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# A Case of Adult Type 1 Gaucher Disease Complicated by Temporal Intestinal Hemorrhage

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## Key Words

Gaucher disease type 1 · Rectal hemorrhage · Thrombocytopenia · L444P/D409H

## Abstract

A 21-year-old man with a history of sudden rectal hemorrhage was referred to our hospital. Examination disclosed thrombocytopenia and hepatosplenomegaly. A liver biopsy specimen demonstrated Gaucher cells in Glisson's capsule. Additional investigations revealed a low level of leukocyte  $\beta$ -glucosidase activity and common mutations of the glucocerebrosidase gene, L444P/D409H. We diagnosed the patient with Gaucher disease type 1. He underwent enzyme replacement therapy. Thrombocytopenia and hepatosplenomegaly improved at a rate of approximately 50 and 20%, respectively, within 6 months. This case suggests that we must pay attention to adult Gaucher disease as a differential diagnosis for cryptogenic thrombocytopenia.

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## Introduction

Gaucher disease is a glucosylceramide lipidosis caused by deficient acid  $\beta$ -glucosidase (glucocerebrosidase, *GBA*; EC 3.2.1.45) enzymatic activity mainly due to *GBA* gene mutations,

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inherited as an autosomal recessive trait [1–3]. GBA catalyzes the hydrolysis of glucosylceramide into glucose and ceramide. Excess accumulation of glucosylceramide within macrophages in various tissues leads to clinical manifestations. Gaucher disease has been classified into three types according to clinical symptoms: non-neuronopathic (type 1), acute neuronopathic (type 2) and subacute neuronopathic (type 3). Type 1 is the most common variant and characterized by relatively later onset and slower progress than the neuronopathic types. Its common symptoms include hepatosplenomegaly, thrombocytopenia due to hypersplenism and bone manifestations. While bleeding complications can be caused as a result of thrombocytopenia, spontaneous intestinal bleeding is extremely rare.

We describe a patient with type 1 Gaucher disease who was diagnosed with the disease by chance because of spontaneous intestinal hemorrhage.

### Case Report

A 21-year-old male patient suffering from sudden rectal hemorrhage was admitted to a general hospital in July 2009. Emergent colonoscopy was performed with the findings of (1) a large amount of blood in the rectum and sigmoid colon and (2) oozing from eroded rectal mucosa. Laboratory investigation revealed thrombocytopenia (platelets  $10.3 \times 10^4/\mu\text{l}$ ). Although the hemorrhage stopped spontaneously and did not occur again, the patient was referred to our hospital for further examinations. He had had no previous significant rectal bleeding. His past medical history was unremarkable except for occasional nasal bleeding during childhood.

On physical examination, the abdomen was soft and flat; a non-tender liver edge descended to 8.5 cm below the right costal margin, and the splenic tip was palpable 11.5 cm below the left costal margin. Neurologic examination revealed no evidence of abnormalities. The laboratory data are summarized in table 1. There were thrombocytopenia and slight leukocytopenia (platelets  $6.7 \times 10^4/\mu\text{l}$ , white blood cells  $3,180/\mu\text{l}$ ). Other laboratory findings disclosed: total bilirubin 1.4 mg/dl (reference range 0.2–1.3), direct bilirubin 0.5 mg/dl (reference range 0–0.3), and prothrombin time activity 77.0% (reference range 90–130). To find out the cause of thrombocytopenia and leukocytopenia, we performed serology tests for infection with hepatitis B virus, hepatitis C virus, Epstein-Barr virus and *Helicobacter pylori*; however, there were no remarkable findings. Anti-DNA antibody test showed a titer of 1:40 (reference range <1:40). His platelet-associated immunoglobulin G (PAIgG) level was elevated to 166 ng/ $10^7$  cells (reference range 9.0–25.0), however anti-platelet antibody (anti-platelet-binding IgG) was negative.

Enhanced computed tomography (CT) showed the extremely enlarged liver and spleen. The splenic and the superior mesenteric vein were dilated and tortuous, whereas no apparent cirrhotic change of the liver was observed (fig. 1a). For further examination, especially for the differential diagnosis of idiopathic portal hypertension, we performed a liver biopsy. The liver biopsy specimen showed that numerous large cells with striated cytoplasm assembled in Glisson's capsule (fig. 2). The cells had abundant eosinophilic cytoplasm with a striated or fibrillar appearance like that of crumpled tissue paper, which is typical of Gaucher cells [4]. There was fibrous expansion of most portal tract areas, but bridging fibrosis was not seen. Additional blood investigations revealed high values of acid phosphatase and angiotensin-converting enzyme (ACE) concentrations (table 1), which is compatible with Gaucher disease [5]. The enzymatic activity of leukocyte  $\beta$ -glucosidase, the measurement of which is necessary for the definitive diagnosis of Gaucher disease, had decreased to 11.67 nmol/h/mg (reference range 56.76–74.85) [6, 7]. We analyzed the seven common

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mutations (N370S, 84GG, F213I, IVS2+1, L444P, R463C and D409H) in the *GBA* gene as previously reported [8–10] with the informed consent of the patient and found the compound heterozygous mutations L444P/D409H. Based on these results, we diagnosed the patient with Gaucher disease type 1.

We started enzyme replacement therapy (ERT). 60 U/kg body weight imiglucerase, a macrophage-targeted recombinant human glucocerebrosidase, was injected every 2 weeks [11]. Figure 1b shows the CT scan 5 months after ERT started. The liver and the spleen were sized down (liver: from 23.3 × 15.4 × 20.3 cm to 22.1 × 15.3 × 17.9 cm; spleen: from 12.8 × 10.5 × 21.1 cm to 11.8 × 9.4 × 17.3 cm). Platelet counts number and ACE concentration, a biomarker of the progress of Gaucher disease [5], were also improved from 7.4 to 11.3 × 10<sup>4</sup>/μl and from 42.5 to 24.7 IU/μl, respectively (fig. 3).

## Discussion

Gaucher disease patients are generally diagnosed by symptoms of hepatosplenomegaly or bone disease in childhood, whereas lesser degrees of hepatosplenomegaly occur in adults [2, 3]. It is extremely rare that a patient with type 1 Gaucher disease is diagnosed by chance because of spontaneous intestinal hemorrhage.

Some reports have described hemorrhagic complications as one of the clinical features of Gaucher disease, which is mostly associated with thrombocytopenia due to splenomegaly or esophageal varices due to liver cirrhosis. Hemorrhage of the stomach or intestine is uncommon; a few cases of gastrointestinal hemorrhage associated with gastric ulcer [12] or ileal lymphoid hyperplasia [13] have been reported.

In the present case, the patient did not have esophageal varices and hemorrhage was recognized at the rectum and sigmoid colon. The endoscopic biopsy specimen of rectal epithelium showed neither particular etiological features leading to hemorrhage nor Gaucher cells (data not shown). It is difficult to identify the clear cause of sudden colorectal hemorrhage. However, CT images showed that the splenic and the superior mesenteric vein were dilated and tortuous, suggesting portal hypertension. It is possible that portal hypertension due to liver enlargement participated in leading to rectal and colonic hemorrhage in the present case. The number of platelets immediately after sudden rectal hemorrhage was 10.3 × 10<sup>4</sup>/μl, which seems not enough to lead to hemorrhage. However, another possible candidate for the etiology of sudden hemorrhage is abnormality of platelet function. Keisey et al. [14] reported two Gaucher disease patients complicating pseudo-pseudo Bernard-Soulier syndrome despite normalization of platelets counts after spleen removal. Concerning PAIgG, Lester et al. [15] reported the occurrence of a high level of PAIgG in a case of Gaucher disease with concurrent immune thrombocytopenic purpura. Although anti-platelet antibody was negative, the PAIgG level was elevated in the present case (table 1). The possibility that PAIgG causes thrombocytopenia and a platelet function disorder is not excluded.

Treatments for Gaucher disease to be considered are reported to be ERT, splenectomy and bone marrow transplantation [6, 7]. We started ERT in our patient and the therapy was very effective. The number of platelets increased at a rate of 53%, and the size of both liver and spleen decreased at the rate of roughly 20% within 6 months.

Patients with type 1 Gaucher disease generally do not have neuropathic symptoms and lesser degrees of hepatosplenomegaly when their symptoms appear in adulthood. Thus, the adult type 1 Gaucher disease patient without bone disease, as in the current case, has poor presentation of specific symptoms, resulting in the disease being difficult to find unless a special event like hemorrhage occurs. In conclusion, although Gaucher disease tends to be

considered as a pediatric disease, we have to pay attention to adult Gaucher disease as a differential diagnosis for cryptogenic thrombocytopenia.

### Disclosure Statement

The authors disclose possible conflicts of interest with Genzyme Japan K.K.

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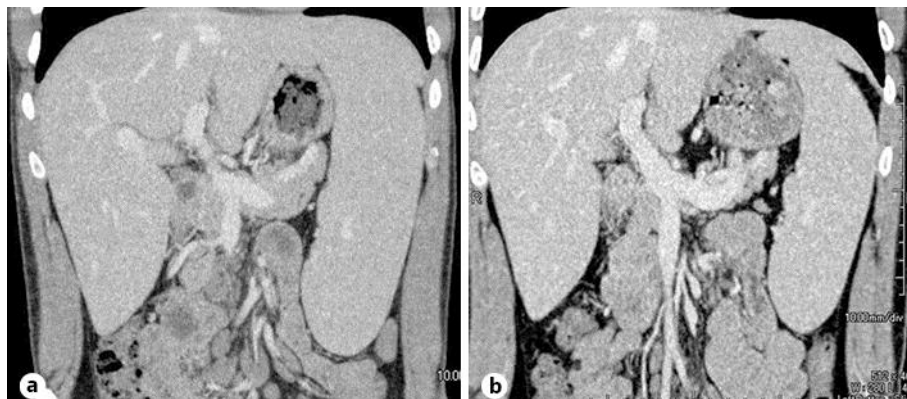
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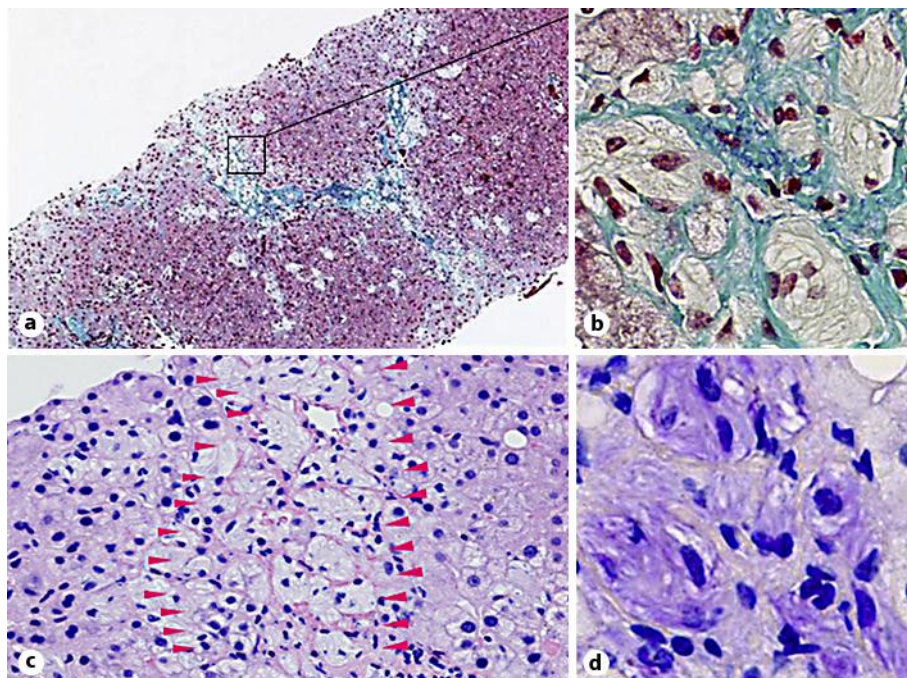
**Table 1.** Laboratory data

<i>Hematology</i>	
White blood cells	3,180/ $\mu$ l
Hemoglobin	14.0 mg/dl
Platelets	$6.7 \times 10^4$ / $\mu$ l
<i>Blood chemistry</i>	
Total bilirubin	1.4 mg/dl
Direct bilirubin	0.5 mg/dl
AST	19 U/l
ALT	17 U/l
Alkaline phosphatase	213 U/l
$\gamma$ -GTP	22 U/l
Total protein	7.6 g/dl
Albumin	4.8 g/dl
Immunoglobulin G	1,580 mg/dl
Immunoglobulin A	272 mg/dl
Immunoglobulin M	146 mg/dl
<i>Coagulation</i>	
PT%	77.0%
<i>Serology test</i>	
HBs-Ag	negative
HCV-Ab	negative
Anti-nuclear antibody	negative
Anti-mitochondrial M2 antibody	negative
EBV-VCA IgM	negative
EBV-VCA IgG	80+
EBNA	80+
Anti-platelet antibody	negative
PAIgG	166 ng/ $10^7$ cells
Anti-DNA antibody	40+
Anti- <i>H. pylori</i> antibody IgG	negative
<i>Others</i>	
Acid phosphatase (8.3–21.4)	26.3 U/l
ACE (<14.4)	42.5 IU/ $\mu$ l
Leukocyte $\beta$ -glucosidase (56.76–74.85)	11.67 nmol/h/mg

ALT = Alanine aminotransferase; AST = aspartate aminotransferase; EBNA = Epstein-Barr virus nuclear antigen; EBV-VCA IgG = Epstein-Barr virus-viral capsid antigen antibody immunoglobulin G; EBV-VCA IgM = Epstein-Barr virus-viral capsid antigen antibody immunoglobulin M;  $\gamma$ -GTP = gamma-glutamyl transpeptidase; HBs-Ag = hepatitis B surface antigen; HCV-Ab = hepatitis C virus antibody; PT% = prothrombin time activity.



**Fig. 1.** Abdominal CT images. **a** Before ERT. Liver size: 23.3 × 15.4 × 20.3 cm. Spleen size: 12.8 × 10.5 × 21.1 cm. **b** 5 months after ERT started. Liver size: 22.1 × 15.3 × 17.9 cm. Spleen size: 11.8 × 9.4 × 17.3 cm.



**Fig. 2.** Microscopic findings of liver biopsy specimen. **a, b** Gaucher cells in Glisson's capsule (Elastica-Masson, **a** ×40, **b** ×400). **c** Arrowheads indicate the assembly of Gaucher cells in Glisson's capsule (hematoxylin and eosin, ×200). **d** The cytoplasm of Gaucher cells is well stained with periodic acid-Schiff (×400).

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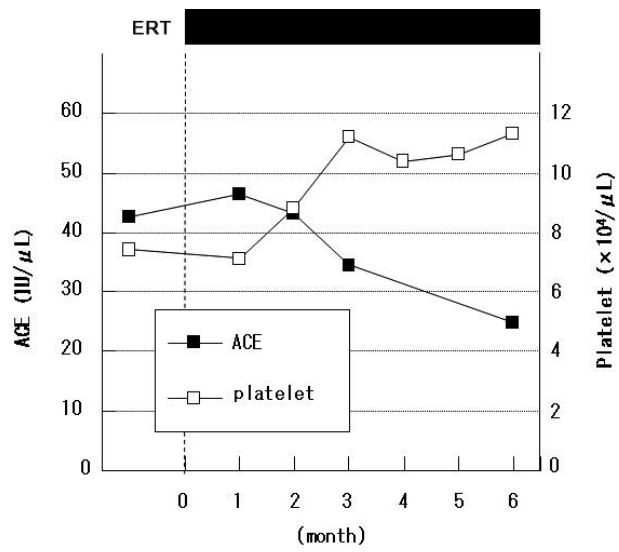


Fig. 3. Changes in platelets count and ACE concentration during the course of ERT.