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Thrombocytopenia, With or Without Other Manifestations Related to Gaucher Disease: A Key Diagnostic Clue in Gaucher Disease

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1. Abstract

1.1. Aim: Gaucher disease (GD) is a rare autosomal recessive genetic disorder caused by a deficiency in the activity of β-glucocerebrosidase, a lysosomal enzyme. Rapid and accurate diagnosis of GD can maximize the effectiveness of treatment effect. However, diagnosing GD is challenging and tends to be delayed because its early clinical manifestations and severity are highly heterogeneous and nonspecific, and may present at any age from early infancy to mature adulthood. This study aimed to provide a diversity of illustrative cases from our center in which incidental thrombocytopenia, with or without other manifestations related to GD, served as an important clue to the diagnosis, besides splenomegaly.

1.2. Methods: We enrolled five GD patients who presented with unexpected thrombocytopenia during laboratory test for various medical reasons between 2019 and 2022 at a single tertiary center. We diagnosed patients with GD when β-glucosidase enzyme activity was decreased and genetic testing confirmed pathogenic variants in the GBA.

1.3. Results: All patients were presented isolated thrombocytopenia. The average platelet count of patients was 74.5 ×109/L (Range 64-81 ×109/L). No other shared abnormal laboratory findings were detected. After diagnosing GD, a review of patients' medical histories and current symptoms revealed the presence of previously overlooked manifestations associated with GD, including fracture events, myoclonic seizures, and skin manifestations, in each patient prior to diagnosis."

1.4. Conclusion: This study focused on thrombocytopenia, discovered incidentally in a blood test performed various medical reasons, with GD-related manifestations other than splenomegaly as an important diagnostic clue for GD from our clinical experience.

2. Introduction

Gaucher disease (GD) is a lysosomal storage disease caused by a pathogenic variant of GBA (OMIM 606463) with autosomal recessive inheritance. GBA encodes one of the lysosomal enzymes, β-glucocerebrosidase, and a deficiency in β-glucocerebrosidase activity causes an accumulation of its substrate, glucosylceramide, inside macrophages [1]. The clinical manifestations of GD are caused by the accumulation of pathological macrophages in multiple organs, including the bone, liver, spleen, gastrointestinal tract, lungs, and nervous system [2-6].

As several therapeutic agents with various mechanisms have been developed for GD, early treatment based on early and accurate diagnosis is key to preventing disease progression and complications [7]. However, diagnosing GD is challenging and tends to be delayed because its early clinical manifestations are heterogene-

ous and nonspecific. The disease can manifest at any age from the neonatal period to adulthood, depending on the type of GD. Some patients with GD may consult several doctors and undergo multiple diagnostic tests before an accurate diagnosis is made—the so-called "diagnostic odyssey" [8]. Among the various clinical manifestations of GD, hematologic signs, including anemia, thrombocytopenia, and bleeding tendency, are common in all types of GD. The International Collaborative Gaucher Group registry reported that anemia and thrombocytopenia are present in 64% and 56% of patients with GD, respectively.6 However, their association with GD can easily be overlooked [2].

Specifically, thrombocytopenia and/or splenomegaly are well-known diagnostic clues of GD, and screening high-risk populations is effective in diagnosing individuals with GD at an early stage [8-10]. However, there are no recommendations regarding screening for GD when thrombocytopenia and other GD-related manifestations are present in the absence of splenomegaly.

This study aimed to provide a diversity of illustrative cases from our center in which incidental thrombocytopenia, with or without other manifestations related to GD, served as an important clue to the diagnosis, besides splenomegaly. We emphasize that an incidental finding of isolated thrombocytopenia or thrombocytopenia detected with GD-related manifestations can be an important diagnostic clue for GD.

3. Materials and Methods

3.1. Participants

We reviewed the records of five Korean patients who presented to Severance Hospital between 2015 and 2022 with thrombocytopenia and various other GD-related manifestations and were subsequently confirmed to have GD. Thrombocytopenia was defined as having platelet levels in peripheral blood ranging from 150,000/μL to 450,000/μL [11]. The diagnosis of GD was confirmed by low β-glucocerebrosidase activity in peripheral leukocytes and the detection of pathogenic variants of GBA as a homozygote or compound heterozygote.

3.2. Clinical Data Collection

The patients' medical and family histories, clinical characteristics, and physical examination findings were extracted from their electronic medical records. Additional laboratory, radiology, and pathology results were collected on each patient.

3.4. Enzyme Essay

β-glucosidase enzyme activity in leukocytes was measured using previously reported methods [4, 12].

3.5. Genetic Analysis and Interpretation of the Pathogenicity of Detected GBA Variants

Two patients underwent Sanger sequencing of GBA, and three underwent whole-exome sequencing (WES) followed by confirmatory Sanger sequencing. Genomic DNA was extracted from leukocytes using DNeasy Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions.

For the Sanger sequencing of GBA, a nested PCR method was used to amplify GBA and not the pseudogene. For WES, a DNA sequencing library was prepared according to the TruSeq Customs Enrichment Kit protocol (FC-123-1096, Illumina, San Diego, CA, USA). DNA sequencing was performed using a HiSeq sequencer platform (Illumina, San Diego, CA, USA), and the sequenced reads were aligned to the GRCh37 human reference genome assembly. If pathogenic variants of GBA were detected in the proband, parental genetic screening was performed to confirm the inheritance pattern.

4. Results

4.1. Patient 1

A 50-year-old man visited the Hematology Department for further evaluation of asymptomatic thrombocytopenia discovered incidentally during a medical health checkup. He had a history of two femoral shaft fractures in his youth. He had two older brothers, of whom one had died of unknown causes during childhood. Physical examination revealed a normal liver size and mild splenomegaly. Hematology showed isolated thrombocytopenia (platelet count: 74×109/L). Neurological examination was unremarkable. Based on the clinical and biochemical findings, idiopathic thrombocytopenia or hematologic malignancy was suspected. A bone marrow smear and biopsy were performed based on clinical suspicion, and typical Gaucher cells were detected. Sanger sequencing was performed to confirm GD and two pathogenic variants of GBA were detected (c.928A>G (p.Ser310Gly)//c.1192C>T (p.Arg398X)). The level of β-glucosidase activity was 5.23 pmol/min/mg. Based on these results, the patient was confirmed to have GD type 1. He was started on enzyme replacement therapy (ERT). A subsequent dual x-ray absorptiometry (DEXA) scan showed osteopenia; therefore, supplementation of calcium and vitamin D complex were initiated.

4.2. Patient 2

A 44-year-old woman was referred to the Clinical Genetics Department with thrombocytopenia identified incidentally on a routine laboratory test before breast cancer surgery. She had no other pertinent family or medical history except for hepatitis B virus carrier status. On her first visit to our hospital, her platelet count was 81×109/L, and her hemoglobin level, white blood cell (WBC) count, and liver enzyme levels were within normal limits. Multiple small, low-attenuating lesions in the spleen were identified on abdominal computed tomography (CT). Moreover, findings suggestive of bone marrow infiltrative disease were detected on positron emission tomography (PET)-CT, in addition to F-18 fluorodeoxyglucose (FDG) uptake in the right breast at the site of a known breast cancer lesion. As isolated thrombocytopenia was persistently reported, biochemical analyses and genetic tests

were performed for suspected GD. The activity of β-glucosidase was decreased (2.6 pmol/min/mg), and two pathogenic variants of GBA were identified as compound heterozygotes (c.1300C>T (p.Arg434Cys)//c.475C>T (p.Arg159Trp). Based on these results, the patient was diagnosed with type 1 GD and started on ERT.

4.3. Patients 3 and 4

Two brothers aged 19 and 21 years, were referred to the Department of Neurology because of drug-resistant generalized tonic-clonic seizures and myoclonus, which had started at the ages of 16 and 18 years, respectively. Despite multiple antiepileptic drug combinations prescribed by another hospital, the seizures and mood instability worsened. According to their mother's report, mild thrombocytopenia was consistently present from the onset of epilepsy but was thought to be a side effect of valproic acid. Physical examination revealed no hepatosplenomegaly in Patient 3 and mild splenomegaly in Patient 4. A complete blood count confirmed the presence of thrombocytopenia in both patients (Patient 3: platelet count, 80×109/L; Patient 4: platelet count, 62×109/L). The results of other laboratory tests, including liver function tests, were normal. Abdominal ultrasonography did not detect any abnormality of the liver or spleen in Patient 3, but detected splenomegaly in Patient 4. Patient 3 had undergone a next-generation sequencing (NGS) panel test containing 20 epilepsy-related genes at another hospital, which had not detected any disease-related pathogenic variants.

Based on the clinical presentations of the two brothers and their family history, WES was performed on a sample from Patient 3 to identify a genetic cause of the epilepsy. Two pathogenic variants of GBA were identified (c.680A>g (p.Asn227Ser)//c.689T>G (p.Val230Gly)), and the same variants were subsequently detected in Patient 4. Both patients were asymptomatic carriers of GBA. β-glucosidase activity was decreased in both patients (Patient 3: 2.7 pmol/min/mg; and Patient 4: 3.2 pmol/min/mg). The patients were diagnosed with GD and started on ERT.

4.4. Patient 5

An infant girl was delivered via cesarean section at a gestational age of 39 weeks, with a birthweight of 2920 g. She had been conceived through in vitro fertilization and had no antenatal abnormalities or family medical history of note. At birth, she developed respiratory insufficiency necessitating intubation and mechanical ventilation in the delivery room. She was enveloped in collodion skin and showed joint contractures of the wrists, elbows, and ankles. Initial laboratory findings revealed thrombocytopenia (platelet count: 84×109/L), with no other hematologic abnormalities. Abdominal ultrasound showed mild splenomegaly. Based on the clinical presentation, congenital ichthyosis was considered as an initial diagnosis, and conservative care was commenced. WES was performed to investigate the genetic cause of the skin disorder. Two pathogenic variants of GBA were identified, confirming a compound heterozygous genotype on parental genetic testing. Low β-glucosidase activity (2 pmol/min/mg) was confirmed, resulting in a diagnosis of type 2 GD.

5. Pattern of Platelet Count in Patients with GD

All patients in this study were diagnosed with GD while investigating the cause of incidental isolated thrombocytopenia or thrombocytopenia with various GD-related manifestations. No other laboratory abnormalities related to GD were observed (Table 1).

The platelet counts of the patients improved after starting GD treatment. Patient 1 was started and maintained on 60 U/kg ERT biweekly. Twelve years after ERT, his platelet count improved (138×109/L), and no definite hepatosplenomegaly was noted. The platelet count of Patient 2 was also normalized and was maintained after starting ERT. Her last platelet count was 141×109/L. She was diagnosed with Parkinson's disease 3 years after starting treatment for GD and died unexpectedly of COVID-19. Patients 3 and 4 started ERT, and their platelet counts improved and have been maintained to date. The platelet count patterns after treatment are shown in Figure 1.

Table 1: The medical data collected after the patients were transferred to our hospital.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Reason for initial blood test	Medical checkup	Preoperative screening	Epilepsy	Epilepsy	Congenital ichthyosis
WBC count (10^3/μL)	5.98	5.77	5.04	4.34	10.98
Hb (g/dL)	15.2	12.6	13.5	14.5	15.3
Platelet count (10^3/μL)	74	81	80	63	84
AST (IU/L)	48	18	26	23	42
ALT (IU/L)	34	16	24	19	38
Total bilirubin (mg/dL)	1.2	1.2	0.5	1	
Abdominal imaging findings	Splenomegaly (15 cm)	Splenomegaly (12.9 cm); Multiple hypoechoic nodular lesions of the spleen	Nothing abnormal detected	Splenomegaly (17.5 cm); Mild hepatomegaly	Splenomegaly (7.1 cm)

Pathogenic variants of *GBA*	c.928A>G (p.Ser310Gly)//	c.1300C>T (p.Arg434Cys)//	c.680A>g (p.Asn227Ser)//	c.680A>g (p.Asn227Ser)//	c.887G>A (p.Arg296Gln)//
	c.1192C>T (p.Arg398X)	c.475C>T (p.Arg159Trp)	c.689T>G (p.Val230Gly)	c.689T>G (p.Val230Gly)	c.719C>A (p.Pro24His)
β-glucosidase activity (pmol/min/mg)	5.23	2.6	2.7	3.2	2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; WBC, white blood cell.

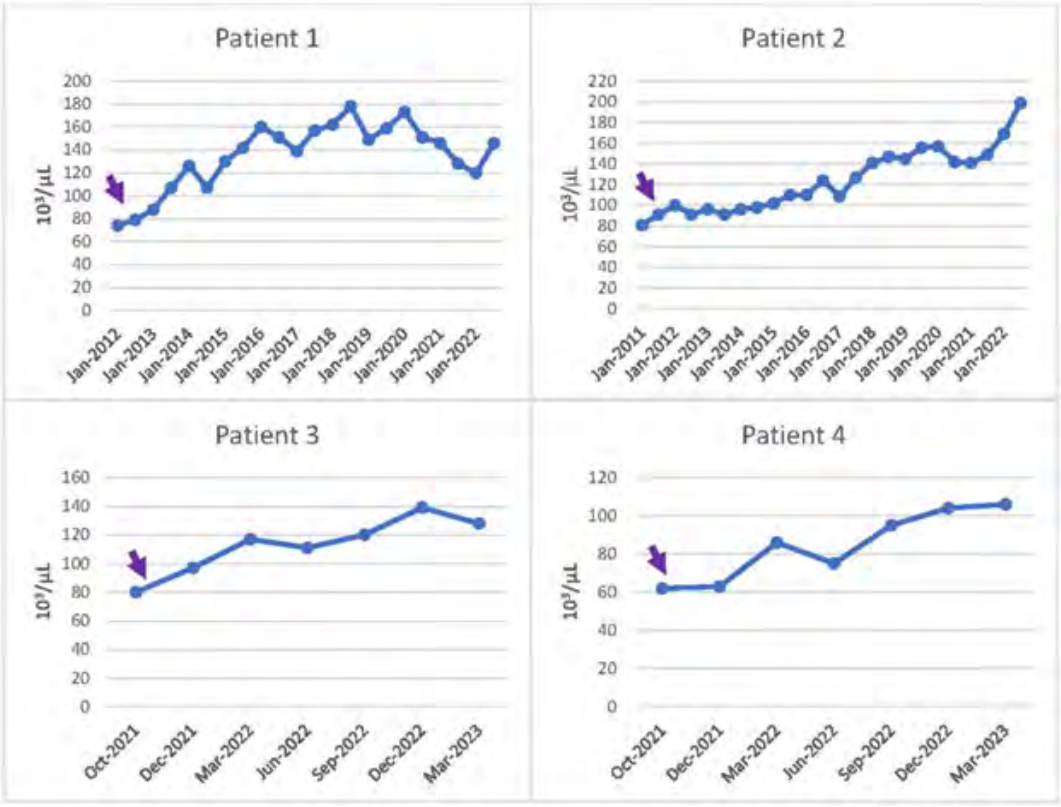

Figure 1: Patterns of platelet counts in various time points
Purple arrow: The period in which enzyme replacement therapy was initiated

6. Discussion

This study demonstrates the importance of incidental finding of thrombocytopenia as the first diagnostic clue for GD. Particularly, if accompanied by clinical signs associated with GD (Table 2) a diagnosis of GD should be considered. The underlying cause of thrombocytopenia in GD is the impairment of megakaryopoiesis due to bone marrow infiltration of Gaucher cells. Moreover, splenic sequestration due to splenomegaly can be an additional cause of secondary thrombocytopenia in patients with GD [2,6,13].

In previous reports, patients have been confirmed with GD based solely on the presence of thrombocytopenia, as in our cases. A 38-year-old woman was diagnosed with GD secondary to idiopathic thrombocytopenia and mild anemia; however, contrary to the cases in this study, she had anemia for three years before the diagnosis [14]. Another 39-year-old man in a cohort diagnosed with GD using an NGS panel presented with thrombocytopenia (118×109/L) and mild splenomegaly [8]. In addition, the first finding in a 68-year-old man diagnosed with GD was isolated thrombocytopenia (73×109/L) without other abnormalities in laboratory tests; he first visited the hospital with bone pain and hepatosplenomegaly was noted on ultrasonography, leading to a bone marrow biopsy. Gaucher cells were detected on the bone marrow biopsy [14].

Of note is that in all the patients in this study, the possibility of GD was not initially considered when thrombocytopenia was identified. However, after the patients were diagnosed with GD, each patient was retrospectively found to have other signs of GD. Patient one had a history of fractures in his teenage years, a possible sign of GD [3]. However, his fracture history was a single event long before thrombocytopenia was detected, making it difficult to link the two manifestations and suspect GD. Patient 2 had breast cancer diagnosed before the GD diagnosis. The possibility of an increased risk of breast cancer has been reported in patients with GD but has not been confirmed [16]. A recent observational study reported the

possibility of a greater risk of hematologic malignancies and certain types of solid tumors, such as liver cancer, melanoma, and renal cell cancer in patients with GD [17]. Further research is needed on the relationship between GD and cancer incidence; however, if thrombocytopenia is detected when a specific cancer is diagnosed, the possibility of GD should be considered. Progressive myoclonic epilepsy is a well-known clinical manifestation of GD type 3. Patients 3 and 4 showed intractable myoclonic epilepsy in their teens, and the possibility of GD was not considered at the time of initial diagnosis because myoclonic epilepsy is a non-specific manifestation. Although thrombocytopenia was confirmed, the diagnosis was delayed because it was detected after the administration of valproate, which can cause thrombocytopenia. Patient 5 had congenital ichthyosis, which is a known clinical manifestation of GD type 2, albeit very rare. Therefore, GD should be considered in neonates with congenital ichthyosis, especially if concomitant thrombocytopenia is present.

Improvements in genetic diagnostic methods using NGS can aid in the rapid and accurate diagnosis of GD. If GD is suspected and NGS is performed for diagnosis, it is important to check that GBA is included within the range of genes to be screened. It should be noted that in Patient 3, the NGS panel had already been performed before the hospital visit, but the diagnosis was not made because GBA was not included in the previous panel. The patient eventually underwent WES and was diagnosed with GD. In addition, the molecular analysis of GBA using NGS can be challenging because of the highly homologous pseudogene within an 85-kb region of GBA and gene–pseudogene recombination/rearrangements. If a patient is highly suspected of having GD based on clinical signs or biochemistry results, further confirmation using Sanger sequencing should be considered, even if the NGS analysis gives a negative result [18].

Through clinical experiences in this study, we emphasize that GD should be kept in mind as differential diagnosis in patients with incidental thrombocytopenia. Particularly in patients presenting with thrombocytopenia and other signs of possible GD, such as splenomegaly, skeletal or neurological manifestations, or malignancies, careful consideration of GD is warranted. Taking a detailed medical history is also essential to improve the diagnosis of GD [5, 6, 19 20].

To facilitate screening in the early phase, further studies are needed to define effective screening guidelines regarding which signs accompanying isolated thrombocytopenia are at high risk for GD.

Table 2: Clinical signs of Gaucher disease that may occur in combination with thrombocytopenia

Organ/system	Manifestations
Visceral manifestation	Splenomegaly (most common), splenic infarction, splenic rupture, hepatomegaly, Gaucheroma in liver/spleen
Hematologic manifestation	Thrombocytopenia, anemia
Bone manifestation	Bone pain, osteopenia, osteoporosis, osteonecrosis, fractures, arthrogryposis
Pulmonary manifestation	Interstitial lung disease, pulmonary fibrosis, pulmonary hypertension
Neurologic manifestation	Progressive myoclonus epilepsy, cerebellar ataxia/spasticity, dementia, psychomotor developmental delay, apnea, oculomotor apraxia, opticokinetic nystagmus
Ocular involvement	Vasculitis, vitreo-retinal involvement, corneal opacity
Skin involvement	Ichthyosis (type 2)
Malignancy	Multiple myeloma

7. Conclusion

Rapid and accurate diagnosis of GD can maximize the treatment effect by providing patients the opportunity to receive treatment at an early stage. Therefore, if patients present with thrombocytopenia with various signs of possible GD, it is necessary to consider the possibility of GD in the differential diagnosis.

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