● Gaucher disease ● Glucocerebrosidase

J Hematol Transfus Med 2017;27:69-74.

Received 17 November 2016 Accepted 28 February 2017

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รายงานผู้ป่วย

Gaucher Disease Type 1 Presenting with Unexplained Hepatosplenomegaly

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บทคัดย่อ

โรคโกเชร์เป็นโรคทางพันธุกรรมหายาก ถ่ายทอดทางพันธุกรรมแบบยีนด้อย (autosomal recessive) อาการของโรคโกเชร์อาจเริ่มตั้งแต่ในวัยทารก ซึ่งพบได้ในโรคโกเชร์ชนิดที่ 2 หรือ อาการปรากฏให้เห็นในวัยรุ่นหรือวัยกลางคนในกลุ่มผู้ป่วยที่เป็นโรคโกเชร์ชนิดที่ 1 และ 3 สาเหตุของโรคโกเชร์เกิดจากขาดเอนไซม์ glucocerebrosidase หรือ β -glucosidase ทำให้เกิดการสะสมของสาร glucosylceramide ในตับ ม้าม สมอง กระดูก ไขกระดูกและปอด อาการแสดงของโรคโกเชร์มีหลากหลายขึ้นกับชนิดของโรค โดยจะพบอาการผิดปกติของระบบประสาทในโรคโกเชร์ชนิดที่ 2 และ 3 นอกจากนี้ยังพบอาการของ ตับโต ม้ามโต ปริมาณเม็ดเลือดขาว เม็ดเลือดแดงและเกล็ดเลือดต่ำ (cytopenia) ปวดกระดูก หรือ กระดูกหัก การวินิจฉัยโรคโกเชร์ในปัจจุบันอาศัยการตรวจระดับเอนไซม์ glucocerebrosidase และการตรวจการกลายพันธุ์ของยีนที่ชื่อว่า glucocerebrosidase (GBA) ในการศึกษานี้ ผู้เขียนได้รายงานผู้ป่วยชาย อายุ 35 ปีมีอาการตับม้ามโต โดยไม่ทราบสาเหตุจากการตรวจเบื้องต้น และมีปริมาณเม็ดเลือดขาว เม็ดเลือดแดง และเกล็ดเลือดต่ำ จากโรคโกเชร์ โดยตรวจพบว่าผู้ป่วยมีปริมาณเอนไซม์ β -glucosidase ในเลือดต่ำ และ มีการกลายพันธุ์ของยีน GBA ชนิด R120W และ D409H

คำสำคัญ ● Hepatosplenomegaly ● Gaucher disease ● Glucocerebrosidase

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2560;27:69-74.

Introduction

Gaucher disease (GD) is a rare metabolic disorder that presents various clinical manifestations. The etiology of GD involves the deficiency of lysosomal enzyme acid β -glucosidase (GBA) produced by the mutation involving the β -glucosidase gene (chromosome 1q21) that leads to accumulated glucocerebroside (glucosylceramide) in tissue macrophage with damage to multiple visceral organs and bony structure. The three types of GD are characterized by anemia, thrombocytopenia, splenomegaly and skeletal abnormality in type 1 (nonneuropathic), whereas type 2 (acute infantile neuropathic) is an acute and severe neuropathic pattern usually occurring among infants with an oculomotor abnormality followed by brainstem involvement. Type 3 GD (chronic neuropathic) also presents neurological involvement including the symptoms of seizure, ataxia and dementia, generally appearing in childhood. Although, type 1 GD is the most common type among adults, it is quite difficult to detect and diagnose GD due to its low prevalence.¹⁻³ Therefore, we reported a unique case of GD that presented unexplained cytopenia and hepatosplenomegaly.

Case report

A 34-year-old male was referred to us to evaluate his pancytopenia before kidney transplantation. He had a diagnosis of malignant hypertension and end stage renal disease (ESRD) for ten years, and was receiving regular dialysis treatment after receiving a diagnosis of ESRD. He underwent kidney biopsy ten years ago, and the pathologic results showed glomerulosclerosis and nephrosclerosis. He also had moderate concentric left ventricular hypertrophy (LVH) and secondary hyperparathyroidism. His current medications were methyl dopa 1,000 mg/day, doxazosin 8 mg/day, metoprolol 100 mg/day, isosorbide dinitrate 30 mg/day, losartan 100 mg/day, hydralazine 200 mg/day, allopur-

inol 100 mg/day, calcium carbonate 1,800 mg/day, sodamint 2,700 mg/day, erythropoietin 8,000 units/week and folic acid 5 mg/day. He had no fever, sweating, loss of appetite, bone pain, abdominal discomfort, chronic fatigue or easy bruising. He had no family history of hematologic malignancy or inherited disease. On physical examination, we found moderately pale conjunctivae, palpable liver 7 cm below the right costal margin and palpable spleen 5 cm below the left costal margin; the other physical and neurological examinations were unremarkable. His complete blood count revealed Hb 6.8 g/dL, Hct 23.2%, MCV 95.8 fL, WBC $2.44 \times 10^9/L$ (PMN 77%, L 15%, M 5%, E 3%) and platelet $111 \times 10^9/L$. The reticulocyte count was 2.2%. He had normal liver function test results with mild hypoalbuminemia (serum albumin level was 3.2 g/dL). Coagulogram results were within normal range. Whole abdominal computed tomography scan revealed a hepatomegaly size 19.3 cm in height in the mid-clavicular line without nodular surface and spleen size 12.5 x 5 x 15.3 cm without mass. The pancreas, adrenal glands, bladder, vessels and lymph nodes were unremarkable. No internal filling defect or dilatation was found of the hepatic, portal and inferior vena cava veins. Bone marrow pathology demonstrated adequate cellular marrow (85%), increased osteoclastic activity and showed focal bone resorption. No overt abnormal morphology or maturation, no increase of lymphocytes and plasma cells, no granuloma or metastasis tumor, mild reticulin fibrosis (MF-1) and negative trichrome stain were observed. Cytogenetic analysis showed normal karyotype. *Janus kinase (JAK) 2* mutation was performed showing wide type JAK2. According to the physical examination and the initial investigations in this patient, no evidence of liver disease, myeloproliferative neoplasm, lymphoproliferative disease, thrombophilia or amyloidosis was found.



Figure 1 An abdominal computed scan shows hepatosplenomegaly without mass. Diffusely increased bone density with 2 small osteolytic lesions (0.7 ± 0.7 cm) at left iliac bone

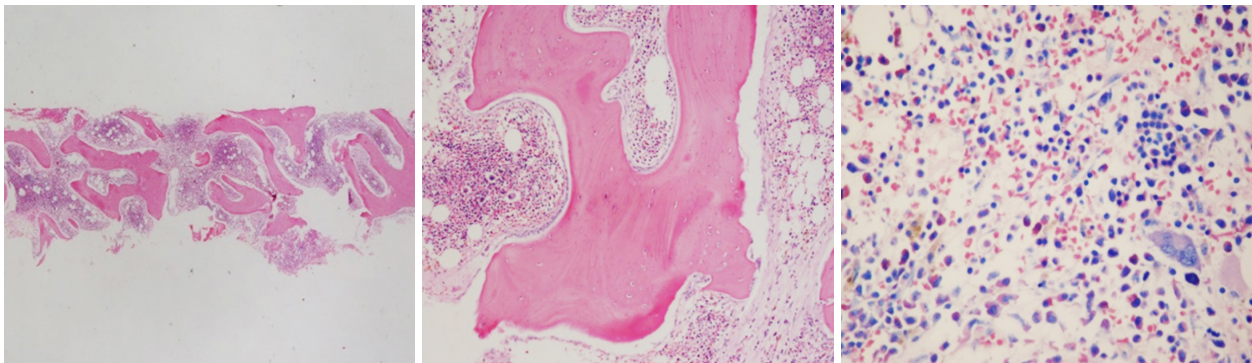


Figure 2 Bone marrow tissue shows adequate trilineage, increased osteoclastic activity and focal bone resorption, without granuloma or Gaucher cells.



Figure 3 The plain film skeletal survey shows increased bone density in the ribs, pelvis and femur

The leukocyte β -glucosidase (glucocerebrosidase) activity was performed indicating low β -glucosidase activity (4.5 nmol/hour/mg protein at PH 5.0 (12.91 ± 4.95)). The molecular analysis was conducted and demonstrated that the patient was compound heterozygous for the R120W and D409H mutations. Therefore, the patient was given a diagnosis of GD. He was treated with intravenous imiglucerase 60 units/kg every two weeks. His cytopenia and hepatosplenomegaly improved after five weeks of enzyme replacement therapy (ERT). He underwent kidney transplantation after treatment with ERT for two weeks. The splenomegaly and cytopenia disappeared after six weeks of ERT. Recently (five months after ERT), he had only mild hepatomegaly (palpable liver 2 cm below the right costal margin).

Summary

In our case, the patient was suspected of having GD type 1 due to his unexplained hepatosplenomegaly even when no Gaucher cell was found in his bone

marrow. In the past, the diagnosis of GD was commonly made by positive Gaucher cells in the spleen or bone marrow; however, the current diagnostic methods for GD rely on clinical manifestations, the level of β -glucosidase enzyme in leucocytes or skin fibroblasts and gene mutation testing. GD is an autosomal-recessive lysosomal storage disorder that is commonly found in Ashkenazi Jews and non Jewish Europeans; only 10% of the Asia-Pacific population has GD. GD is not a common disease, and is caused by various mutations (> 100 mutations) in the glucocerebrosidase (GBA) gene for which the most common mutations are N370S, L444P, D409H, R463C, 1263del55, RecNciI, and RecTL.^{4,5} In this report, the patient presented low glucocerebrosidase enzyme activity and had D409H and R120W point mutations which have been reported in GD. Therefore, the unexplained hepatosplenomegaly in this patient was an important clue to suspect GD. A diagnostic approach to adult patients with hepatosplenomegaly is outlined in Figure 4. The other clinical presentations of GD type 1

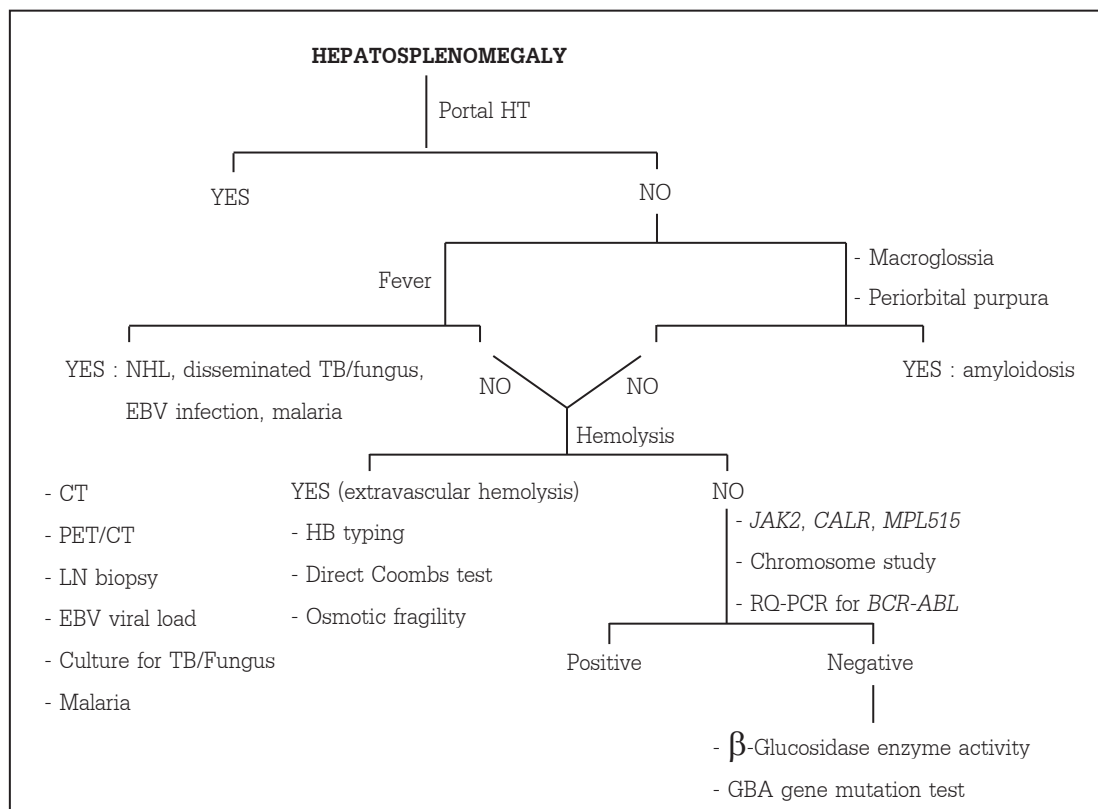


Figure 4 A diagnostic approach to adult patients with hepatosplenomegaly

include cytopenia, dyspnea caused by lung infiltration, bone and joint pains due to osteonecrosis of the hip, knee and shoulder, osteopenia and osteolytic lesion, while visual gaze palsies, myoclonic epilepsy, nerve deafness and parkinsonism in middle life are clinically suspected in GD type 3. Moreover, GD it was found to be associated with an increased risk of monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, amyloidosis, B cell non-Hodgkin lymphoma and hepatocellular carcinoma.^{2,6} Enzyme replacement therapy is the current standard treatment for GD whereas substrate reduction therapy (SRT; miglustat and eliglustat) is recommended for patients unsuitable for ERT.⁶⁻¹² Four different human recombinant enzymes have been approved by the food and drug administration: alglucerase (ceredase), imiglucerase (cerezyme), velaglucerase alfa and taliglucerase alfa. The dosage of ERT is generally 15-60 units/kg/dose and given intravenously every two weeks; an allergic reaction is commonly found in 7% after ERT.^{2,6} The rise in hemoglobin and platelet levels and the reduction of spleen and liver size usually occur within six months after initiating ERT.^{2,6} Moreover, providing good supportive care is also important to prevent further complications associated with bone damage, cytopenia and neurological disorder.

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