



(CASE REPORT)



Place of cytology in the diagnosis of Gaucher disease: About a case

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Abstract

Gaucher disease is an autosomal recessive genetic disease caused by a deficiency in a lysosomal enzyme, beta glucocerebrosidase. This disease is characterized by deposits of glucosylceramide in liver, spleen and bone marrow cells. The presentation of MG is very heterogeneous, ranging from the asymptomatic form to the lethal form. Neurological forms (types 2 and 3) are present in only 5% of patients with MG and are less frequent than non-neurological forms (type 1). The formal diagnosis is established by measuring the activity of beta glucocerebrosidase in circulating leukocytes. The accumulation of glucosylceramide in macrophages gives them a characteristic morphological appearance and they are called "Gaucher cells" thus making it possible to evoke the diagnosis. We describe through this observation the practical side of hematological cytology in the diagnostic orientation of this rare and often misunderstood pathology.

Keywords: Gaucher Disease; Splenomegaly; Pancytopenia; Left-Handed Cells; Beta Glucocerebrosidase

1. Introduction

Constitutional storage diseases are rare diseases, often linked to a gene mutation affecting the activity of one of the lysosome enzymes or activating proteins. Depending on the deficient enzyme, there will be an accumulation of sphingolipids, mucopolysaccharides or both in certain cells of the organism, in particular macrophage cells [1]. Gaucher's disease, identified in 1882 by Philippe Gaucher [2], is the most frequent lysosomal enzymopathy. It is a rare, autosomal recessive genetic disorder, due to a deficiency in the activity of a lysosomal enzyme, glucocerebrosidase, which hydrolyzes glucosylceramide into ceramide and glucose. The accumulation of glucosylceramide in macrophages gives them a characteristic morphological appearance, and they are called "Gaucher cells" allowing the diagnosis to be evoked [3].

We report the case of a 2-year-old infant, in whom the diagnosis of left-handedness was suggested thanks to the particular cytological aspect and subsequently confirmed by the enzymatic assay.

2. Case presentation

A 2-year-old infant from a non-consanguineous marriage, the last of three siblings, was referred for consultation for failure to thrive in a context of impaired general condition. He had no particular pathological history, neither medical nor surgical. No similar case in the family has been reported. On clinical examination, there was splenomegaly at two fingerbreadths with hepatomegaly, without lymphadenopathy. The patient had no neurological signs.

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Complete blood count showed microcytic hypochromic anemia at 7.3 g/l of hemoglobin, leukopenia at 3510/mm³ with neutropenia at 1035/mm³ and thrombocytopenia at 56000/mm³. The blood smear showed the presence of a few red cells in rolls, which may be related to inflammation. Biochemical assessment showed hyperferritinemia at 800 µg/L, serum protein electrophoresis identified polyclonal hypergammaglobulinemia. Faced with pancytopenia and splenomegaly of unclear etiology, a spinal tap was performed. Bone marrow smears stained with MGG, objectified a marrow very rich in cells, with the presence of very many large macrophages with monolobed nuclei with dense chromatin and low basophilic cytoplasm having a laminated "crumpled paper" appearance (Figures 1 and 2). It is a characteristic morphological aspect of Gaucher cells, thus making it possible to evoke the diagnosis of Gaucher's disease. This diagnosis was subsequently confirmed by an enzymatic assay which objectified an enzymatic activity of glucocerebrosidase at 20% of the normal value.

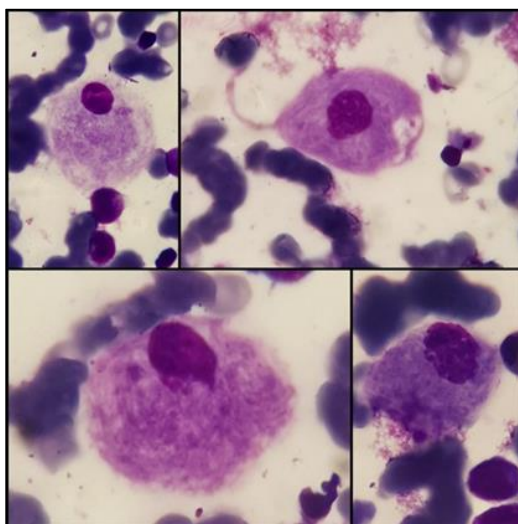


Figure 1 Cytological aspects of left-handed cells on bone marrow smear (MGG × 1000)

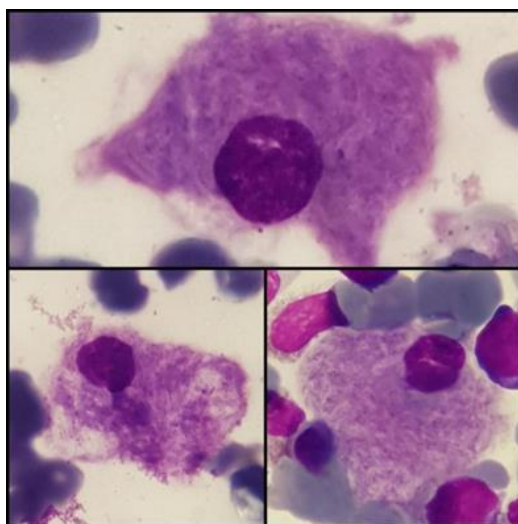


Figure 2 Cytological aspects of left-handed cells on bone marrow smear (MGG × 1000)

3. Discussion

Gaucher disease (GD) is the most common lysosomal storage disease. It is a genetic disease with autosomal recessive transmission due to an enzymatic deficiency in glucocerebrosidase (GCCase) or exceptionally in its activator, saposin C [1]. Its average prevalence is around 1/60,000 in the general population [2].

Mutations in the GBA1 gene cause decreased GCCase activity. Its substrate, glucosylceramide, then accumulates in the lysosomes of cells of the reticuloendothelial system, in particular macrophages, leading to their transformation into

Gaucher cells [3]. They infiltrate the hepatic and splenic tissue, the bone marrow, but also other organs resulting in organomegaly, bone weakening, by promoting trabecular resorption and the appearance of areas of cortical thinning and bone lysis. Macrophage accumulation of glucosylceramide generates an activated macrophage phenotype, with a cytokine profile conferring a systemic character to GD. In GD patients, lysosomal enzymes including chitotriosidase, cytokines, and chemokines (including IL-1 beta, IL-6, TNF alpha, IL-10, IL-18 and CCL18) are found at high blood levels [4]. CCL 18 and chitotriosidase appear to be directly secreted by the Gaucher cell and are both biomarkers of MG activity and progression [3]. The accumulated glucosylceramide is also the substrate for a different pathway, transforming it into sphingosine [5]. This increase in sphingosine could explain central nervous system damage in patients with a neurological phenotype, because Gaucher cells do not accumulate in the brain [6].

The presentation of GD is very heterogeneous, ranging from the asymptomatic form to the lethal form. Three phenotypes and a fetal form are classically distinguished:

- Type 1 GD is the most common (95% of cases), with a median age at first symptoms of 15 years and a median age at diagnosis of 22 years [7]. Its clinical presentation is variable, ranging from forms with few or no symptoms throughout their life, to very severe forms. Splenomegaly is one of the main clinical signs, present in more than 90% of patients. It may be associated with hypersplenism, an essential mechanism leading to cytopenias dominated by thrombocytopenia. The latter, when significant, is responsible for bleeding and anemia [8]. It is often associated with hepatomegaly, present in 60 to 80% of cases. Bone involvement responsible for painful crises and chronic pain is common (80%). Preferred locations are the spine, pelvis and lower limbs [5].
- GD type 3 accounts for less than 5% of cases. As with type 1 MG, the clinical expression of type 3 MG is very heterogeneous, with onset generally before the age of 2 years. Some more slowly progressive cases are diagnosed in adulthood. In addition to type 1 damage, there are also neurological signs, ranging from moderate damage with supranuclear horizontal ophthalmoplegia, to more disabling forms: cerebellar syndrome and progressive encephalopathy [9]. Neurological signs may occur several years before other clinical manifestations.
- Type 2 GD is rarer, and generally begins in infants aged 3 to 6 months with hepatosplenomegaly and neurological involvement. The association of neck stiffness or opisthotonos, bulbar signs and horizontal oculomotor paralysis is suggestive [10]. The evolution is unfavorable, with the appearance of psychomotor retardation, myoclonic epilepsy, as well as laryngeal spasms, leading to apnea. Death occurs before the 3rd year of life, with a median survival of 11.7 months (2–25 months), in particular due to infiltrative pulmonary involvement or central apnea.
- The fetal form (anasarca fetalis, ichthyosis, arthrogryposis, etc.) of GD is exceptional, responsible for death in utero or just after birth [11].

As for the biological assessment, thrombocytopenia is frequent (90% of cases) and of variable degree. Anemia is present in 56% of cases, often moderate, with a hemoglobin level rarely below 9 g/dL. Leukopenia can be observed, but is rare [12]. Hemostasis disturbances can be observed, with a prolongation of prothrombin time (PT) and/or partial thromboplastin time + activator (TCA). Plasma protein electrophoresis and immunofixation show polyclonal hypergammaglobulinemia in 25-91% of cases [13].

Due to the usual modes of revelation of type 1 GD, the myelogram is frequently performed in the presence of cytopenia or in the presence of the association of cytopenia and splenomegaly. It orients the diagnosis by highlighting the Gaucher cells: these are cells with a grayish and striated cytoplasm, with numerous colorless, fibrillar, curvilinear and tangled inclusions, giving the cell an onion skin appearance [14]. It is this cytological aspect found in our patient that made it possible to evoke the diagnosis of GD. The diagnosis of GD should be confirmed by measuring glucocerebrosidase activity in leukocytes, mononuclear cells or fibroblasts. Demonstration of an enzyme deficiency (10 to 30% of normal activity) is the only definitive test [14]. The analysis of the glucocerebrosidase gene (GBA1) located on chromosome 1 must then be carried out in order to identify the pathogenic variants of the 2 alleles. Currently, more than 300 mutations have been described. Some are very common, such as the p.Asn409Ser mutation (old nomenclature: p.N370S), and p.Leu483Pro (old nomenclature: p.L444P) [15]. Genotype can provide information about prognosis as well as phenotype. Currently, the most useful biomarkers in monitoring patients with GD are chitotriosidase, CCL18, glucosylsphingosine and ferritin. Conventional treatments were purely symptomatic (transfusions, analgesics, total or partial splenectomy). These treatments have now been replaced by administration of modified placental glucocerebrosidase (alglucerase or Cérézyme®) and especially since November 1996 of recombinant glucocerebrosidase (imiglucerase or Cérézyme®).

4. Conclusion

The rarity of Gaucher disease and its great variability in clinical presentations lead to diagnostic delays. When diagnosed and treated in time, complications can be avoided due to the effectiveness of available treatments allowing a better

quality of life. There is a strong need for better knowledge of its symptoms by doctors, in order to reduce irreversible complications. A simple message to remember is to think of GD in the face of the association of thrombocytopenia with splenomegaly of unclear etiology, regardless of age and clinical history. It is in this context that the diagnosis was made in our patient.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Statement of informed consent

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

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