Gaucher Disease revealed by bone biopsy in a child with recurrent osteomyelitis

Maladie de Gaucher révélée par une biopsie osseuse chez un enfant avec osteomyélite récurrente

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ABSTRACT

Gaucher disease is the most common lysosomal storage diseases. Clinical symptoms are due to the accumulation of glucosylceramide in the reticuloendothelial cells of liver, spleen, and bone marrow. Bone involvement in type 1 Gaucher disease is common. It ranges from simple asymptomatic osteopenia to more serious condition such as osteomyelitis, which could be observed at the onset, or in the course of the disease. Bone marrow biopsy to detect Gaucher cells has not been longer recommended, supplied by biochemical and molecular techniques which are more specific and less invasive. We report the case of a child with recurrent osteomyelitis diagnosed with Gaucher disease after a bone marrow biopsy and confirmed by enzymatic dosage.

Key words : Gaucher disease; osteomyelitis; bone biopsy.

RÉSUMÉ

La maladie de Gaucher est la maladie lysosomiale la plus courante. Les symptômes cliniques sont dus à l'accumulation de glucosylcéramide dans les cellules réticulo-endothéliales du foie, de la rate et de la moelle osseuse. L'atteinte osseuse dans la maladie de Gaucher de type 1 est fréquente. Elle va de la simple ostéopénie asymptomatique à une affection plus grave comme l'ostéomyélite, qui peut être observée au début ou au cours de la maladie. La biopsie de la moelle osseuse pour détecter les cellules de Gaucher n'est plus recommandée car remplacée par des techniques biochimiques et moléculaires plus spécifiques et moins invasives. Nous rapportons l'observation d'un enfant se présentant avec une ostéomyélite récurrente. La maladie de Gaucher a été évoquée sur le résultat de la biopsie de la moelle osseuse et confirmée par le dosage enzymatique.

Mots clés : Maladie de Gaucher ; Ostéomyélite ; biopsie osseuse.

INTRODUCTION

Gaucher disease (GD) is the most common lysosomal storage diseases. It is quite uncommon in the general population, affecting 1 of approximately 100 000 newborns, with the exception of Ashkenazi Jews, in whom its incidence can be up to 450-fold higher [1].Clinical symptoms are due to the accumulation of glucosylceramide in the reticuloendothelial cells of liver, spleen, and bone marrow (BM). Bone marrow biopsy to detect Gaucher cells (GCs) has not been longer recommended [2], supplied by biochemical and molecular techniques which are more specific and less invasive.Bone involvement in type 1 Gaucher (GD1) disease is common. It ranges from simple asymptomatic osteopenia to more serious condition such as osteomyelitis. Osteomyelitis could be observed at the onset or in the course of the disease; however its bacterial origin is still difficult to diagnose because of clinical similarity to aseptic osteomyelitis, which is more common.We report the case of a child with recurrent osteomyelitis diagnosed with Gaucher disease after a bone marrow biopsy and confirmed by enzymatic dosage.

CASE REPORT

A 6 -year-old girl was admitted in the department of orthopedic surgery with a pain in the inferior extremity of the right femur associated with a fever. Four months ago, she had been treated for acute osteomyelitis by antibiotics for 21 days with surgical aspiration of a sub-periosteal abscess in the left femur.At admission, physical examination, revealed fever at 39° c, a good general state, swelling, induration and tenderness over distal right femur. Passive movements of hip and knee joint were free, except for limitation of terminal flexion at the knee join.

She has difficulty bearing weight and walks with a slight limp.Abdominal examination showed splenomegaly of 15 cm below the costal margin without hepatomegaly or lymphadenopathy.
Neurological exam was normal. On biological findings Hb : 8.6 g/dl, WBC : 4500/mm3 (PNN 1700/mm3) and platlets counts : 118.000/mm3. The C-reactive protein rate was 100 mg/L.Femur X-Ray did not show any significant abnormalities. The diagnosis was osteomyelitis of the right femur with suspected underlined hematological disease. Bacteriological samples from blood cultures and bone marrow aspiration were negative. The MRI showed diffuse infiltration of bone marrow (Figure 1 and 2).

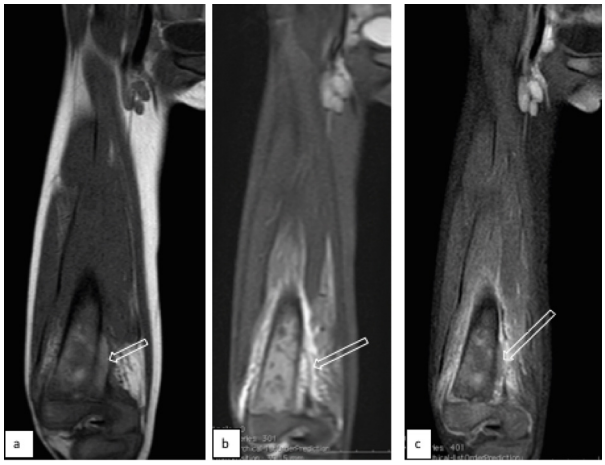

Figure 1 (a, b, c) : Coronal oblique T1 (a), weighted images of the le lower third of right femur showing heterogeneous signal of the right femoral distal metaphyseal bone marrow. Coronal STIR (b) demonstrating multiple bone marrow edema low signal areas surrounded by infiltrative marrow edema which extends to adjacent soft tissues areas.

Coronal T1 fat suppressed weighted image after gadolinium injection (c) showing contrast uptake around the bone marrow low signal areas and in the soft tissues around the femur. Note sub periosteal collection at the postero medial aspect of distal right femur (large white arrow) displaying high signal in T1 (a) and STIR (b) weighted images with low signal intensity in T1 fat suppressed weighted image after IV contrast administration (c).

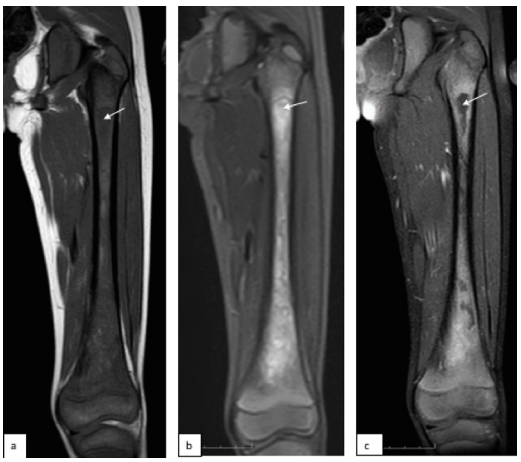

Figure 2 (a, b, c) : Coronal T1 (a), weighted images of the le left thigh showing diffuse heterogeneous signal of the left femoral bone marrow. Coronal STIR (b) and coronal T1 fat suppressed after gadolinium injection (c) weighted images revealing multiple low signal areas (thin white arrow) surrounded by a serpiginous high signal rim characteristic of a bone infarct.

A bone marrow biopsy demonstrated scattered large cells with abundant slightly fibnillar or granular cytoplasm and eccentric nucleir which had the appearance of histiocytes filled with fat, consistent with Gaucher cells (Figure 3).

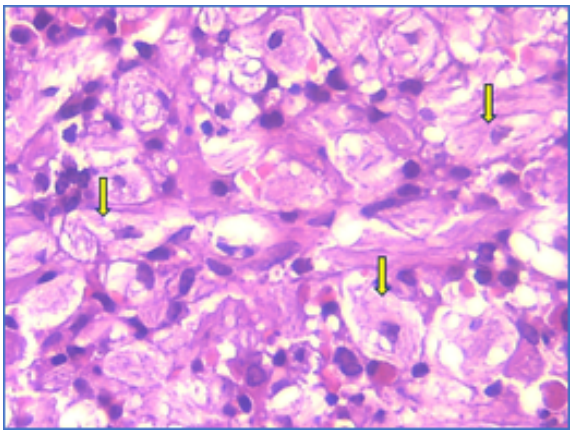

Figure 3 : Bone marrow biopsy : medullary spaces are largely infiltrated by histiocytes with eccentric nuclei and abundant cytoplasm of laminated, "crinkled paper" appearance.

Assessment for beta glucosidase enzyme activity test was compatible with type 1 Gaucher disease (GD1), revealing 0.55 µKat/Kg protein which is much lower than the reference limit of 4 µKat/Kg protein.The child was referred to tertiary center of metabolic diseases for further management. Enzyme replacement therapy (ERT) was indicated but was not initiated because of its high cost.

DISCUSSION

Our reported case is a rare revelation circumstance of Gaucher disease. The diagnosis was made by identifying the Gaucher cells in a bone marrow biopsy. Gaucher cells are typically very large cells with a diame-

ter of 20-80 µm, round or polyhedral with a small, usually eccentrically placed nuclei and cytoplasm with characteristic wrinkles or striations [3].In some developing countries, where diagnosis of Gaucher disease could not easily confirmed by biochemical or genetic methods, the diagnosis is based on clinical examination, bone marrow and liver biopsy [4]. In a questionnaire-based-survey assessing hematology–oncology specialists, more than half among them indicated that bone marrow biopsy and bone marrow aspirate are considered the method of diagnosis [5].However, histo-pathological diagnosis is considered to be not accurate, since many storage cells or "pseudo-Gaucher cells" could be confused with Gaucher cells on the marrow examination. These are found in several hematological conditions including chronic myelogenous leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, Hodgkin lymphoma, multiple myeloma, idiopathic thrombocytopenia, and hemoglobinopathies [6]. Moreover, the result of biopsy cannot be considered definite, since at the onset of disease, bone marrow infiltration could be delayed. Consequently, not finding Gaucher cells in biopsy does not exclude Gaucher disease in case of splenomegaly. Even though the clinical utility of BM study in GD is controversial, Gaucher cells detected in BM have been the most important diagnostic indicator in our patient. In fact, the child had bone pain, splenomegaly, pancytopenia and MRI suggesting hematological disorders or storage disease. Thus, it would be very useful to practice a BM biopsy to rule out other diagnosis. The gold standard for diagnosing Gaucher disease is still measurement of glucocerebrosidase enzyme activity in leucocytes or skin fibroblasts [7]. In the present case, beta glucosidase enzymes activity assessed in leucocytes was very low, confirmed expected hsitopathological diagnosis. Usually, Bone marrow examination may be indicated in Gaucher diseases if the splenomegaly does not regress on treatment or patient develops enlarged lymph nodes or symptoms suggesting lymphoma [8]. Clinical manifestations of GD1 are due to deficiency of glucocerebrosidase, which hydrolyzes glucosylceramide to glucose and ceramide [9]. Accumulation of glucosylceramide in splenic macrophages and in the Kupffer cells of the liver is associated with enlargement of these organs; the resulting hypersplenism produces progressive anemia and thrombocytopenia. In bone marrow, the diaphyseal region of the femur and humerus are initially affected [10].

The progressive accumulation of glucocerebrosides within the bone marrow cavity leads to a progressive centrifugal expansion of the red bone marrow. There is a possible alteration in local vascularity and pressures leading to localized thrombosis or infarction by Gaucher cells, and inducing macrophage activation. This could explain bone manifestations such as bone crises, avascular necrosis, bone infarcts, and localized cortical thinning. Bone involvement in GD is known to be frequent : according to literature, it occurs in approximately 75% of GD1 patients [11]. Acute hematogenous osteomyelitis is uncommon feature of GD1. Rossi and al [10] reported 11 patients onset with bone symptoms, among them six had major skeletal event, three had bone pain, one bone crisis and only one had a misdiagnosis of osteomyelitis of the hip. However, febrile bone crisis, which is difficult to differentiate from acute osteomyelitis, occurs frequently as onset of the disease.

It is considered as aseptic osteomyelitis or pseudo-osteomyelitis [12]. Clinical differentiation between aseptic and acute hematogenous osteomyelitis is difficult or even impossible at the time of onset [8]. Imaging and biological findings (WBC and CRP) are almost always not conclusive proof in both situations. However, positive bacteriological culture is a strong argument supporting acute hematogenous osteomyelitis. Bacteriological analysis should include bone samples, which have a higher diagnostic yield in comparison with blood cultures [13].Thus, the 2 conditions must be differentiated on the basis of clinical findings, imaging studies and sample cultures that should not, in any case, delayed anti-microbial prescription.In our case, negative blood cultures and aspirates made pyogenic osteomyelitis less probable in the second hospitalization.ERT has revolutionized the treatment of Gaucher disease and has now become the standard of care [14]. Our patient is a candidate to ERT since, she had hematological involvement. However, because of its expensive cost, bone marrow transplantation can be an interesting alternative in some cases [15].

CONCLUSION

In the present case, GCs detected in BM leads to the correct diagnosis of GD. This emphasize the clinical utility of BM study for GD, especially in cases with reccurent osteomylitis with prominent hematologic abnormalities. This would lead to an effective treatment with enzyme replacement, which reduces as far as possible the visceral and skeletal complications.

RÉFÉRENCES

[1] Zimran A, Gelbart T, Westwood B, et al. High frequency of the Gaucher disease mutation at nucleotide 1226 among Ashkenazi Jews. Am J Hum Genet. 1991;49:855–859.

[2] Mistry PK, Cappellini MD, Lukina E, et al. A reappraisal of Gaucher disease-diagnosis and disease management algorithms. Am J Hematol. 2011;86:110–115.

[3] Gözdaşoğlu S. Gaucher Disease and Gaucher Cells. Turk J Hematol. 2015;32(2):187-188.

[4] Jain VV, Yelwatkar S. Unusual presentation of adult Gaucher's disease: A long and difficult road to diagnosis.Indian J Endocr Metab 2011;15:224-6.

[5] Mistry PK, Sadan S, Yang R, et al. Consequences of diagnostic delays in type I Gaucher disease: the need for greater awareness among hema-

tologists-oncologists and an opportunity for early diagnosis and intervention. Am. J. Hematol.2007;82:697–701.

[6] Sokołowska B, Skomra D, Czartoryska B, et al. Gaucher disease diagnosed after bone marrow trephine biopsy - a report of two cases. Folia Histochem Cytobiol. 2011;49(2):352-6.

[7] Ho MW, Seck J, Schmidt D, et al. Adult Gaucher's disease: kindred studies and demonstration of a deficiency of acid beta-glucosidase in cultured fibroblasts. Am J Hum Genet. 1972;24:37–45.

[8] Mikosch P, Hughes D. An overview on bone manifestations in Gaucher disease. Wien Med Wochenschr. 2010 Dec;160(23-24) :609-24.

[9] Grabowski GA, Horowitz M. Gaucher's disease : molecular, genetic and enzymological aspects. Baillie`res Clin Haematol. 1997;10:635–656.

[10] Rossi L, Zulian F, Stirnemann J, et al. Bone involvement as presenting sign of pediatric-onset Gaucher disease. Joint Bone Spine. 2011 Jan;78(1):70-4.

[11] Germain DP. Gaucher's disease: a paradigm for interventional genetics. Clin Genet. 2004 Feb;65(2):77-86.

[12] Bilchik TR, Heyman S. Skeletal scintigraphy of pseudo-osteomyelitis in Gaucher's disease. Two case reports and a review of the literature. Clin Nucl Med, 17: 279–282, 1992.

[13] Schubiner H, Letourneau M, Murray DL. Pyogenic osteomyelitis versus pseudo-osteomyelitis in Gaucher's disease. Report of a case and review of the literature. Clin Pediatr (Phila). 1981 Oct;20(10):667-9.

[14] Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency–macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med. 1991;324:1464–1470.

[15] Ringden O, Groth CG, Erikson A, et al. Ten years' experience of bone marrow transplantation for Gaucher disease. Transplantation. 1995;59:864–870.