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ORIGINAL ARTICLE

Clinical and Laboratory Characteristics of Gaucher Disease Caused by Complex Heterozygous Mutation

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SUMMARY

Background: **This study aimed to investigate and review the clinical and laboratory characteristics of Gaucher disease type 1 (GD1) caused by the heterozygous mutation of the Glucocerebrosidase (GBA) gene.**
Methods: **In this study, the bone marrow smear and biopsy slice were observed using Wright-Giemsa as well as Hematoxylin and Eosin (HE) stains, respectively. Furthermore, peripheral blood leukocyte lysosomes were monitored by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The patient's and her parents' peripheral blood DNA were extracted, and the mutation sites of the GBA-related genes were sequenced via Sanger sequencing.**
Results: **It was revealed that the Gaucher cells in the bone marrow smear and biopsy slice had large volume, were round, ovoid or irregular, occasionally binucleated or multinucleated, with chromatin roughness and occasional nucleoli, rich in the cytoplasm, bluish or grayish-red colored, and with many cytoplasmic onion-skin-like striped structures. Furthermore, the expression of GBA was decreased, while glucosylsphingosine levels were elevated. Moreover, the patient had a heterozygous complex mutation in the GBA gene (GBA NM_001005741.2): c.1604G > Ap.Arg535Hi (R496H) from her mother and c.1448T > Cp. Leu483Pro (L444P) at chromosomal locations chr1:155204793 and chr1:155205043, respectively.**
Conclusions: **The results show that a heterozygous complex mutation of R496H and L444P in the GBA gene causes the development of GD1. Clinical, enzyme activity-based assays, biological markers, and genetic analysis can significantly improve disease diagnosis and are important for early intervention and GD treatment.**
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KEYWORDS

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INTRODUCTION

Gaucher disease (GD) is an autosomal recessive disorder caused by deficiency of the lysosomal hydrolase glucocerebrosidase (GBA), which is required for glycosphingolipids degradation. GBA deficiency causes the accumulation of glucosylceramide (its immediate substrate) and glucosylsphingosine (its deacetylated form), predominately in cell lysosomes of the reticuloendothelial system [1]. Furthermore, GD is a multi-system disorder characterized by peripheral blood cytopenia, hepatosplenomegaly, bone disease, and, in some patients, neurological manifestations. Moreover, GD is predominantly prevalent in Ashkenazi Jews globally but can also occur in other races [2].
The standard for GD diagnosis is GBA activity analysis. Most GD patients indicate GBA defects; however, few patients with normal GBA activity may have sphingolipid-activated protein defects. The GBA (MIM; 606463) gene is localized at 1q21 [3], and GBA gene sequencing is an effective method for confirming the diagnosis. The human genome mutation database has revealed that there are > 500 different disease-causing GBA mutations with varying prevalence in different races [2]. For instance, c.1604G > A (R496H) is common in Ashkenazi Jewish patients with GD type 1 (GD1) [4], while c.1448T > C (L444P) mutation is frequently found in Chinese patients. This study analyzed the gene-phenotype correlation and laboratory characteristics of a Chinese patient diagnosed with GD1 caused by a heterozygous complex mutation of the GBA gene in R496H and L444P.

CASE PRESENTATION

A 28-year-old female patient of 152 cm in height and 45 kg in weight indicated abdominal swelling for more than 20 years. Furthermore, she had pain in her left hipbone and lower limbs for the past 8 years. There was no family history, and parents and brothers were all healthy. In 2001, she was diagnosed with "splenomegaly" due to a swollen abdomen and underwent splenectomy. The pathology prompted GD, PAS (+), and iron reaction (+). In 2014, she experienced severe pain in her left hipbone and lower limbs and could not walk down the ground. The check-up prompted "left femoral head necrosis". She took oral Chinese medicine for half a year, and the pain was relieved. In 2020, the abdomen increased even more and was accompanied by bloating; gradually the abdominal distension worsened. Local medical treatment with oral "ossification triam, vitamin AD, calcium carbonate D3, sodium aluminate tablets, ambroxol hydrochloride tablets" was administered; however, there was no significant change in abdominal distension.
At the Second Hospital of Hebei Medical University, the laboratory analyses revealed that white blood cell count was 10.51×10^9/L, red blood cell count was 2.91×10^{12}/L (↓), hemoglobin was 89 g/L (↓), Ret was 129.9×10^9/L (↑), Ret% was 4.46% (↑), and large immature cell count was 2.66% (↑). Serum immunofixation and electrophoresis were within normal limits. The abdominal ultrasound indicated hepatomegaly, post-splenectomy, and no space-occupying lesions in the gallbladder or kidneys. The liver was subcostal and large, the right lobe diameter was 17 cm, the upper and lower diameters were 17 cm, the anterior and posterior diameters were 9.5 cm, and the portal vein diameter was 1 cm.

Full-length X-ray of the spine

Cervical curvature was straightened, and the remaining bones of the whole spine showed no abnormality. Bone density analysis revealed osteoporosis of the lumbar spine and both hips, indicating an increased risk of fracture.

Pedigree investigation

The genetic sequence results indicated that the patient had a heterozygous complex mutation of R496H and L444P; her mother was a carrier of R496H, while her father carried L444P. The Pedigree analysis revealed that the patient inherited the disease from her parents with the disease-causing mutations, whereas her parents and other pedigree members were phenotypically normal (Figure 1).

MATERIALS AND METHODS

Morphologic examination of bone marrow cells (smear)

Wright-Giemsa staining method

The bone marrow smear was covered with the drops of Wright-Giemsa staining solution A and then mixed with the staining solution B by blowing with an aurilave to stain the smear. Lastly, the slides were rinsed with water and dried before the morphological characteristics of the cells were observed via a microscope.

Cytochemical staining method

Periodic acid Schiff (PAS)

The bone marrow smear was fixed with 95% ethanol, treated with periodic acid, rinsed with distilled water, and stained with Schiff reagent and hematoxylin staining solution, respectively. Then, the smear was rinsed with water, dried, and stained cells were observed via a microscope.

Acid phosphatase stain (ACP)

Bone marrow smears were fixed with APC fixative, washed with water, and placed in ACP staining solution (azo-coupling reaction) in the dark. Then, the smears

were rinsed, re-stained with hematoxylin staining solution, rinsed again, and dried before the microscopic examination of stained cells.

Bone marrow biopsy pathologic examination
The bone marrow specimen was fixed in 10% formalin, paraffin-embedded, sectioned, and then subjected to dewaxing using xylene. The sections were then rehydrated using different concentrations of ethanol and distilled water before hematoxylin and eosin (HE) staining. The sections were dehydrated by the action of anhydrous ethanol and xylene and sealed by coverslips with neutral resin. Cell morphology was observed, and they were classified and counted under the microscope.

Analysis of leukocyte lysosomal activity (GBA and Lyso-GL-1 assay)
The patient's peripheral blood samples were mixed with an acetonitrile aqueous solution containing glucocerebrosidase and glucosylsphingosine isotopes, respectively, for LC-MS/MS analysis.

Molecular genetic analysis
Extraction of genomic DNA
The patient's peripheral blood DNA was extracted using the phenol-chloroform extraction method. The signed informed consent was acquired from the patient before the experiments, and the study was approved by the Ethics Committee of the Second Hospital of Hebei Medical University.

GBA gene sequence analysis
The Sanger sequencing was performed for direct sequencing. Briefly, the primers for the (12) exon sequences of the GBA gene were designed, and PCR amplification was performed by chain termination method [5]. The acquired PCR products were subjected to agarose gel electrophoresis, and results were utilized for direct sequencing. The gene sequences of the patient and her parents were compared with the GBA gene in the database.

RESULTS

Morphologic examination of bone marrow cells
It was observed that the bone marrow nucleated cells were actively proliferating, and granulocytes of all stages were prevalent, with predominating middle and late-stage cells. Bone marrow aspiration showed erythroid hyperplasia, with polychromatophilic normoblast and orthochromatic normoblast predominantly, and platelets in piles. Furthermore, at the end of the smear, scattered or clustered Gaucher cells were observed. These cells were mostly large in volume, round, ovoid or irregular, occasionally binucleated or multinucleated, with chromatin roughness and occasional nucleoli, rich in the cytoplasm, bluish or grayish-red in color, and with many cytoplasmic onion-skin-like striped structures (Figure 2A - B). The cytochemical stains utilized were strong positive PAS (Figure 2C) and strong positive ACP (Figure 2D).

Bone marrow biopsy pathologic examination staining for glycogen
The biopsy revealed that the bone marrow had a significantly active proliferation rate (> 90%). Gaucher cells were also markedly increased, with focal and patchy distribution, large cytosol, rich cytoplasm, rounded or irregular nuclei, centered or deviated nuclei with some obvious nucleoli, scattered and patchy distribution of maturation stage erythroid cell, and increased quantity of megakaryocytes, with a predominance of lobulated nuclei (Figure 3A - B).

Leukocyte lysosomal activity
GBA: 1.22 µmol/L/h (reference range: 1.26 - 22.23 µmol/L/hour);
Lyso-GL-1: > 400 ng/mL (reference range < 17.41 ng/mL).

Genetic analysis
Each parent had a heterozygous mutation variant site in the GBA gene: c.1604G > A p.Arg535His and c.1448T > Cp.Leu483Pro heterozygous mutations at chromosomal locations Chr1(GRCh37): 155204793 and Chr1: 155205043, respectively (Table 1). Furthermore, two heterozygous mutation GBA gene variant sites were acquired; one from the mother (GBA NM_001005741.2) of the proband: c.1604G > Ap.Arg535His heterozygous mutation (codon R496H) and the other from the father c.1448T > Cp.Leu483Pro (a known mutation [6], codon L444P, a hotspot mutation). It is suggested that the compound heterozygous mutation in the GBA gene is the molecular pathogenesis of GD1 (Table 2).

DIAGNOSIS AND TREATMENT

Based on the aforementioned analyses and clinical manifestations, the diagnosis included GD1, anemia, spleen removal, and left femoral head necrosis. After admission, the patients received the general treatment, imiglucerase was prescribed for the symptom, and vitamin D calcium chew tablets and other comprehensive treatments were also prescribed. The infusion of imiglucerase is a smooth process and treats primary onset. The patient did not complain about the discomfort and asked to be discharged automatically. After explaining the necessity of hospital observation, she still requested a discharge and signed a waiver to be discharged from the hospital for automatic discharge.

DISCUSSION

The incidence of GD is approximately 1/40,000 to 1/60,000 births in the general population; however, in

Table 1. The report of Sanger sequencing.

Result			
Site information	**Origin**	**Result**	**Method**
GBA NM_001005741.2:c.1604G>A p.Arg535 His Chr1(GRCh37):155204793	Mother	Heterozygous	Sanger
GBA NM_001005741.2:c.1448T>C p.Leu483Pro Chr1(GRCh37):155205043	Mother	N	Sanger
GBA NM_001005741.2:c.1604G>A p.Arg535 His Chr1(GRCh37):155204793	Father	N	Sanger
GBA NM_001005741.2:c.1448T>C p.Leu483Pro Chr1(GRCh37):155205043	Father	Heterozygous	Sanger

Table 2. Analysis of GBA gene mutation in Gaucher disease patients.

Gene and transcript	Disease	Chromosomal location	Variable Site	Exon/ Intron	Heterozygous	Maximum frequency of gnomAD
GBA NM_001005741.2	GD	chr: 155204793	c.1604G>A p.Arg 535His	12	Heterozygous	0.0025
GBA NM_001005741.2	GD	chr: 155205043	c.1448T>C p.Leu 483Pro	11	Heterozygous	0.0034

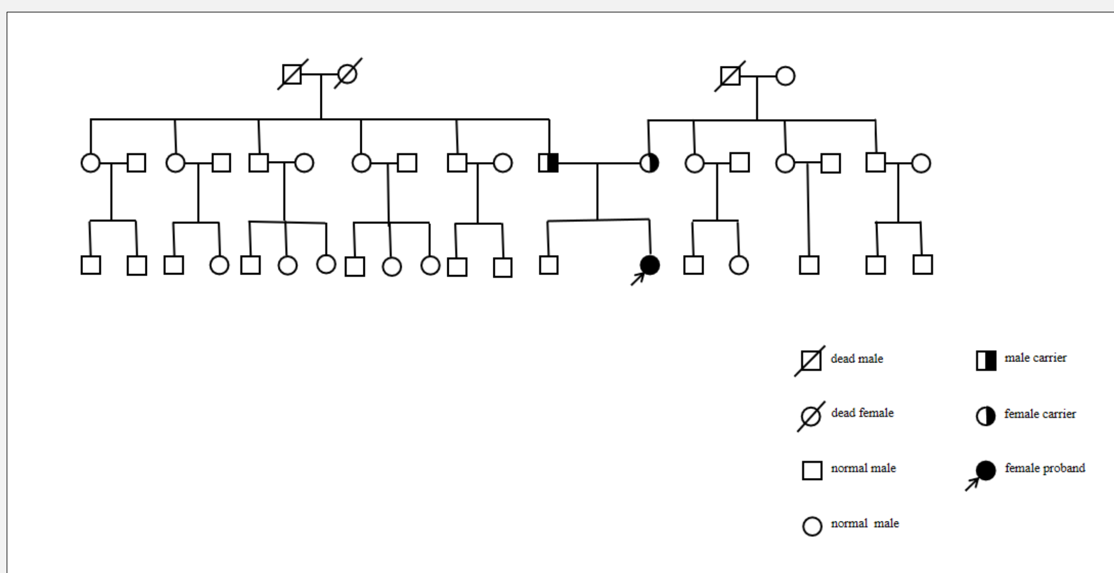

Figure 1. Family diagram of GD patients.

the Ashkenazi Jewish population it can reach up to 1/800 births [2]. GD1 is manifested with reduced central nervous system (CNS) control and accounts for approximately 95% of GD cases among Caucasians (Charrow et al., 2000). GD2 is a severe neuronopathic condition with infantile-onset and a life expectancy of < 2 years, whereas GD3 has more attenuated neurological features with a pathognomic supranuclear horizontal

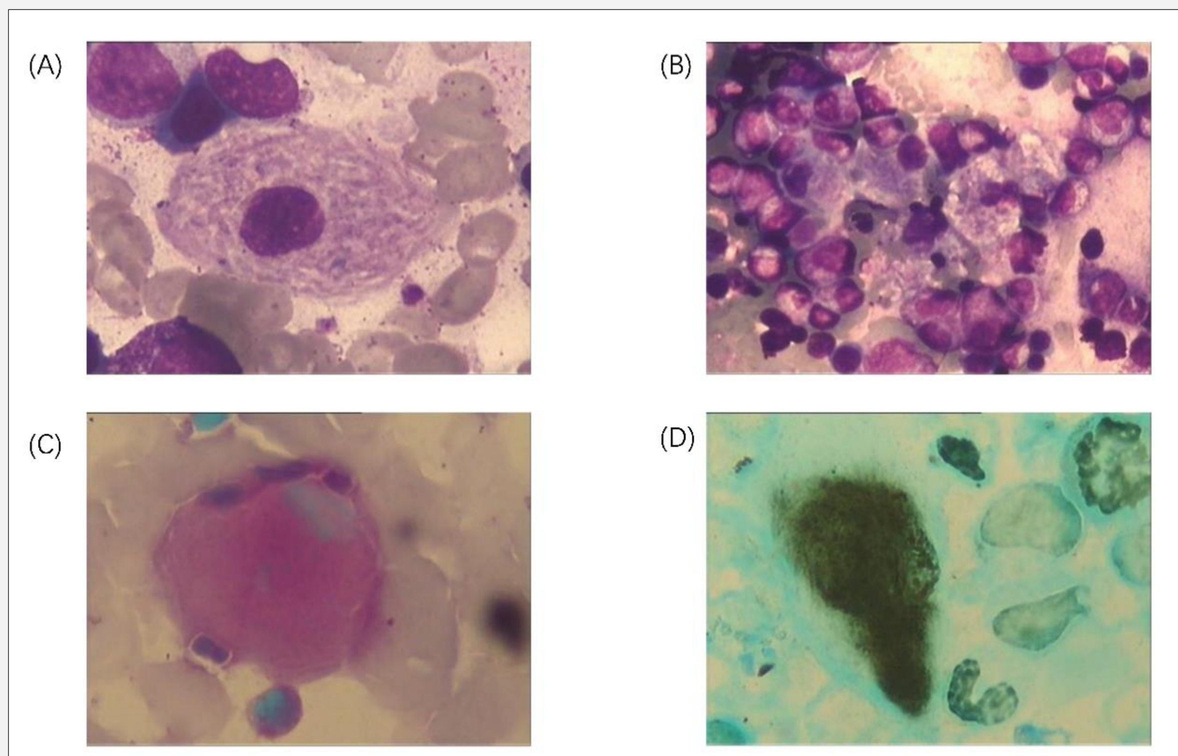

Figure 2. The results of bone marrow smear.
A) Wright-Giemsa, 1,000 ×. B) Wright-Giemsa, 400 ×. C) Staining for glycogen, 1,000 ×. D) Acid phosphatase staining, 1,000 ×.

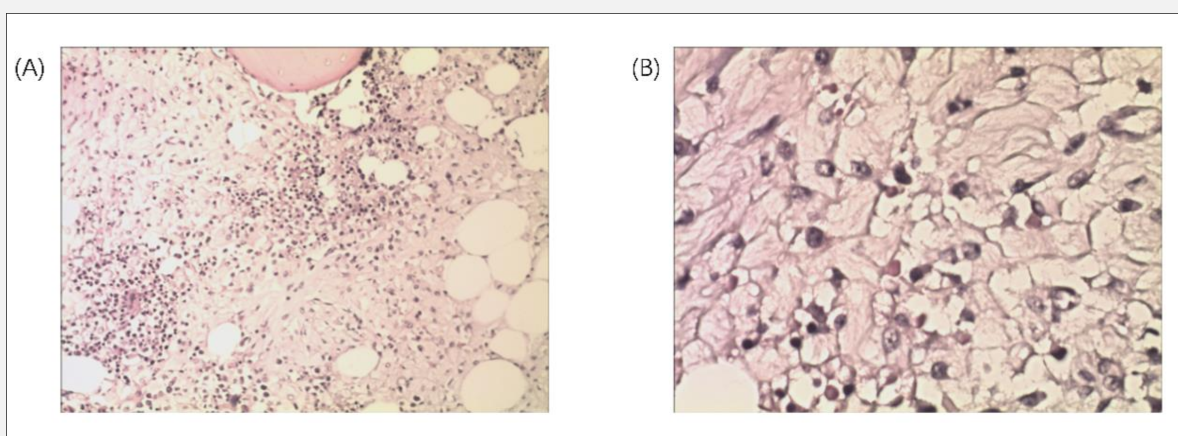

Figure 3. The results of tissue biopsy.

A) HE staining, 100 ×. B) HE staining, 400 ×.

gaze palsy, accompanied by visceral involvement and survival into adulthood.
It has been observed that GD patients with different genotypes can present similar clinical features, while patients with the same genotype can indicate different clinical features; therefore, their treatment is also different. The main clinical manifestation of GD includes splenomegaly, dyspnea, anemia of varying degrees, thrombocytopenia, bone involvement, growth retardation, limb tremor, ocular paralysis, ataxia, convulsive attack, etc.
The most common GD presentations are splenomegaly, anemia, and thrombocytopenia. Most patients are initially referred to hematologists for differential diagnosis of leukemia, lymphoma, or immune thrombocytopenia [7]. The diagnosis of GD patients is usually delayed for up to 10 years [8].
Approximately 95% of children diagnosed with GD have splenomegaly, which usually precedes other symptoms [2]. The patient enrolled in this study had abdominal bulges for more than 20 years. In 2001, she was admitted to the county hospital with splenomegaly and underwent a splenectomy, resulting in misdiagnosis. The risks of splenectomy include infection, thrombosis, etc. Furthermore, it also increases the risk of hepatic fibrosis, cirrhosis, hepatic carcinoma, and pulmonary hypertension, which further worsen GD [2]. For splenomegaly due to an unknown cause, a bone marrow cytology examination should be performed for early Gaucher cell detection and definitive diagnosis. In the absence of Gaucher cells, further diagnosis should be performed to exclude GD. Enzyme replacement therapy (ERT) with substrate reduction therapy (SRT) is an effective method for treating GD. Therefore, splenectomy should be avoided once diagnosed, and pharmacotherapy should be initiated. Splenectomy is only advisable in a few special cases, such as persistent severe cytopenia and failure of ERT [2]. The literature has indicated that ERT and SRT have a significant therapeutic effect on GD patients' splenomegaly, and the combined ERT and SRT treatment has a better therapeutic effect in reducing splenomegaly [9]. Therefore, early diagnosis and appropriate treatment are important for disease progression and prevention of complications.
It has been observed that GD causes lipid accumulation and multiple organ dysfunction. Bone diseases such as decreased bone density and osteonecrosis are typical clinical manifestations in GD patients. In GD patients, the accumulation of glucocerebroside, glucosylsphingosine, and other lipids affects hematopoiesis, as well as the number and activity of osteoblasts and osteoclasts, which results in disorders of trabecular and cortical structure, cortical thinning, fragility fracture, osteonecrosis, and related symptoms [2]. In 2014, our patient developed pain in the left hipbone and lower limb and was diagnosed by the local hospitals with "necrosis of the left femoral head". It is mainly related to Gaucher cell infiltration in bone marrow, and the patients did not receive timely GD-related treatment. Studies have found that patients who started treatment 2 years after diagnosis or later have a higher risk of osteonecrosis than those who received ERT treatment in time [10]. Furthermore, the patient had a history of splenectomy, another high-risk factor for osteonecrosis. Splenectomy causes more serious bone diseases because of potential chronic inflammation and also induces Gaucher cells to infiltrate the bone marrow, thereby further promoting the severity of bone marrow diseases [11]. Early and continuous treatment is crucial for GD patients, and active treatment with ERT or SRT can better control the development of bone disease [9]. Therefore, constant bone-related examination, vitamin D supplementation for improved bone health, as well as orthopedic care and management for patients with symptoms of bone disease are recommended [11].
The literature has indicated that GD is the most common lysosomal storage disease and an autosomal recessive disorder caused by mutations in the GBA gene. The GBA gene is located at chromosome 1q21 [3] and encodes GBA. Under normal circumstances, senescent erythrocytes and leukocytes are phagocytized by macrophages of the mononuclear macrophage system to produce glycolipids, which are broken down into glucose and ceramides by GBA in macrophage lysosomes. Furthermore, GBA also breaks down glucosylceramide into glucose and ceramide. GBA gene mutation reduces and inhibits its activity; therefore, the substrate cannot be broken down, which results in the accumulation of various substrates in mononuclear macrophages of different tissues or organs. The inhibition of GBA activity also affects the liver, spleen, bone, and other organs, while glucosylceramide inhibition causes nervous system damage.
Detection of GBA activity is the gold standard for GD diagnosis. In GD patients, the activity of GBA is between 0 - 30% of the lower limit value of normal people, whereas in Chinese, it is < 28% of the lower limit value of normal people. Studies have shown that the residual activity of GBA in peripheral leukocytes of GD patients is related to the type of GBA gene mutation [12]. Here, it was observed that the patient's enzyme activity was reduced, but > 30% of the lower normal limit, while the residual enzyme activity was sufficient to correct GBA catabolism in neurons. Therefore, the patient had no neurological symptoms, which might be associated with the type of GBA gene mutation in the patient.
Glucosylceramide is the main GBA substrate, which is accumulated in GD patients due to reduced GBA activity [13]. Glucosylsphingosine (Lyso-GL-1) acts as a downstream glucosylceramide metabolite and is formed by ceramidase-mediated partial diacylation of glucosylceramide long-chain fatty acids. Furthermore, it is directly associated with bone pathology and chronic inflammatory reactions in GD [14]. Moreover, in recent years, glucosylsphingosine has been used to diagnose and monitor GD. Here, the patient had elevated glucosylsphingosine levels, which assisted in the diagnosis of GD.

Most GD patients' morphological examination of bone marrow cells has indicated cells with large volume, small nuclei, and onion-skin-like striped structures in the cytoplasm. Combined with the results of cytochemical staining (PAS, ACP), the comprehensive analysis showed the cells were typical "Gaucher cells". Other diseases such as leukemia, thrombocytopenic purpura, and thalassemia major have also cells similar to Gaucher cells in the bone marrow; therefore, a differential diagnosis should be carried out. When there are GD-related clinical symptoms or Gaucher cells are observed in the bone marrow and GD is suspected, a comprehensive judgment should be made by combining multiple examinations. In the present case, the splenectomy was performed at the initial diagnosis because of the incomplete understanding of morphology and clinical features.

The GBA gene mutation leads to the accumulation of glucocerebroside in mononuclear macrophages, and the reticuloendothelial system is infiltrated by lipid-filled macrophages [15]. Tissue biopsies mostly indicate the presence of Gaucher or foam cells with a "crumpled tissue paper" appearance [16]. Here, the bone marrow smears and pathological sections of the patients had typical Gaucher cells, which further confirmed the diagnosis of GD.

There have been more than 500 different disease-causing GBA mutations to date, with varying prevalence in different races according to the human genome mutation database [2]. These mutations can be single base, splicing, deletions, insertions, or gene rearrangements (the Human Genome Mutation Database, May 21, 2021, http://www.hgmd.org) [17]. Furthermore, > 20 recombinant alleles have been identified, with RecNcil and Recdelta55 being the most common alleles, either alone or in combination with additional point mutations and numerous deletions [18-20]. Most recombination pathogenic mutations occur between intron 8 and 3' untranslated regions, where genes and pseudogenes have 98% sequence homology.

Different GBA mutant genes can have different effects on GBA activity, and mutations near the GBA gene may also affect its expression; for example, Metaxin [14] downstream of the GBA gene and the PSAP [21] encoding the SaposinC protein (a sphingolipid activator protein). Kang et al. reported a case of a GD1 patient with normal enzyme activity but significantly elevated levels of biomarkers, which was found to be associated with PSAP mutation, which caused GD due to the lack of SaposinC protein encoded by PSAP [22]. Currently, GBA gene mutation is also considered a risk factor for Parkinson's disease (PD); however, not all GBA gene carriers or GD patients with GBA gene mutation develop PD [23]. Some reports have indicated that the incidence of PD in 80-year-old GD patients is 30%; however, further verification is required [23]. To study the association between the GBA gene and PD the pathogenesis of PD has been a hotspot in research. At present, it is believed that GBA gene mutation leads to two main mechanisms of PD, such as it causes GBA misfolding and accumulation in neuronal endoplasmic reticulum, thereby resulting in dopaminergic neuronal damage. Furthermore, decreased GBA causes the accumulation of α-synuclein, leading to the damage of neurons [24].

The patient had a heterozygous complex mutation of R496H and L444P, and both these are pathogenic mutation sites in the presented case. The pedigree analysis and GBA gene sequencing results indicated that the GBA mutant gene in the patient was inherited from her parents, who were carriers. The molecular pathogenesis was a GBA gene missense mutation, which caused the translation of amino acid 483 from leucine to proline in the exon 11 gene and amino acid 535 from arginine to histidine in the exon 12 gene, resulting in enzyme defects.

Some research has reported [25-27] that L444P is a common mutation type in the Asian population and is mostly associated with neurological symptoms. Furthermore, GD2 and GD3 have been indicated to be more prevalent in Asian races [28]. R496H mutation is relatively rare in Asian population [29]. Recently, among 58 GD patients studied in South Korea, only 2 carried the R496H mutation gene [25], while the R496H mutant gene carried by GD patients has not been found in Japanese and Chinese studies. According to some studies, the clinical symptoms of GD patients carrying R496H are mostly mild [30]. When one gene is heavily expressed and the other is mildly expressed, the clinical presentations are usually mild [30]. The clinical manifestations of the L444P complex heterozygous mutation are often related to the other mutation gene. GD1 patients with no nervous system-related symptoms may be linked to R496H. However, the relationship between GBA gene mutation and phenotype is complex, and most mutant genes do not show a strong correlation with phenotype. The literature has indicated that mutant genes might be related to modified genes, such as the SCARB2 gene encoding the GBA transporter LIMP-2 and the PSAP gene encoding the SaposinC protein [31]. Comprehensive analysis of modified genes in phenotypes is essential for the diagnosis and treatment of different diseases. Therefore, further studies, such as whole genome sequencing, are required to identify genes associated with the disease heterogeneity that could be used as new therapeutic targets.

CONCLUSION

In summary, R496H mutation is rare in Chinese GD1 patients. Furthermore, this case has expanded the genotype and phenotype library of GD in the Chinese population. Comprehensive analysis of clinical and laboratory characteristics of GD patients through bone marrow cell morphology assessment, enzymology, and gene sequencing can better avoid misdiagnosis, facilitate early diagnosis and treatment, and reduce the risk of disease progression.

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Ethical Approval Statement:
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Statement:
Informed consent was obtained from all individual participants included in the study.

Declaration of Interest:
The authors declare that they have no conflicts of interest.

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