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Case report

An Unusual Presentation of Gaucher's Disease: Aortic Valve Fibrosis in a Patient Homozygous for a Rare G377S Mutation

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A B S T R A C T

Gaucher's disease (GD) has variable presentations, but cardiac involvement is a generally uncommon clinical manifestation of the disease. In the past 25 years, the underlying genetic disorder in GD has been well characterized, with almost 300 mutations identified in the glucocerebrosidase gene (GBA). Nevertheless, clear genotype-phenotype correlations have been confirmed only for the most frequent mutations. We present a female patient, who was known to have aortic valve pathology from the age of 30. Despite medical follow up, at the age of 60 she presented with heart failure (NYHA III). At that time echocardiography showed severe fibrosed aortic valve stenosis. Valvuloplasty was planned, when thrombocytopenia, previously considered to be autoimmune, became severe. Anemia and leukopenia were also noted. Moderate splenomegaly and severe bone marrow infiltration were found on MRI. Bone marrow aspiration revealed typical Gaucher cells and the enzyme activity assay confirmed the diagnosis. DNA investigation showed that the patient is homozygous for the G377S mutation. To our knowledge, of all mutations identified so far, only homozygosity for the D409H mutation has been associated with cardiovascular valvular disease in patients with a rare type 3c GD. G377S, found in our patient, is a rare mutation, previously reported as a 'mild' mutation, because of the finding that homoallelic patients were essentialy asymptomatic or had mild disease. Our patient, also homozygous for G377S mutation, had a severe form of type 1 GD, with rare cardiac valve involvement, which is a previously unreported clinical presentation for this mutation. This case further proves that patients with the same genotypes can have different phenotypes, emphasizing the influence of other genetic and/or environmental factors.

***Key words**: Gaucher's disease, aortic valve fibrosis, G377S mutation*

Introduction

Gaucher's disease (GD), described for the first time in 1882[1] is the most prevalent lysosome storage disorder[2], with highest prevalence in Askhenazi Jews, about 1/855, compared to 1/100,000 in other populations[3,4]. Inherited in an autosomal recessive way, this defect of the lysosomal enzyme glucocerebrosidase leads to glucocerebroside accumulation in the reticuloendothelial system[5]. Clinically, it is a multisystemic disease, with variable expression, generally characterized with hepatosplenomegaly, anemia, thrombocytopenia, bone lesions and sometimes involvement of lungs, which occur in all types of GD[5].

The presence and severity of neurological symptoms distinguish 3 clinical types of GD[6]; type 1 (non-neuronopathic), which contributes for 95% of cases, type 2 (acute neuronopathic), characterized with early onset and survival of up to only 2 years, and type 3 (chronic

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neuronopathic), with infantile or juvenile onset and survival into adulthood[7]. Over time it has become clear that GD patients can have disease manifestations on a continuum of clinical expressions (i.e. different phenotypes), ranging from only a few signs or laboratory abnormalities on one end of the spectrum to the very severe forms of the disease on the other[8].

Gaucher's disease is caused by mutation in the glucocerebrosidase (GBA) gene, which was mapped to 1q21. Almost 300 unique mutations have been reported so far in the GBA gene[9]. In non-Jewish population the most common mutations are L444P and N370S[10]. Generally, GD-causing mutations are classified as mild, severe or null alleles[11]. The presence of a mild mutation protects from neurological involvement and leads to a type 1 of GD, even in combination with a null allele or a severe mutation. The neuronopathic formes of GD are due to severe mutation homozygosity or the severe mutation and a null allele combination. The well known genotype-phenotype correlation predicts that the N370S (mild mutation) protects from neurological symptoms (type 1 GD)[12,13], as well as homozygosity for L444P (severe mutation) predicts chronic neuronopathic form (type 3 GD)[14–17]. Despite the genotype-phenotype correlation, a variable expression of clinical symptoms is present in patients with the same genotype, indicating that other factors, genetic and/or enviromental, influence the phenotype[18].

Cardiac involvement is a generally uncommon manifestation of the disease. Valvular calcifications[19–21], constrictive pericarditis[22,23] and infiltration of ventricular myocardium[24–27] have been reported so far.

Case Report

We report a female patient, with unremarkable family history and no previous medical history until the age of 30, when she presented with exertional dyspnea and syncope. Physical examination at that time revealed only abnormal heart sounds – murmurs compatible with aortic valve insufficiency. During next years of cardiological follow up, echocardiography revealed fibrotic changes of the aortic valve. She developed and was treated for arterial hypertension. At the age of 40 she had prolonged postapendectomy recovery due to sepsis and newly diagnosed mild thrombocytopenia (100,000/mm^3). Physical examination at that time showed no organomegaly. Sternal puncture was performed in local hospital, interpreted as unremarkable with no characteristic pathology found.

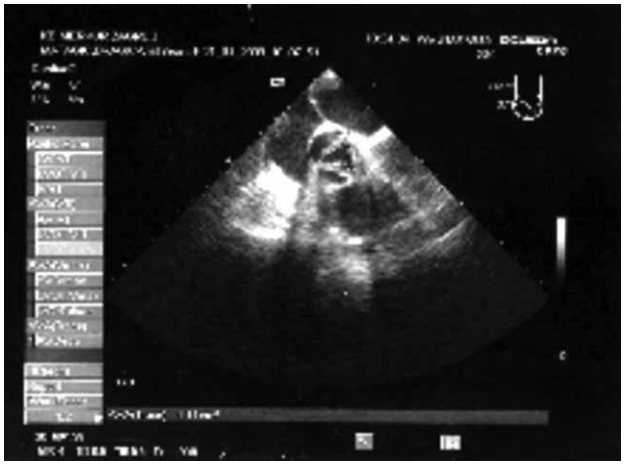

Fig. 1. Echocardiography of aortal valve.

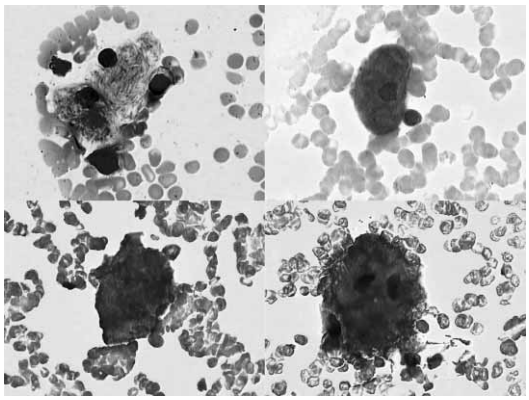

Fig. 2. Typical Gaucher cells in bone marrow aspirate (clockwise from top left: May-Grünwald-Giemsa staining, cytochemical staining – alpha naphthyl acetate esterase, immunocytochemical staining for HLA-DR and CD68).

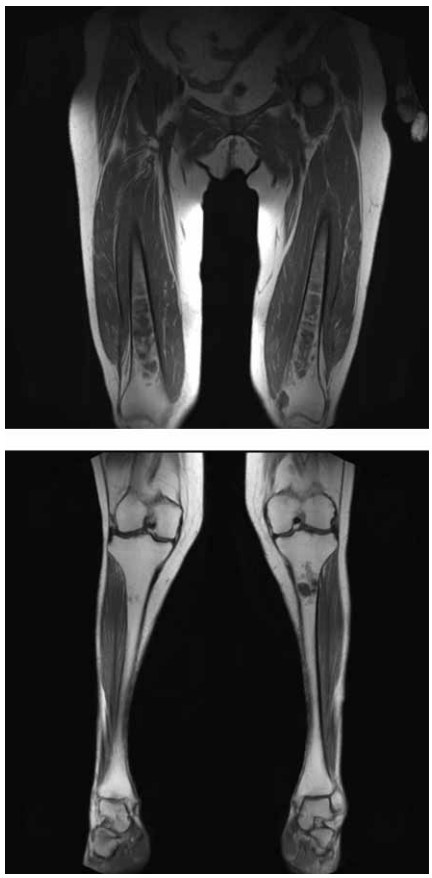

Fig. 3. Magnetic Resonance Imaging (MRI) findings of bone involvement.

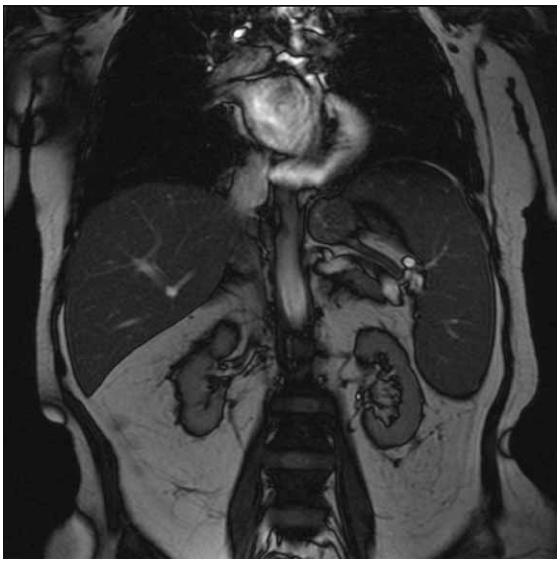

Fig. 4. Magnetic Resonance Imaging (MRI) finding of splenomegaly.

The patient was followed up for possible autoimmune thrombocytopenia, with no requirement for treatment. Despite medical treatment and close follow up, at the age of 60 she presented with heart failure (NYHA III). At that time echocardiography showed severe fibrosed aortic valve stenosis with a maximum AV gradient of 70 mmHg and concentric left ventricular hypertrophy (Figure 1). Valvuloplasty was planned, but was contraindicated due to severe thrombocytopenia (30,000/mm^3). Anemia (Hb 7.5 g/dL) and leukopenia (2,500/mm^3) were also noted, for the first time, as well as mild splenomegaly on physical examination. She also had elevated blood concentrations of ferritin and angiotensin converting enzyme (ACE) with increased liver function tests and erythrocyte sedimentation rate. Bone marrow aspiration was performed again, this time in our institution. A significant number of macrophages/histiocytes with a small and single nucleus in each cell were found; with pale blue to gray cytoplasm and a striated pattern resembling wrinkled tissue paper, typical for Gaucher cells (Figure 2). The diagnosis of Gaucher's disease was confirmed by enzyme activity assay, which showed low β-glucocerebrosidase activity. (20% of normal enzyme activity). Molecular analysis (direct sequencing) showed the patient to be homozygous for the G377S mutation. Skeletal survey showed severe bone disease. A plain radiograph revealed typical Erlenmeyer flask deformity in both distal femurs, and bone densitometry of the lumbar spine and at the femoral neck was 80% of that expected for her age. Magnetic resonance imaging showed severe bone marrow infiltration (Figure 3) and moderate splenomegaly (Figure 4) with spleen volume of 1830 mL. Enzyme replacement therapy (imiglucerase 60 U/kg every two weeks) was promptly initiated. Patient's response to treatment was rapid and sustained – she promptly became transfusion independent and presently, 6 months after treatment start, remains so. Hemoglobin levels increased to 10 g/dL, platelet numbers recovered to 100,000/mm^3, and normalisation of both leukocyte and liver function tests was also observed.

Discussion

This case of a patient with Gaucher's disease shows not only that this lysosome storage disorder can have many faces, but once again underlines the importance of collaboration between medical specialists of different profiles in establishing accurate diagnosis on time. The role of an experienced cytopathologist was decisive for establishing GD diagnosis in our patient, as it has certainly been the case in many other patients, especially those with mild forms of Gaucher's disease.

Although uncommon, cardiac involvement in Gaucher's disease has been reported, affecting the pericardium[22,23] and myocardium[24–27], potentially causing restrictive cardiomiopathy. Several case reports[19–21] described calcifications in aortic and mitral valves as well as valvular apparatus, with subsequent aortic and mitral stenosis. All these patients were homozygous for the D409H mutation, which is associated with cardiovascular valvular disease in the 3c GD clinical form, in which neurological involvement includes only oculomotor apraxia. In these deffective valves, Gaucher cells have been identified[21,28], and are postulated to play a role in the valvular calcification pathogenesis. Not infrequently, Gaucher's disease is diagnosed in adult, even geriatric population; The Gaucher Registry shows that 7% of the patients are 50 and over[29], and often with a significant gap between the initial onset of symptoms and time of diagnosis, which is reported to be 13 years in a 2004 survey among patients from Scandinavia[30].

Our patient was diagnosed GD at the age of 60, after developing severe aortic stenosis, at that time already with severe bone infiltration, severe thrombocytopenia, anemia and leukopenia, and moderate splenomegaly. G377S mutation, found in our patient, is a rare mutation, described before as a 'dosage effect' allele, where homozygosity for the mutation appeared to result in type 1 while compound heterozygosity with a null allele leads to type 3 phenotype[31]. This mutation has generally been reported as a 'mild' mutation[32], because of the finding that homoallelic patients were essentially asymptomatic or had mild disease. Our patient, also homozygous for G377S mutation, has a severe form of type 1 GD, with rare cardiac valve involvement – which, based on its early onset and absence of any other known predisposing pathology, we suspect is related to Gaucher's disease. To our knowledge, this is a previously unreported clinical presentation for this mutation. Furthermore, this case proves that patients with the same genotype can have different phenotypes, emphasizing the influence of other genetic and/or environmental factors.

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NEOBIČNA KLINIČKA SLIKA GAUCHEROVE BOLESTI: FIBROZA AORTNOG ZALISTKA KOD BOLESNICE HOMOZIGOTNE ZA RIJETKU G377S MUTACIJU

SAŽETAK

Gaucherova se bolest (GB) može prezentirati raznolikom kliničkom slikom, ali rijetko zahvaća kardiovaskularni sustav. U posljednjih je 25 godina genetski poremećaj u podlozi ove metaboličke bolesti dobro istražen, s gotovo 300 identificiranih mutacija u genu za lizosomski enzim glukocerebrozidazu. Ipak, jasne genotipsko-fenotipske korelacije, potvrđene su samo za najčešće mutacije. Kod naše pacijentice, patološke promjene na aortnom srčanom zalistku otkrivene su prvi put u dobi od 30 godina. Usprkos redovitom praćenju, bolesnica se u dobi od 60 godina javlja s kliničkom slikom teškog zatajenja srca (NYHA III). Tada učinjeni UZV srca pokaže tešku aortnu stenozu. Planirani operacijski zahvat zamjene aortne valvule kontraindicira se, zbog progresije trombocitopenije, dotad smatrane autoimunog porijekla. Tada se prvi put zamijete i anemija te leukopenija. MR čitavog tijela pokazuje uvećanu slezenu, te difuznu infiltraciju koštane srži. Citološkom se punkcijom koštane srži otkriju tipične Gaucherove stanice, a nalaz snižene aktivnosti enzima glukocerebrozidaze potvrdi dijagnozu. Genetskom se analizom ustanovi da je pacijentica homozigot za G377S mutaciju. Prema dosadašnjim spoznajama, samo je homozigotnost za D409H mutaciju povezivana s kardiovaskularnim oblikom GB, klinički tipom 3c. G377S mutacija, pronađena kod naše pacijentice, opisivana je dosad kao »blaga« mutacija, zbog nalaza da se kod homozigota javlja asimptomatski ili blagi oblik bolesti. Međutim, naša pacijentica, također homozigot za G377S mutaciju, ima uznapredovali oblik tipa 1 GB, s rijetkim zahvaćanjem aortnog zalistka, što je, prema našim saznanjima, još neopisana klinička slika uz ovu mutaciju. Ovaj slučaj još jednom potvrđuje utjecaj i drugih genetskih i/ili okolišnih faktora na kliničku prezentaciju Gaucherove bolesti.