

Persistent Massive Splenomegaly: Gaucher Disease Masquerading as Visceral Leishmaniasis

Chrysoula Perdikogianni^{1*}, Maria Moudatsaki¹, Maria Raissaki², Evangelia Dimitriou³, Marina Moraitou³ and Emmanouil Galanakis¹

¹Department of Paediatrics, University Hospital of Heraklion, Medical School University of Crete, Heraklion Crete, Greece

²Department of Radiology, University Hospital of Heraklion, Medical School University of Crete, Heraklion, Crete, Greece

³Department of Enzymology and Cellular Function, Institute of Child Health, Athens Greece

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***Corresponding author:** Chrysoula Perdikogianni, Assistant Professor of Paediatrics University Hospital of Heraklion Medical School University of Crete Heraklion Crete, Greece, Tel: +302810392290, Fax: +302810392827, E-mail: perdikogian@uoc.gr

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ABSTRACT

Gaucher Disease is an autosomal recessive lysosomal storage disease characterized by glucosylceramide deposition in cells of the macrophage-monocyte system due to deficiency of the activity of the lysosomal hydrolase β -glucocerebrosidase. We present a case of a 4.5-year-old boy initially diagnosed with visceral leishmaniasis. Diagnosis of Gaucher Disease type I was considered at a later stage, based on persistent massive splenomegaly, occasional bone pain and demonstration of bone involvement by magnetic resonance imaging. Diagnosis of Gaucher Disease was established following enzyme and genetic testing. A novel mutation of *GBA1* gene has been identified in our case. We discuss the unusual co-occurrence of Gaucher disease and visceral leishmaniasis and highlight the importance of early diagnosis of GD in cases of excessive splenomegaly when other causes have been excluded.

Keywords: Gaucher Disease, Visceral Leishmaniasis, Child; *GBA1* gene

Introduction

Gaucher Disease (GD) is the most common lysosomal storage disorder with an incidence estimated at around 1/40,000 to 1/60,000 births¹ that can reach 1/800 births in high-risk populations of certain origins^{1,2}. We present a case of a patient with GD in whom the diagnosis was challenging because massive splenomegaly was initially attributed to Visceral Leishmaniasis (VL). Consent has been received from the family.

Case Presentation

A 4.5-year-old boy was referred to the Paediatric Emergency Department due to splenomegaly, fatigue and low-grade fever for 2 days. The boy was born to non-consanguineous parents,

following a full-term normal pregnancy, was fully vaccinated for his age, and lives in a rural area. No history of traveling was reported. Personal medical history included surgery for cryptorchidism and was otherwise unremarkable. Family history included heterozygosity for beta-thalassemia in the paternal family.

The child's physical development was borderline normal, with weight and height at the lowest percentiles for age. Physical examination revealed pallor, a palpable non-tender spleen of 8 cm below the left costal margin and a 5 cm palpable liver below the right costal margin. Laboratory investigations showed pancytopenia with leucopenia (WBC 3200/ μ l), lymphocytopenia (700/ μ l), anemia (Hb 10 g/dl), thrombocytopenia (PLT 104000/

μl) with normal renal and hepatic function. Peripheral blood PCR was positive for *Leishmania infantum* and treatment with liposomal amphotericin-B was initiated. The fever subsided but anemia and excessive splenomegaly persisted (**Figure 1**).

Mantoux, viral markers, blood and urine cultures were negative. Chest x-ray, hemoglobin electrophoresis and coagulation assays were also found to be normal.

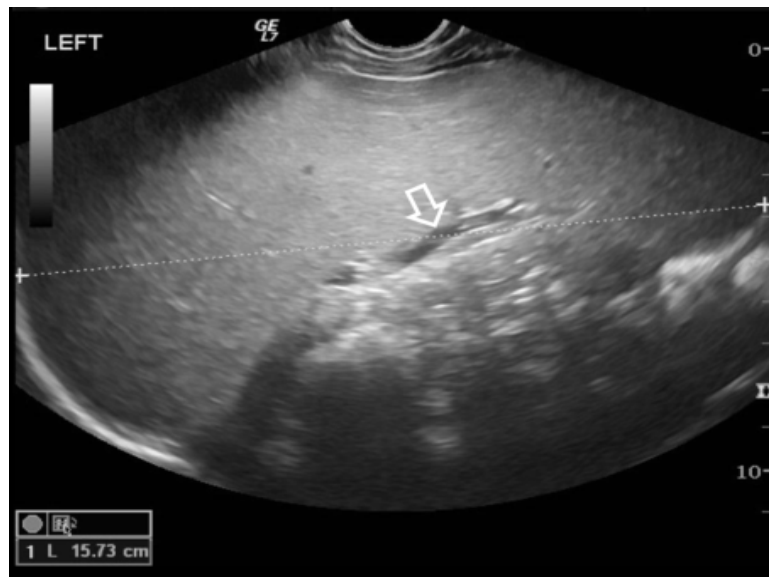


Figure 1: Abdominal Ultrasound scan. Longitudinal image through the left hypochondrium shows excessive splenomegaly. The spleen measures 15.7 cm (between cursors) with no focal lesions and normal diameter of splenic vein (arrow).

Subsequent bone marrow microscopic examination revealed amastigotes of *Leishmania* and PCR was found positive for *Leishmania* 40 days following initial diagnosis. Two more courses of liposomal amphotericin B and a course of glucantime and fluconazole were administered for supposed resistant leishmaniasis in the context of a possible immune defect affecting intracellular pathogens' killing. Analysis of lymphocyte subpopulations in peripheral blood, IL-2/INF- γ axis, vaccine-induced antibody titers, flow cytometry and karyotype of bone marrow cells were all normal.

The patient remained afebrile with occasional bone pain. All serological tests for anti-leishmania antibodies and subsequent peripheral blood PCR were negative for *Leishmania*.

Elevated lyso-GL-1 (309.7, cut-off value <14.0 ng/mL), elevated plasma chitotriosidase activity (4476, normal value 0-150 nmoles/ml/h) and low β -glucocerebrosidase activity in

leukocytes (1.3, normal value 6-23 nmoles/mg protein/h) were supportive of Gaucher disease. An abdominal MRI confirmed isolated excessive splenomegaly without significant intra-abdominal lymphadenopathy (**Figure 2**). Lower femoral MRI revealed abnormal bone marrow signal for age with mild Erlenmeyer deformity, suggestive of Gaucher disease (**Figure 3**).

Genetic testing by PCR followed by automated sequencing confirmed the diagnosis of Gaucher disease type 1. Two mutations in the *GBA1* gene were detected: N370S, already described as pathogenic for GD, and D283N, a novel mutation not previously identified. The pathogenicity of the latter was confirmed by in silico tools. Family members' molecular analysis revealed heterozygosity for the D283N allele in the father and for the N370S allele in the mother. Enzyme replacement therapy with imiglucerase was initiated.



Figure 2: Abdominal MRI scan, Tw-w sequence, coronal plane. The spleen (S) is excessively large, extending to the left lower abdomen. There is also isolated mild lymphadenopathy (arrow) at the upper limits of normal for this location (1 cm short axis).



Figure 3: MRI scan of femurs, coronal plane. A. STIR sequence, shows intermediate signal intensity at proximal (arrow) and distal (*) femoral metaphyses which would be expected only for proximal metaphyses at this age. B. T1-w sequence shows areas of hypointense bone marrow. There is minimal widening of distal femoral metaphyses consistent of Erlenmeyer flask deformity (arrowheads). C. Chemical shift opposed-phase image, confirms signal drop at areas of normal red bone marrow (arrow) and lack of signal drop at infiltrated metaphyses (*) and at areas of fatty marrow at epiphyses (e) and diaphyses (d).

The boy's clinical condition gradually improved with significant decrease in the spleen size, absence of bone pain and hemoglobin levels at the lower normal percentiles for his age.

Discussion

Gaucher Disease is a rare autosomal recessive disorder and it is caused by mutations in the *GBA1* gene, located on the long arm of chromosome 1 (1q21), resulting in deficiency of the lysosomal hydrolase β -glucocerebrosidase activity¹. More than 500 mutations have been described in GD³. One of the 2 mutations in our patient, the D283N, is a novel one, while the N370S mutation is a frequent one. In a recent 35-year cohort study the estimated incidence of GD in Greece is 2.8/100,000 births, and N370S was one of the most frequently identified mutations accounting for 49.2% of the alleles³. This mutation is considered neuroprotective and is found only in patients with type 1 GD³. The D283N mutation has not been previously described and is one of the 7 novel mutations in the cohort of GD patients diagnosed in Greece³. Its pathogenicity, along with other novel mutations according to the same study, was evaluated with different, well-established predictive tools (Polyphen2, SIFT and Mutation Taster) and was classified as disease-causing³.

The clinical manifestations of GD are highly variable. Phenotypic diversity has been described even in the same genotypic group. GD is subdivided into three phenotypes. GD type 1 is the most prevalent subtype in the Western world accounting for ~90% of patients worldwide, 85.1% in the Greek cohort^{3,4}.

Our case is a rare occurrence of GD masquerading as visceral leishmaniasis (VL). Mediterranean basin remains an endemic area for *Leishmania Donovanii*, *Leishmania infantum* and *Leishmania* and an increasing incidence of VL has been reported in Crete⁵. To our knowledge, two additional cases of VL associated to GD have been published^{6,7}. Whether infection by *Leishmania* may trigger the clinical manifestation of GD or co-occurrence is a coincidence cannot be defined. This possible new association supports the need for further studies on GD pathophysiology.

Imaging is important in supporting the diagnosis and for the follow-up of children with GD⁸. Ultrasonography and abdominal MRI are the preferred methods. Abnormal bone marrow involvement in MRI in GD is a prominent finding,

almost uniformly noted in type 1 patients, involving the spine, femurs, tibias, and less commonly the humeri⁸.

We report this unusual case to raise awareness of the possibility of co-existence of GD and VL in the pediatric population, especially in leishmaniasis endemic areas where unusual presentations can occur. Diagnosis of GD was confirmed with genetic testing that revealed a novel, disease-causing mutation of the *GBA1* gene. GD should be suspected in persisting massive splenomegaly, especially in combination with hematological abnormalities and bone pain given that other causes are excluded. Imaging has its role in the diagnosis of GD. The availability of a lifelong treatment with favorable outcome in type 1 Gaucher disease mandates early recognition and appropriate treatment.

Summary-Learning points

Gaucher Disease should be suspected in persisting massive splenomegaly, especially in combination with hematological abnormalities and bone pain given that other causes are excluded.

The diagnosis of visceral leishmaniasis especially in endemic areas must not prevent from testing for Gaucher Disease in the appropriate clinical setting.

Imaging has its role in the diagnosis of Gaucher Disease

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References

1. Grabowski GA. Phenotype, diagnosis, and treatment of Gaucher's disease. *The Lancet* 2008;372:1263-1271.
2. Grabowski GA. Gaucher disease: Gene frequencies and genotype/phenotype correlations. *Genet Test* 1997;1(1):5-12.
3. Dimitriou E, Moraitou M, Cozar M, et al. Gaucher disease: Biochemical and molecular findings in 141 patients diagnosed in Greece. *Mol Genet Metab Rep* 2020;24:100614.

4. Charrow J, Andersson HC, Kaplan P, et al. The Gaucher registry: Demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch Intern Med* 2000;160:2835-2843.
5. Antoniou M, Messaritakis I, Christodoulou V, et al. Increasing incidence of zoonotic visceral leishmaniasis in Crete, Greece. *Emerg Infect Dis* 2009;15:932-934.
6. Gupta SS, Mondal P, Basu N, Mallick M. Gaucher's disease with uncommon presentations. *J Cytol* 2009;26:117-119.
7. Zoulati G, Maiga R, Elkhiyat M, Amrani M. Visceral Leishmaniasis and Gaucher disease: Case report of an unusual association. *Ann Case Rep* 2020;5:520.
8. Degnan AJ, Ho-Fung VM, Ahrens-Nicklas RC, et al. Imaging of non-neuronopathic Gaucher disease: Recent advances in quantitative imaging and comprehensive assessment of disease involvement. *Insights Imaging* 2019;10(1):70.