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Research paper

Gorham–Stout disease of the proximal fibula treated with radiotherapy and zoledronic acid

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ABSTRACT

Gorham–Stout disease is a rare disease characterized by anarchic lymphovascular proliferation causing resorption of bone sometimes leading to disastrous complications. Bone tissue is progressively replaced by angiomatic and lymphangiomatic tissue and finally by fibrous tissue. This disease is known to be ubiquitous and of complex etiology.

We present a case of Gorham–Stout disease of the proximal fibula invading the proximal tibia and soft tissues of the popliteal space that was successfully treated with radiotherapy and zoledronic acid.

1. Introduction

Gorham–Stout Disease (GSD), also known as 'massive osteolysis' and 'vanishing bone disease', is a rare bone condition characterized by spontaneous, idiopathic, and progressive proliferation of thin-walled vascular and lymphatic vessels replacing bone and marrow space by fibrous connective tissue. It leads to bone destruction which may sometimes be followed by new bone production [1]. In 1838 Jackson described the first case of a patient with a "boneless arm" [2]. Clinical and anatomopathological features were described by Gorham and Stout in 1955. They showed that this disease leads to progressive massive osteolysis by invasion of bone by lymphangiomatic tissue [3]. GSD mostly occurs in young adults; mean age is 25 years. Male and female are equally affected, without inheritance pattern or race predilection [4]. Clinical symptoms vary based on the location of bone involvement. This disease is most often regional and may involve several bones around a joint. Evolution may differ from one patient to another, GSD can be benign with a tendency to self-limitation or even spontaneous regression but it can also be very disabling [3]. Known to be ubiquitous, it frequently affects the skull and maxillofacial bones, ribs, cervical vertebrae, shoulder and pelvic girdle bones [5,6]. The affected bone(s) weaken(s) progressively, and pain and spontaneous fractures are the most common clinical features besides swelling and progressive deformity of the affected extremity. When localized at a lower extremity, limb length discrepancy and axial deformation may lead to gait abnormalities and major limping can occur [7]. Depending on location, it may also lead to neurological complications and paralysis (in case of vertebrae involvement), respiratory insufficiency and sometimes to death [8].

X-rays commonly show a typical licked candy stick appearance, based on concentric bone resorption. Common blood tests are usually normal, but bone alkaline phosphatase (BAP) may be elevated if a fracture occurred [8]. GSD is a diagnosis of exclusion. Diseases responsible of bone osteolysis such as infections, inflammatory or endocrine disorders, intraosseous malignancies or metastases should be considered [1].

Radiographic and anatomopathological characteristics are used as pathognomonic features for the diagnosis of GSD [1]. Treatments include surgery, radiation and medical therapy. Surgery is reserved for severe cases, e.g. when pathological fractures need to be fixed or when en bloc resection is required. Reconstruction is achieved with bone grafts or alloplastic prostheses if instability occurs. Interventions are often quite invasive. Recurrence rate is close to 20% [1]. Radiotherapy is usually chosen in order to reverse the progression of the lymphangiomatosis and to treat lesions that are not surgically resectable, at least without major consequences. Post-operative radiotherapy is required when the lesion could not be resected in one piece [9]. There are no "Food and Drug Administration" (FDA) approved therapies for the treatment of GSD. Several drugs have nevertheless been tried, including bisphosphonates (etidronate, clodronate, pamidronate and zoledronic acid) [10–14], interferon alpha-2b [14,15], anti-VEGF-A antibody, bevacizumab, propranolol [16], low molecular weight heparin, steroids, vitamin D and calcitonin [17,18]. However the experience with these compounds, including bisphosphonates, is extremely limited. We found only one report of a patient treated with zoledronic acid [11]. On the opposite, the use of zoledronic acid,

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the most powerful bisphosphonate, has become an integral component of cancer treatment in patients with metastatic bone disease. The drugs markedly delay and decrease the occurrence of skeletal-related events [19].

Etiology and mechanism of bone resorption in GSD remain poorly understood [3,7,8,20]. In a recent review the potential role of endothelial cells, macrophages, osteoclasts and osteoblasts is discussed. Active lymphangiomatosis and haemangiomatosis may be triggered by secretion of VEGF through activation of receptors of lymphatic and blood endothelial cells. Patients presenting GSD have high VEGF-A and -C blood levels whereas anti-lymphagiogenic factors levels (VEGFR2, TGF-beta, IFN-gamma, etc.) are reported to be low, maybe contributing to uncontrolled growth of lymphatic vessels in the affected bones [21]. Osteoclastic activity may vary according to the phase of the disease. On the one hand, osteoclast differenciation is stimulated by macrophages, VEGF-A, -C, -D and IL-6. On the other hand, high levels of TNF-alpha (produced by macrophages) inhibit osteoblastogenesis and promote osteoclastogenesis. Inhibition of osteoprotegerin and enhanced production of RANKL contribute to stimulate bone resorption. Bone homeostasis appears to be unaffected in other parts of the skeleton [21–22].

Bone is in a constant state of remodeling. The functions of osteoblasts and osteoclasts are well balanced to maintain bone homeostasis [23]. Bone diseases such as bone metastases that alter this equilibrium in favor of osteoclasts can induce loss of structural integrity of the skeleton. In this situation osteoclasts resorb bone by secreting proteases that dissolve the matrix and acids that release bone mineral into the extracellular space. In GSD the situation is more complex because of replacement of the bone by a fibrous tissue [23].

Nevertheless, considering the existence of a high osteoclastic activity, use of combination of radiotherapy and bisphosponate has been tried in a few patients. Bisphosphonates have been chosen because of their anti-osteoclastic but also anti-angiogenic activities. Side effects of zoledronic acid are usually mild and, although renal function has to be checked before each infusion, the risk of osteonecrosis of the jaw is not negligible at high doses [23–24].

2. Case report

We report on a 28-year-old male without any past medical history. After a minor work accident (professional mechanic) he noticed significant pain in his left knee. The pain increased over time and a radiograph was taken. It showed minor bone resorption at the neck of the left proximal fibula (Fig. 1). The patient was treated by minor pain medications. Despite 6 months of symptomatic care, pain did not resolve and limping appeared. Another X-ray was taken that showed a concentric shrinkage of almost all proximal fibula, a typical “licked candy stick” appearance. This image led to the radiological presumption of bone tumor. Bone scan showed increased Technetium uptake in the left tibial plateau extending to both the left tibial tuberosity and the left proximal fibula (Fig. 2). Computed-tomography scanner (CT-scan) showed bone resorption in those areas. Around the tibial metaphysis there was an area of massive osteolysis that looked like a pathological fracture. Magnetic resonance imaging (MRI) emphasized involvement of the left fibula and tibia by exuberant disorganized vessels also invading soft tissue of the popliteal space (Fig. 3). Biopsy was taken and histology described a diffuse lymphangioma, showing irregular vascular channels lined by a single epithelial layer, which were embedded in a fibrous stroma also containing residual bone trabeculae (Fig. 4). Endothelial cells did not display any atypia. They expressed podoplanin (D240), which confirmed their lymphatic differentiation. Radiologic imaging combined with histopathology confirmed the diagnosis of Gorham–Stout disease.

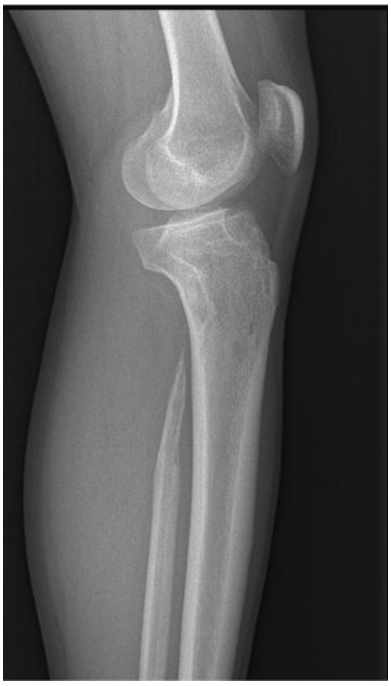

Fig. 1. X-ray shows complete disappearance of the proximal part of fibula and a typical licked candy stick appearance.

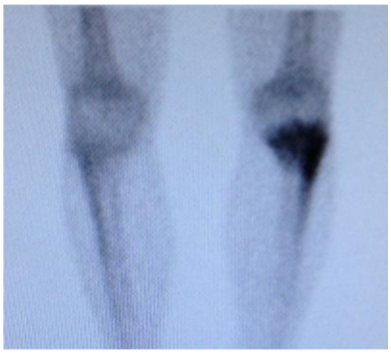

Fig. 2. Bone scan – hypercaptation of the left proximal fibula and tibial plateau.

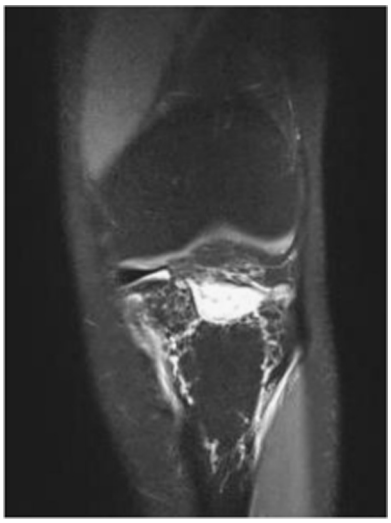

Fig. 3. MRI shows lymphangiomatosis infiltrating left popliteal space, fibula and tibia.