Gorham-Stout disease

Cinzia Aurilia[1], Gaia Palmini[1], Simone Donati[1], Irene Falsetti[1], Teresa Iantomasi[1], Maria Luisa Brandi[2]

[1] Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy
[2] F.I.R.M.O., Italian Foundation for the Research on Bone Disease, Florence, Italy

ABSTRACT

Gorham-Stout disease (GSD), also called vanishing bone disease, is an extremely rare skeletal disorder characterized by destruction of osseous matrix due to a massive process of osteolysis and proliferation of blood and lymph vessels, followed by a lack of deposition of new bone matrix. GSD can occur either at the level of a single bone or affect several bones, although the bones of the upper part of the skeletal system, especially at maxillofacial level, seem to be preferentially involved. To date, the diagnosis of GSD, mainly based on radiographic and histological analyses, is often made by excluding the presence of other diseases. Unfortunately, despite the several studies on GSD that have been carried out since its discovery, the pathogenesis of this disease is still unknown. Consequently, the therapies currently used are mainly aimed at keeping the disease under control, trying to avoid its progression, but they are not decisive, and this is in fact due to the lack of knowledge of its pathogenetic and pathophysiological bases.

This concise review aims to provide a brief overview of the state of the art of current research regarding the etiopathogenesis of GSD and the discovery and development of new and different diagnostic and therapeutic methods.

KEYWORDS

GSD, lymph vessel, blood vessel, bone cells

General overview

Gorham-Stout disease (GSD) is an extremely rare bone disease, described in only 350 patients worldwide. It is characterized by massive active osteolysis, which appears to be due to a conspicuous proliferation of both lymphatic and blood vessels [1,2].

This syndrome was first reported by J.B.S. Jackson in 1838, but it was L.W. Gorham and A.P. Stout who, in 1955, described its main clinical signs (i.e., osteolysis and lymphangiomatosis) [3]. No race, age, or gender preference was observed, although the prevalence of GSD appears to be higher in adult men [2]. Furthermore, since no familial inheritance was described, GSD has been defined as "non-hereditary single-center osteolysis", or as type IV of osteolysis according to the classification of Hardegger *et al*. [4].

Clinical signs

Even though all bones can be affected by GSD, the upper ones seem to be the most affected. In fact, the osteolysis primarily involves the skull, clavicles, ribs, vertebrae, and pelvic bones. Although most cases present monostotic disease, there are cases in which GSD appears as a polyostotic form [1].

Although the disease course is still not entirely clear, P.M. Johnson and J.G. McClure divided GSD progression into two stages:

a) an early intraosseous stage, characterized by multiple intramedullary and subcortical radiolucencies and osteoporosis, and
b) a later extraosseous stage, characterized by rupture of the cortex and complete bone resorption [5].

Since all bones in the body can be affected by the disease, the clinical spectrum is broad. Generally, the first symptoms patients experience are localized pain, swelling, and functional impairment in the affected area, which may be caused by the onset of nontraumatic fractures or by a minor trauma [6]. Certainly, the patient's complaints and prognosis depend on the area affected and the extent and severity of GSD. In fact, in cases where the disease affects the long bones of the lower limbs, and in which there is severe bone resorption not followed by deposition of new tissue, there is significant impairment of the patient's motor capacity and consequently of their lifestyle. At the same time, if the osteolysis occurs at the vertebral level, there can be life-threatening complications, precisely because of the potential involvement of the spinal cord [2].

It has also been reported that about 17% of GSD patients develop chylothorax and pleural effusion as a result of the disappearance of chest bones and invasion of lymphatic tissue at lung level [7].

Clearly, therefore, individuals with involvement of the bones that protect the lungs and spinal cord will have a much more complex clinical picture, and worse prognosis, than those with involvement of the limb bones, for example [8].

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Contact
Maria Luisa Brandi; marialuisa@marialuisabrandi.it
F.I.R.M.O., Italian Foundation for the Research on Bone Disease
Via San Gallo 123 - 50129 Florence, Italy - Phone: +39 055 2336663

Etiopathogenesis

To date, the biological mechanisms underlying the onset and progression of GSD are not fully known, although several hypotheses have been formulated, which include the involvement of blood and lymph vessels and also of bone cells (i.e., osteoclasts and osteoblasts).

Two interesting theories have been advanced to explain the involvement of the vascular system in GSD. First, L.W. Gorham and A.P. Stout [9] hypothesized that excessive vessel proliferation observed at bone tissue level could cause an increase in mechanical force and a change in local pH that would lead to subsequent tissue resorption.

Heyden *et al*. [10], on the other hand, believed that a state of hypoxia in the affected area due to slowed blood flow could cause a lowering of pH and a consequent increase in lytic enzyme activity.

However, to date, the main aspect brought out by different studies is the key role that lymphatic tissue could play in the pathogenesis of GSD. Indeed, not only were endothelial cells seen to be present in osteolytic lesions, most of them were also positive for the lymphatic vascular endothelial marker hyaluronan recepter-1 (LYVE-1) [11]. These cells could play a really important role in the pathogenesis of GSD thanks to their ability to secrete pro-lymphangiogenic factors, such as platelet-derived growth factor-BB (PDGF-BB), which is involved in angiogenesis and implicated in the formation of abnormal lymphatics, as well as factors affecting osteoclastic and osteoblastic activity [1, 12]. It has been observed, for example, that these latter factors could inhibit the differentiation of osteoblast progenitor cells.

In addition, it has been seen that there is a local increase in the levels of vascular endothelial growth factor C (VEGF-C), which promotes lymphatic vessel growth through the PI3K/AKT/mTOR pathway, in the portion of bone tissue affected by the resorption process [13]. It has also been found that GSD patients could present high serum levels of VEGF-C and of other pro-lymphangiogenic factors.

Osteoclasts are among main cell types possibly implicated in the onset and progression of GSD. Interestingly, however, histopathological analyses show that mature osteoclasts are rarely found in the affected area, leading researchers to presume that an alteration of the lymphatic system underlies the osteolytic process [2].

Both Devlin *et al*. [14] and Hirayama *et al*. [15] observed increased osteoclastic activity, mainly due to the action of several factors, such as macrophage colony-stimulating factor (M-CSF), receptor activator of NF-ϰB ligand (RANK-L), and interleukin-6 (IL-6); and it is interesting to note that some patients showed an increase in serum IL-6 itself [1,14,16].

Moreover, there could also be increased sensitivity of progenitor cells to the action of humoral factors that promote osteoclastic differentiation [17]. Additionally, histochemistry and electron microscopy studies performed on GSD tissues showed an accumulation of macrophage-like cells in bone lesions. These cells could secrete VEGF-A, VEGF-C, and VEGF-D, which would stimulate osteoclastogenesis and lymphatic vessel formation [13,18,19].

As it has been reported before, the disappearance of portions of bone is not subsequently replaced by the formation of new bone tissue.

This could be due to reduced osteoblast activity or early degeneration [20]. In recent years, it has been remarked that osteocytes could also contribute to the pathogenesis of GSD. In fact, these cells have been seen to exhibit a different morphology in the osteolytic zone, as pyknotic nuclei respect to osteocytes present in the areas of healthy bone tissue [10]. This feature might indicate that osteocytes are unable to regulate the secretion of cytokines inhibiting osteoblast differentiation, and consequently contribute to the failure to repair the injured tissue [1].

A curious aspect emerged from research by Korsic *et al*. [21], who noted that a patient with thyroid gland C-cell agenesis developed GSD. This could be attributed to the lack of production of the hormone calcitonin, which is able to bind to its own receptor present on osteoclasts and inhibit their activity.

Finally, Rossi *et al*. [16,22] recently hypothesized that epigenetic regulation may be involved in the pathogenesis and progression of GSD.

Diagnosis and treatment

As GSD is an extremely rare bone disease, no guidelines have been written for either its diagnosis or its treatment.

Diagnosing GSD is not easy, and the diagnosis is often made after excluding the presence of infection, inflammatory disease, or cancer.

Imaging plays an important role in the diagnosis of GSD. X-rays can show subcortical and intramedullary radiolucent foci in the early stages of the disease, as well as pathologic fractures in the more advanced stages.

Computed tomography (CT), on the other hand, can help identify the extent of soft tissue involvement, while magnetic resonance imaging can clearly identify the vascular system within the bone lesions.

Important results have been obtained with bone scintigraphy and 99 mTc(V)-DMSA, a technique that can be used to estimate the multifocality and extent of the syndrome. Finally, it was observed that the use of 18F-NaF in PET/CT could provide good sensitivity and specificity in identifying osteolytic foci [2]. To date, blood tests are not useful for diagnosing GSD as no reliable ones have yet been identified, i.e., ones that, being specific for GSD, can distinguish this syndrome from other diseases.

Nevertheless, to confirm the diagnosis of GSD, blood tests are performed to assess the levels of various molecules, like alkaline phosphatase, which always shows normal blood levels, and IL-6, VEGF-A, sclerostin, and pyridinoline cross-linked carboxyterminal telopeptide of type I (ICTP), which often show increased levels in GSD patients [1,16].

Finally, the diagnosis of GSD could be confirmed by histopathological analysis of biopsy samples [23].

An interesting framing of the diagnostic criteria for the detection of GSD was provided by Heffez et al., who suggest that the diagnosis of this syndrome may be based on eight main points: 1. presence of vascular tissue in the biopsy sample; 2. absence of cellular atypia; 3. minimal or no osteoblastic re-

sponse and absence of dystrophic calcifications; 4. evidence of local progressive bone resorption; 5. non-expansive, non-ulcerative lesion; 6. absence of visceral involvement; 7. osteolytic radiographic pattern; 8. negative hereditary, metabolic, neoplastic, immunologic, and infectious etiology [24].

Hence, based on what has been reported, to make a diagnosis of GSD, it is important to adopt a multidisciplinary approach.

In the case of GSD, we should speak of disease management rather than treatment, since there is no targeted therapy that can completely cure the patient. Like the diagnostic approach, treatment is also multidisciplinary, being based on a combination of surgery, radiotherapy, and the administration of different drugs [25].

Ionizing rays may reduce the proliferation of blood and lymph vessels as well as the size of the osteolytic area before the surgery.

Nevertheless, in 77.2% of cases, radiotherapy alone was also seen to be effective in controlling bone degradation locally [26]. The side effects of radiotherapy are by no means negligible, for although they are rare, there is a possibility the patient may develop a secondary malignancy [8].

When patients have large osteolytic lesions that impair their movement or cause them severe pain, surgical treatment is usually chosen in order to curb the affected area or remove and replace the injured bone fragment [27,28]. As regards the pharmacological approach to treatment, two or more drugs are often used in combination with each other. Drugs such as calcium, vitamin D, corticosteroids, bisphosphonates, and interferon α-2b usually tend to be used [3,29].

Bisphosphonates have shown good results in treating the condition, as they are able to inhibit osteoclastic activity and thus the mechanism of bone resorption. Commonly, bisphosphonates are administered in combination with radiotherapy or interferon α to simultaneously block the process of angiogenesis as well, or with vitamin D and calcium to promote the regeneration of new bone tissue [30,31].

In 2005, an interesting study in a 2-year-old child with multifocal osteolytic lesions showed the beneficial effects of interferon α-2b, whose anti-angiogenic properties resulted in complete remission [32].

Finally, in recent years, treatment with sirolimus has given promising results in GSD patients. First, Triana *et al*. [33] observed that 7/8 patients responded well to this therapy, while several subsequent studies also showed a more-than-50% reduction in bone injury after sirolimus administration [34-36].

Conclusions

GSD is an extremely rare skeletal disorder with the potential for serious complications that can even lead to death.

As has been illustrated here, the diagnosis of GSD remains a critical aspect because of the lack of markers that can be used to draw a specific profile of the syndrome. For this reason, it still cannot be diagnosed rapidly. Moreover, as the pathogenesis of GSD is still not entirely clear, treatment remains conservative, aimed at halting the process of bone resorption, as well as improving the patient's quality of life. Fortunately, in recent years researchers have begun to study its causes and progression, laying the foundations for the development of new therapies and diagnostic methods.

However, further studies are needed to uncover, in detail, the molecular and cellular mechanisms underlying GSD onset and progression, and thus pave the way for the development of innovative diagnostic and therapeutic strategies for this extremely rare bone disease.

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