Gaucher disease – bone involvement

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Abstract

Gaucher disease (GD) is a rare genetic disease caused by the enzymatic deficiency of beta-glucocerebrosidase. This will lead to the accumulation of sphingolipids in various organs, such as liver, spleen, bone marrow. Bone involvement is frequent in Gaucher patients, leading to bone pain, necrosis and even fractures or growth deficiency in children, with painful surgeries and progressively decreasing quality of life. The early treatment initiation in symptomatic patients is very important in lowering bone complications frequency and improve general status. We present the case of a young patient whose first manifestation of GD was a bone cystic lesion and the clinical evolution until treatment.

Keywords: Gaucher disease, bone, Gaucheroma

Gaucher disease (GD) is a rare autosomal recessive disorder caused by the enzymatic deficiency of glucocerebrosidase. This will lead to the substrate accumulation (glucosylceramide) in the macrophages. The most frequently affected organs are the liver and spleen (leading to hepato- and splenomegaly), bone marrow (leading to hematological manifestations like anemia and low platelets count), and less frequently, lungs (leading to pulmonary hypertension) and the brain (there is a correlation with Parkinson disease) [1].

There are 3 types of GD. Type 1, non-neuropathic, is the most frequent form in adults, up to 95% of the total cases. As the clinical evolution is chronic, there is more likely for a patient with type 1 GD to experience bone complications of GD. The type 2 (acute neuropathic) and type 3 (neuropathic form) are characterized by neurological symptoms as major clinical aspects of GD, with low life expectancy in type 2 but with better outcome in type 3.

Bone involvement in GD includes pain or bone crises, avascular necrosis (AVN), even fractures. Bone pain and kyphosis are considered major signs in GD, by the latest consensus [2]. Increasing the mobility is also a management goal, including reduced bone pain (if not related to irreversible causes like AVN or fractures), reducing bone involvement (using Dusseldorf scoring system in MRI evaluations), increasing bone density (using DEXA scan if possible at periodical evaluations) in adults, or attain ideal peak skeletal mass or normalize growth in children, as short time goals. As osteoporosis is more frequent in GD patients, long term goals include, besides lessen pain and avoid or decrease antalgic medication usage, reducing osteopenia or osteopororis status evaluated by DEXA scan, which aim to increase general mobility [3]. Osteocytes also suffer in GD, with affected osteoblastic activity and high osteoclastic activity as a possible effect of glucocerobrosidase on enhancing bone resorption and osteoclasts transformation from monocytes [4].

Reduced bone mineral density will appear in the early years and. if not treated, it can increase the risk of pathological bone fractures. Bone marrow is affected by GD trough infiltration with substrate that will accumulate freely in the absence of enzymatic elimination. The mineralized component is affected as well, with cortical thinning, lytic lesions and fractures due to decrease resistance but it might be involved

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also in extended AVN or other osteonecrosis related lesions, fearsome and painful complications of GD [5]. Modeling and remodeling are affected, with sphingolipids accumulation in the bone, substrate which will become bioactive. Erlenmeyer flask deformity of the femur is easily recognizable for an experienced radiologist's eye. It is the result of the metaphyseal enlargement of the bone. The Dusseldorf score (performed in MRI examination), especially in adults, along with Bone Marrow Burden and Vertebra to disk Ratio are able to quantify bone infiltration and affected area expansion, making them powerful tools in monitoring the treatment response. Depending on the score/scale used, it can take between 2 to 7 years of treatment for the maximum response [6].

Kyphosis and spine deformity can occur in young patients leading to growth deficiency. The early treatment in symptomatic young patients is mandatory to avoid such complications. As bone manifestations can occur at any age in GD patients, causing possible irreversible complications, the correct management and proper treatment is necessary. Up to 94 percent of type 1 GD patients have bone involvement considering Gaucher registry, if highly investigated [7].

Osteolytic lesions are frequent radiological findings. The "worm eaten" aspect of the bone due to progressive lesions is another diagnostic and management tool in GD patient. Bone crisis, characterized as severe bone pains, is the consequence of limited bone infarctions and can be a precursor of future osteonecrosis and consecutive fractures. Along with progressive substrate accumulation, the cortical bone is affected, but rarely the Gaucher cell can be found extreaosseus, except after severe cortical involvement or orthopedic maneuver [8].

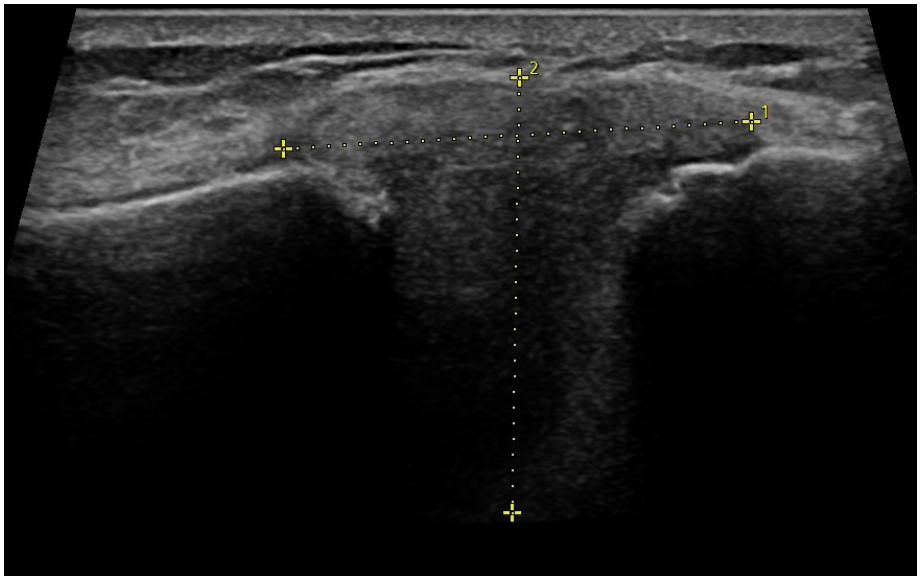

Figure 1. Gaucheroma of the bone.

Frequently, before the era of easy diagnosis tools such as dried blood sample, the avascular necrosis and osteolytic lesions were treated without considering GD as a main cause. The repeated orthopedic surgeries led to severe pain and lowered the quality of life of many young patients in the absence of any specific treatment.

Case report

We report the case of a young female patient, 11 years old, with a BMI of 16, who was admitted for the persistence of right shoulder pain, before the enzymatic treatment being available worldwide. The radiographic diagnosis was humeral cyst and the patient was referred to orthopedic department. The humeral cyst is considered one of the most frequent benign bone tumors in young patients, with up to 3% in imaging findings, even asymptomatic. The treatment options were the surgical removal or the glucocorticoid infiltration [9]. The choice at the time was the surgical removal, with histopathological test showing histiocytic proliferation, a storage disease being considered. After returning to the pediatric department for further investigations, other osteolytic lesions were found in the skull, along with "honeycomb appearance" of the lung, so this step diagnosis was a Langerhans cell histiocytosis and the patient was referred to the pediatric oncology department The reevaluation at the admittance showed no thrombocytopenia, slightly under normal hemoglobin levels (11.5 g/dL), but the clinical examination

found a slightly enlarged spleen and liver. Therefore the reevaluation of the case, with first clinical appearance, histopathological examination and later the biological findings, led to the Gaucher disease diagnosis. Biological markers were determined, and low beta-glucocerebrosidase levels were found (0.1 nmol/prot gr, NV >2.5 nmol/prot gr) and high chitotriosidase levels (12.500 nmol/h/mL; NV <60 nmol/h/mL). DNA testing showed a N370 S mutation, and Type 1 GD was the final diagnosis. As no specific treatment was available at the time, the patient was followed by the pediatrician. Low platelets level appeared in early puberty, with various degrees of anemia, until the enzyme replacement therapy became available and the patient received the treatment. The anemia and platelets levels normalized in the first 2 years, with hepato-splenomegaly progressive regression.

We presented a GD pediatric patient in which the bone involvement was the first clinical appearance, before the hematological or other clinical significantly changes. The importance of clinical evaluation and extensive biological evaluation in any patient having bone involvement (tumor-like lesions, osteolytic or necrosis lesions of the bone) is mandatory , as easy diagnosis tools are available (dried blood samples) and a wide access to genetic centers for DNA sampling.

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