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Gaucher disease: an underdiagnosed pathology in the Eastern Moroccan population

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ABSTRACT

Gaucher disease (GD) is a lysosomal storage disease. It corresponds to a congenital deficit in β-glucocerebrosidase. This pathology should be considered in the presence of unexplained splenomegaly, with or without signs of haemorrhage, skeletal manifestations or hepatomegaly.

The diagnosis is based on the measurement of the β-glucocerebrosidase activity but the preanalytical process should be respected in order to avoid the under-diagnosis of this disorder and the delay of its management. We report two cases of Gaucher disease collected at Mohammed VI University Hospital and Al Farabi regional hospital in Oujda. We have emphasized the need for a reference center for overload diseases.

INTRODUCTION

Gaucher disease is a lysosomal storage disease, the transmission is autosomal recessive.

It follows a mutation in the GBA gene coding for a lysosomal enzyme: β-glucocerebrosidase, which hydrolyzes glucosylcerebroside (glycosyl ceramide) into ceramide (cerebroside) and glucose.

There are three subtypes of the disease. The most common is type 1, known as the non-neuropathic form. Pancytopenia, hepatosplenomegaly and bone lesions occur as a result of glucocerebroside accumulation in the liver, lung, spleen and bone marrow in these patients.

The two other phenotypes include a severe neurological involvement in type 2 that affects infants and is deadly; in type 3 the neurological involvement is less severe and is also associated with features of types 1 [1].

CASE 1

A 37-year-old male, was admitted to the internal medicine department of the regional hospital of Oujda for the management of anemic syndrome with splenomegaly. The clinical examination found mucocutaneous paleness with voluminous splenomegaly, the rest of the clinical examination is without particularity. Laboratory tests revealed bicytopenia with normochromic anemia (Hb at 6.3 g/dL) and thrombocytopenia at 140 G/L , leukocytes at 5 G/L . Liver and renal functions were normal, the serologies of hepatitis B, hepatitis C and HIV were negative. The abdominal ultrasound showed a huge splenomegaly, a normal-size liver without signs of portal hypertension. The myelogram showed a marrow, with cellular abundance a hyperplasia of the erythroblastic line with the presence of many Gaucher cells. X-ray of the skull, thoracolumbar spine, and pelvis were normal. The chest CT scan revealed the presence of alveolar syndrome with a small left pleural effusion. The abdominal computed tomography showed significant heterogeneous splenomegaly with compression of adjacent organs and a small fluid effusion in the Douglas cul-de-sac.

Subsequently, β-glucocerebrosidase [7.5 U/L (reference range: 6.5 - 10.5 U/L)], Chitotriosidase [2980 nmol/h/mL (normal value <120 nmol/h/mL)] and ferritin [833 µg/L (reference range: males 20-200 µg/L)] measurement was done.

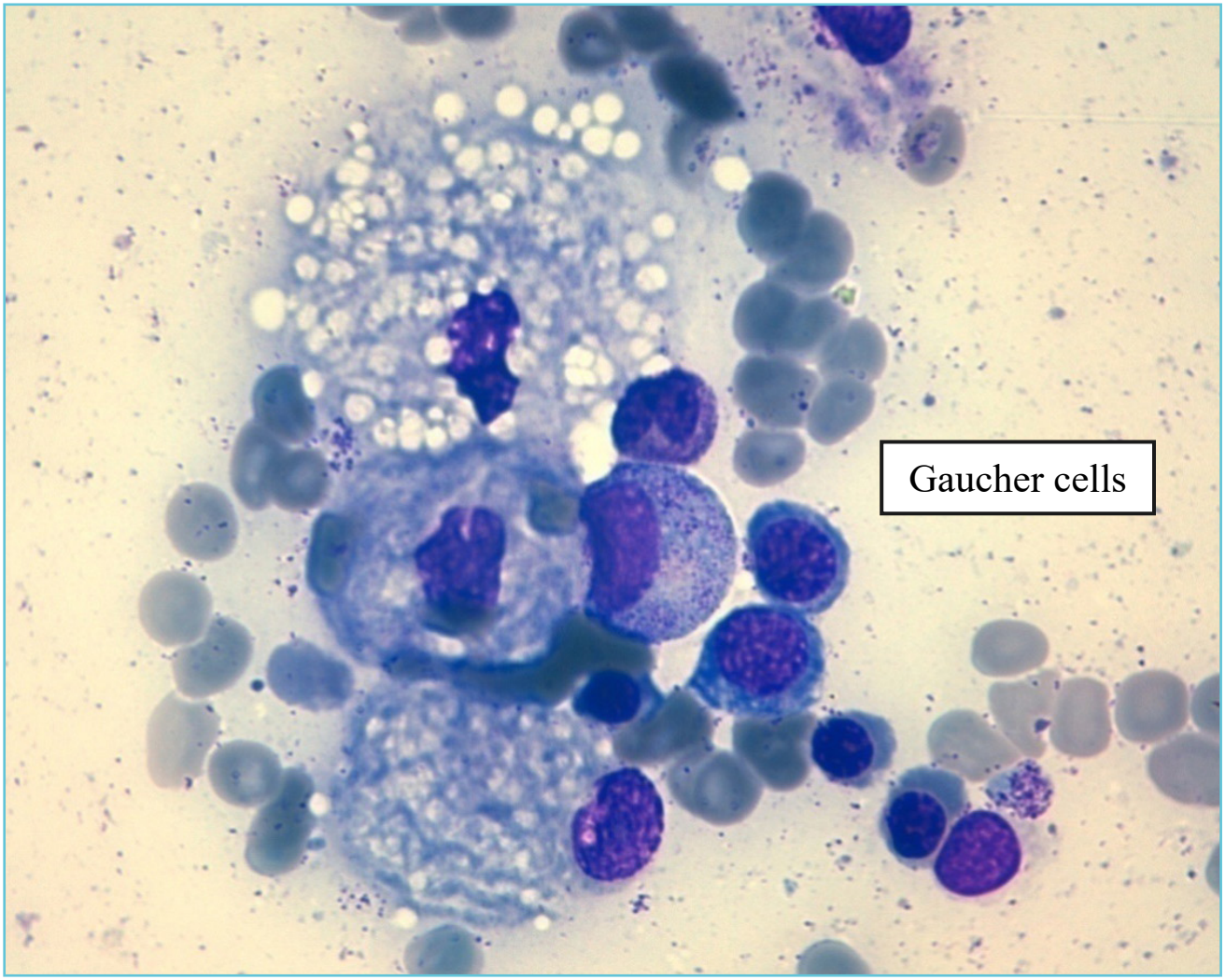
The diagnosis of Gaucher disease type 1 was based on clinico-biological data, the cytological aspect of the marrow and the results of the biomarkers, without enzymatic evidence. The patient was splenectomized; and the pathological examination of the spleen showed sub capsular splenic infarction with presence of Gaucher cells.

CASE 2

A 26-year-old male, with no significant medical history was admitted to the Department of Internal Medicine of Mohammed VI University Hospital for the management of splenomegaly with anemic and haemorrhagic syndrome. The history of the disease dated back to 6 months before admission by the progressive appearance of anemic syndrome constituted by cutaneous pallor, asthenia and fatigability, associated with a hemorrhagic syndrome demarked by episodes of repeated epistaxis and diffuses bone pain. The symptomatology constituted hepatic, colic and left hypochondrial pain.

Clinical examination found a cutaneomucous pallor with splenomegaly exceeding the white line of the abdomen, without hepatomegaly or other associated signs. Blood test found a hemoglobin level at 12 g/dL (reticulocyte: 1.54%), platelet count at 40 G/L and leucocytes at 3940/ µL. The serologies of hepatitis A, B and C and leishmaniasis were negative. The myelogram showed the presence of many Gaucher cells (Figure 1).

Figure 1 Gaucher cells on medullary smear



The histological aspect of the bone marrow biopsy (BMB) suggesting a storage disease (in particular Gaucher disease). Abdominal CT showed portal hypertension with huge heterogeneous splenomegaly including areas of necrosis. Standard radiography was normal and osteo-densitometry displayed osteopenia.

The result of the β-glucocerebrosidase assay was 6 U/L (reference range: 6.5 - 10.5 U/L). But given that the bone marrow aspiration showed typical cytological image of Gaucher disease; a new measurement was requested which showed a deficit at 1.6 µkat/kg (reference range: 4.2 to 8.1 µkat/kg). The levels of chitotriosidase, hexosaminadae and ferritin were 3380 nmol/h/mL, 1500 nmol/h/mL and 690 µg/L, respectively. The diagnosis of Gaucher disease type 1 was retained. While waiting for enzymatic substitution treatment, the patient was treated by corticosteroids.

Beta-glucosidase activity was determined in the lymphocytes by the fluorimetric method using a synthetic substrate 4-methylumbelliferyl-β-glucopyranoside. Taurocholic acid was used as an activator at pH 5.5. In parallel, the control activity of N-acetyl-β-D-glucosaminidase was performed using the fluorogenic substrate 4-methyl umbelliferyl-N-acetyl-β-D-glucopyranoside to validate the quality of the specimen.

DISCUSSION

The diagnosis of metabolic disorders could be difficult and time consuming. Pancytopenia, organomegaly (especially splenomegaly) and bone symptomatology are the most typical signs of type 1 Gaucher disease, the most common form [2]. Neurological signs are typical for types 2 and 3 of the disease [3].

For both patients, the diagnosis was made in adulthood, at an average age of 32 years. These data are consistent with previously published results [4]. However, Charrow and al [5] report, in their study of the international register containing the records of 1698 patients, an average age of diagnosis of 17.4 years.

It should be noted, however, that in this study, 50% of patients were diagnosed before the age of ten, because of severe symptoms, requiring special medical care and thus an earlier empiric diagnosis was possible [6].

When the clinical presentation is insufficient and in the absence of signs of orientation in the family, Gaucher disease remains a diagnostic challenge. It is often not included in the differential diagnosis of thrombocytopenia, and can present a challenge even to an experienced hematologist [7].

However, the presence of the most common initial symptoms, splenomegaly, cytopenia with cytological and biochemical exploration can lead to the diagnosis [8].

Demonstration of reduced enzymatic activity of β-glucocerebrosidase is required for definitive diagnosis of GD. However, our patients in whom enzymatic assays was carried out displayed subnormal values of the GBA activity.

By analyzing the clinical and biological contradiction, we emphasize the importance of the preanalytical process, especially the one pertaining to the maximum sample transportation time of 48 hours.

We reiterate the importance of standardizing diagnostic methods and setting up specialized laboratories. Given the critical role of the preanalytical phase, screening tests using dried blood spots can be an optimal and alternative solution to the enzymatic activity assay on blood specimens.

Under-diagnosis of Gaucher disease in developing countries is explained among other factors by the lack of referral centers specialized in the diagnosis and management of this pathology.

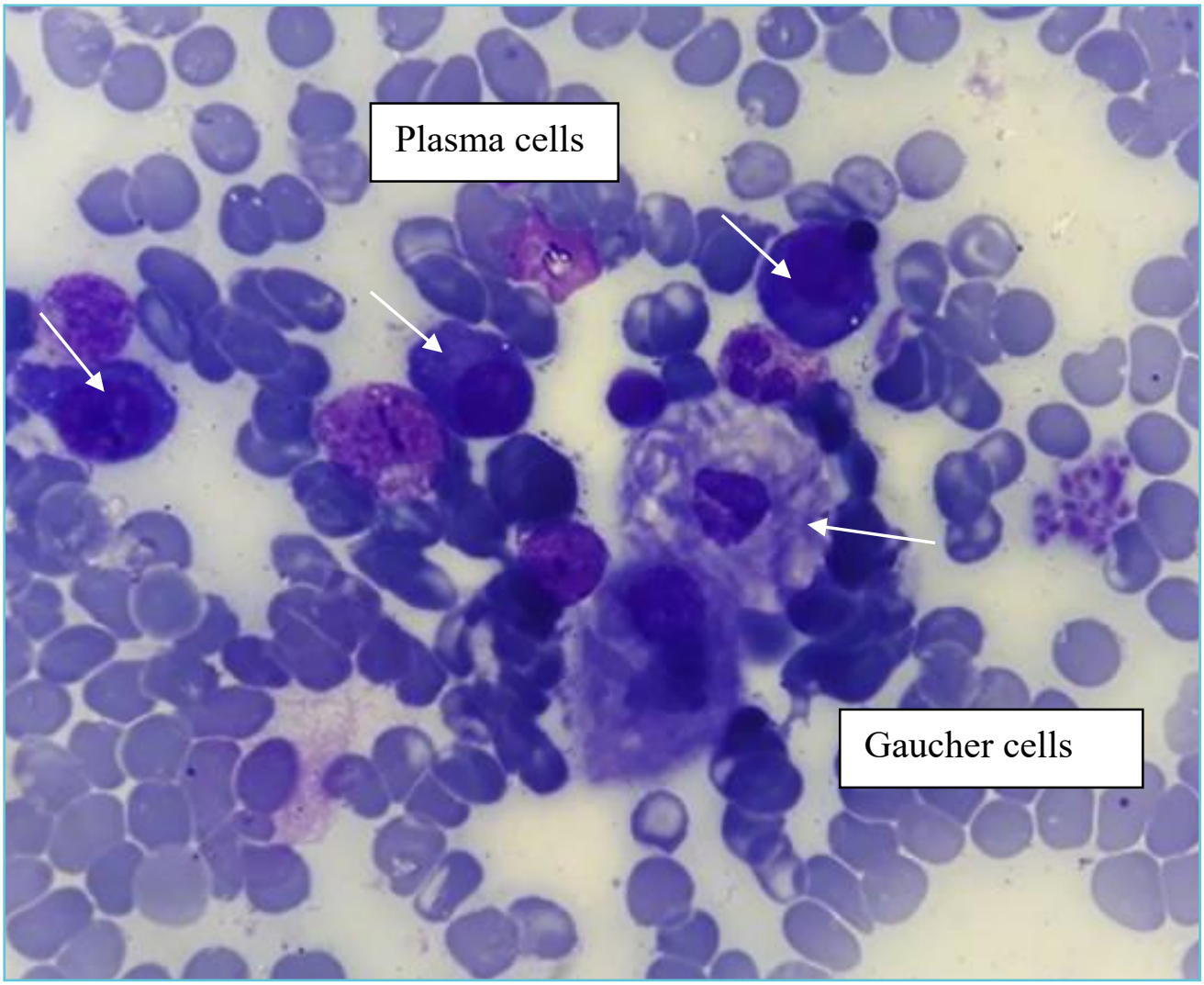
Apart from the pre-analytical and analytical problems, the case with normal β-glucocerebrosidase activity can be explained either by the mutation of its activator “Saposin C” (PSAP), or it is a heterozygosity resulting in a borderline enzyme result (knowing that heterozygotes have 15 to 20% of the normal enzymatic activity of β-Glucocerebrosidase) [9].

Chitotriosidase is a sensitive biological marker. This is a good diagnostic guide and is especially useful for monitoring the course of the disease [10]. It is also elevated during sarcoidosis, leishmaniasis and other storage diseases. Although, its rate is moderate compared to the values found in the GD [11]. The assay of chitotriosidase activity was performed in our two patients and in both cases showed high activity.

The evolution of Gaucher disease could be complicated by the appearance of haematological diseases (malignant or not) [6,11], or solid cancers [6]. We also identified a patient aged 59 years, diagnosed with type 1 Gaucher disease, who developed multiple myeloma with Ig G kappa monoclonality after 23 years, unfortunately due to lack of medical documents we did not report his case (Figure 2).

The therapeutic management has been revolutionized by enzyme replacement therapy. Because of its high cost, access to this therapy remains limited in developing countries. The clinical trials of gene therapy have given very promising prospects.

Figure 2 Medullary smear showing Gaucher cells with plasma cells in a patient with Gaucher disease complicated by multiple myeloma



CONCLUSION

Gaucher disease is not exceptional in our country. Type 1 is the most common. Given the frequency of consangu neous marriages, we insist on the importance of a regional registry and the need for the establishment of a reference center for Gaucher disease and metabolic diseases in general, to allow early diagnosis and adequate care.

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