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Contribution of Radiology in the Diagnosis of Gaucher Disease: A Case Report

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Abstract **Case Report**

Gaucher disease is a rare, autosomal recessive genetic disorder; caused by a deficiency in the activity of the lysosomal enzyme glucocerebrosidase which is responsable for the degradation of glucosylceramide. The enzyme substrate, accumulates in the body, predominantly in the liver, spleen, and bone marrow causing hematological abnormalities, splenohepatomegaly, and skeletal disorders. The Gaucher disease has been classified into 3 phenotypes, distinguished on the basis of the absence or presence and severity of central nervous system damage, type I with no neurological involvement is the most common. The diagnosis is suspected when there is a combination of clinical, biological and radiological evidence and is confirmed by an enzyme assay showing deficient glucocerebrosidase enzyme. MRI is the most appropriate examination to visualize the different aspects of gaucher diseas. Gaucher disease is the first lysosomal disease to benefit from enzyme replacement therapy; ERT was effective in reducing the liver and spleen size, the bone symptoms, and improving blood counts.

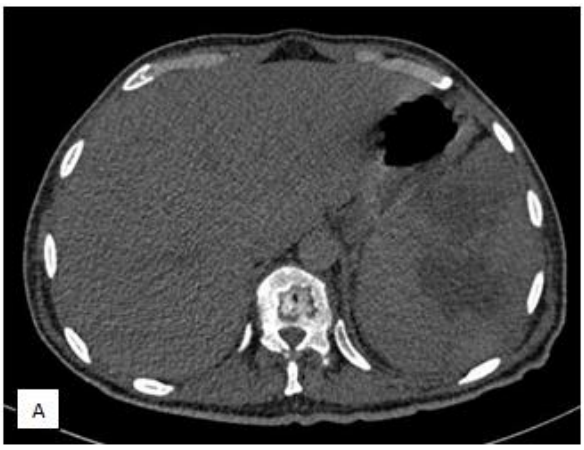
Keywords: Gaucher disease; Glucocerebrosidase; bone infarcts; hepatosplenomegaly; enzyme replacement therapy.

INTRODUCTION

Gaucher disease is a rare genetic disorder of autosomal recessive inheritance due to acid b-glucosidase deficiency. It leads to pathological accumulation of its main substrate, glucosylceramide mainly in the liver, spleen and bone marrow [1]. Gaucher disease has significant phenotypic variability and three major types are classically distinguished on the basis of the absence or presence and severity of central nervous system damage [1]. Bone manifestations of the disease are common (70-100% of cases) and are the major cause of morbidity and disability [2].

CASE REPORT

The patient H.M is 50 years old, transferred to the infectious disease department for major hyperleukocytosis with eosinophilic predominance. The history goes back to 3 months of his admission, by the progressive installation of an abdominal distension with feeling of heaviness of the HCD, The patient was referred to the haematology department where he underwent several examinations including: CBC, myelogram, blood smear, karyotype in search of haemopathy and myeloproliferative work-up, all of which came back negative, as well as the search for clonal or para-clonal eosinophilia by immunophenotyping, which also came back negative. The patient underwent an abdominal ultrasound scan, which revealed hepatosplenomegaly, and a complementary CT scan was requested, which revealed an enlarged liver with a hepatic arrow at 25 cm, nodular splenomegaly and a tortuous splenic artery with parietal calcifications, associated with lumbar adenopathies.



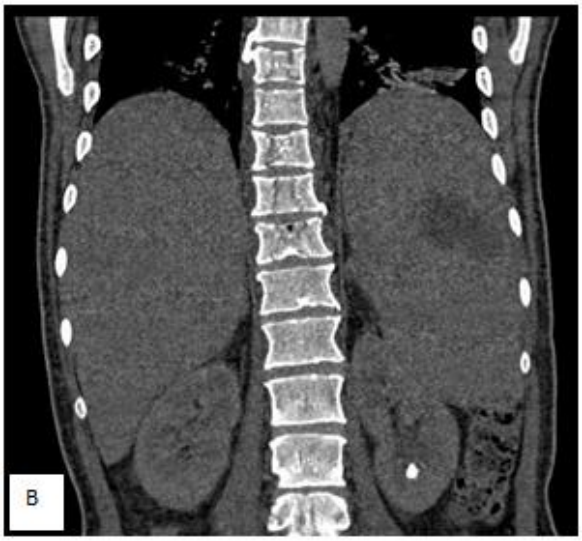
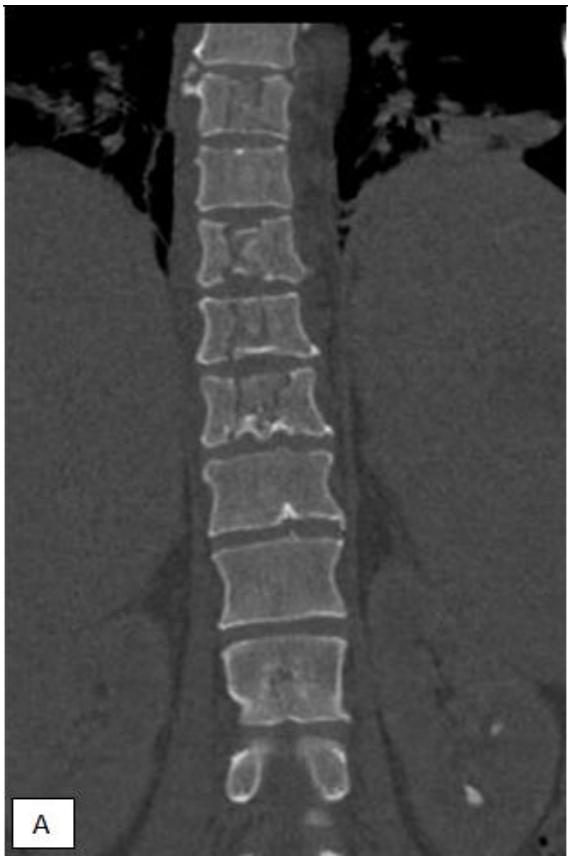


Fig-1: Axial (A) and coronal (B), CT scan reconstructions; abdominal window: showing an enlarged liver with a hepatic arrow at 25 cm, and nodular splenomegaly



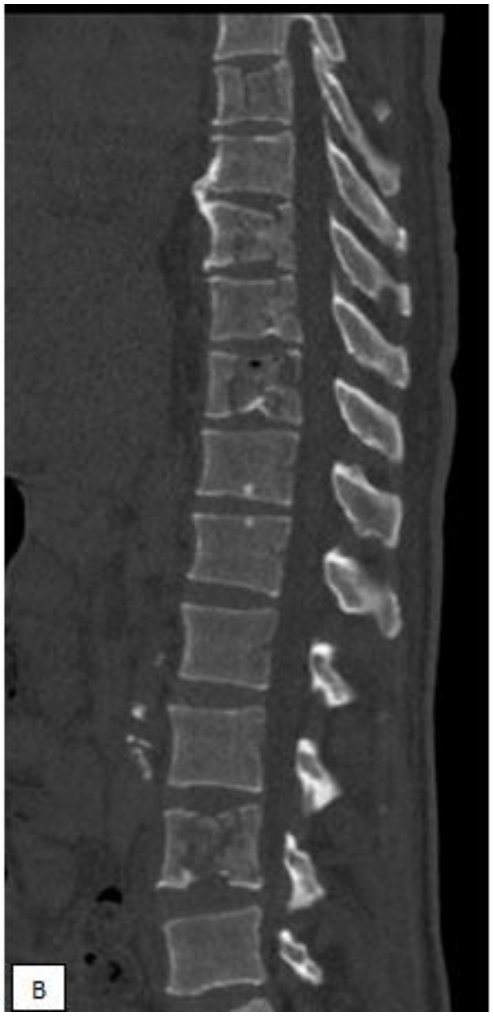


Fig-2: Coronal (A), and sagittal (B) CT scan reconstruction; bone window: Geographic osteolytic lesions of dorso-lombar vertebrae, related to bone infarcts

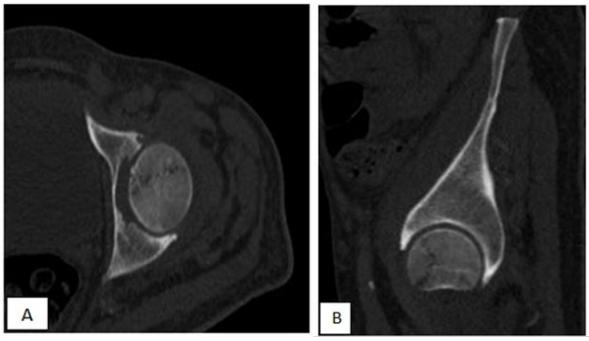


Fig-3: Axial (A) and Coronal (B), CT scan reconstructions, bone window: Geographic osteolytic lesions of left femoral epiphysis related to bone infarcts

The patient underwent a liver biopsy in order to distinguish between Gaucher disease, an infectious, parasitic or hematological origin. The histopathologic result showed the presence of intrahepatocytic macrophagic cells compatible with mild to moderate hepatocyte overload lesions. The clinical and

radiological aspects associated with the histopathological results made it possible to retain the diagnosis of Gaucher disease.

DISCUSSION

Gaucher results from deficiency of a lysosomal enzyme glucocerebrosidase (also known as acid beta-glucosidase, GBA). The enzyme acts on the substrate glucocerebroside which is a component of the cell membrane. In the normal lysosome, protein saposin C presents glucocerebroside to GBA which activates the enzyme. This enzyme is responsible for hydrolytic breakdown of glucosylceramide to glucose and ceramide. Deficiency of the enzyme leads to accumulation of glucosylceramide and other glycolipids in the lysosomes of macrophages, primarily in the spleen, liver, bone marrow, brain, osteoclasts and less often the lungs, skin, kidneys, conjunctivae and heart [3].

Gaucher disease (GD) is the most prevalent lysosomal storage disorder worldwide [4], it is pan-ethnic with a prevalence classically estimated at 1 in 50,000, but is much higher in Ashkenazi Jews. Because some patients remain asymptomatic and undiagnosed, this prevalence is likely to be underestimated [1].

Gaucher disease has been classified into 3 phenotypes

- Type 1: Non-neuronopathic form of GD, concerns 95% of patients, as is the case of our patient. The clinical spectrum varies widely, ranging from complete absence of symptoms to severe organ involvement with disability and occasionally a fatal outcome. The course is slowly progressive. Symptoms include hematological abnormalities (thrombocytopenia, anemia and sometimes neutropenia), organ involvement (splenohepatomegaly), and skeletal disorders (pain, bone infarction, osteonecrosis...), By far, patients with GD1 do not have neurological involvement. Hepatic and splenic infarction may be observed, manifesting with acute pseudo-surgical abdominal pain. Up to 40% of GD1 patients have a focal lesion in the liver and/or spleen. A gaucheroma is the most likely diagnosis, but a hepatocellular carcinoma or a lymphoma of the spleen is other possible diagnoses. Gaucheromas have varied imaging characteristics and it is therefore difficult to distinguish a gaucheroma from another lesion [5].
- Type 2: Acute neuronopathic GD, this is both the most severe and the rarest form of Gaucher disease, it concerns children and associates an attack of the brain stem from the first year of life, rapidly evolving, and an organomegaly. The triad consisting of rigidity of the neck and trunk (opisthotonus), bulbar signs (particularly severe swallowing disorders), and oculomotor paralysis (or bilateral fixed strabismus) is very suggestive of the disease [6].
- Type 3: The chronic neuronopathic form, affects the child or adolescent and is characterized by a milder neurological involvement compared to that seen in GD2, in addition to the visceral and bone marrow involvement as in GD1 [7] three subtypes of GD3 have been described.
- Type 3a is characterized by progressive dementia, ataxia, and myoclonus.
- Type 3b has extensive visceral and bone involvement with CNS involvement limited to supranuclear gaze palsy (saccade initiation failure, with compensatory head thrusting), either alone or a more slow progressive neurodegenerative syndrome.
- Type 3c (cardiovascular form) is rare and characterized by supranuclear gaze palsy, corneal opacity, and cardiovascular calcification, with little visceral disease. It is a unique phenotype commonly found in the Mediterranean population [3].

Gaucher disease should be considered in any child or adult who presents with a splenohepatomegaly with cytopenia which is unexplained and should not be dismissed as a malarial spleen or tropical splenomegaly [3].

Osteoarticular manifestations are often inaugural; it does not always correlate with the systemic severity of the disease, but is the major cause of morbidity and disability associated with Gaucher disease [2].

Diagnosis of Gaucher disease is made on the basis of clinical history, physical examination, laboratory test, imaging results, and confirmed by a blood test showing deficient glucocerebrosidase enzyme and genetic mutation studies when the diagnosis is doubtful. History of consanguinity and family history of suspected or proven GD will support the diagnosis [3].

Abdominal magnetic resonance imaging (MRI) is the most appropriate examination to assess dimensions (organ volume) and morphology of the liver and spleen. The spleen may have nodules suggestive of lymphoma. When MRI is not available or in cases of uncontrollable claustrophobia, abdominal ultrasound may be used instead. Bone magnetic resonance imaging (MRI) is the test of choice for assessing the effects of Gaucher disease on bone.

Bone marrow infiltration is predominant in the proximal and distal extremities. T1-weighted sequences are recommended to detect and quantify bone marrow infiltration, whereas T2-weighted sequences are used to detect complications such as bone infarcts. Hypointense signals are usually seen in T1-weighted sequences,

reflecting the replacement of normal bone marrow fat by Gaucher cells.

Whole-body MRI reduces examination time, especially for disease monitoring. Standard bone radiographs were previously used to detect femoral deformity with widening of the lower leg; this deformity may be accompanied by thinning of the cortical bone. Initial evaluation should include radiologic imaging of the pelvis, spine, femurs, tibias, and humeri. The use of multiple radiographs is no longer standard practice given the limited knowledge they provide and the risk of radiation exposure.

Bone scintigraphy is sometimes used to localize bone lesions throughout the skeleton (especially the spine, femur, pelvis, or tibia) when MRI is not available; it allows the detection of clinically asymptomatic lesions or sequelae of bone infarction in atypical sites (jaws, hands, or feet) [8].

The differential diagnosis of GD is mainly of disease associated with splenomegaly and cytopenia. These would include hematological malignancies and storage disorders like Niemann–Pick. Most of these disorders have characteristic clinical, radiographic, or laboratory features that distinguish them from GD [9].

The goal of therapy is to reduce the accumulation of the toxic substrate glucocerebroside and other glycolipids to prevent progressive disease with debilitating complications. This could be achieved by either by Enzyme replacement Therapy (ERT) where the deficient enzyme is administered in its modified form to metabolize the substrate or inhibition of substrate synthesis by inhibiting the enzyme–glucosylceramide synthase through substrate reduction therapy [3] Enzyme replacement therapy should be given to all children with type 1 Gaucher disease. In adults, the need for treatment should be evaluated based on symptom severity [10].

CONCLUSION

Gaucher disease is a rare genetic disease, in our patient we suspected this diagnosis in front of the association of the clinical and radiological presentation which objectified the association of a nodular splenomegaly, a hepatomegaly and a bone infarction; the confirmation was made following the histological study of a hepatic biopsy. The absence of the neurological damage allowed classifying it as a type I.

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