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Review

Viewpoints on vessels and vanishing bones in Gorham–Stout disease

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ABSTRACT

Gorham–Stout disease (GSD) is a rare disorder characterized by the proliferation of endothelial-lined vessels in bone and the progressive destruction of bone. Although Jackson described the first case of GSD in 1838, the clinical and histological features of GSD were not defined until Gorham and Stout published their report on massive osteolysis in 1955. In the years since Gorham and Stout's groundbreaking publication, more than 300 cases of GSD have been described in the literature. These reports have revealed that the progressive resorption of bone in GSD causes severe physical deformities, disabilities, and life-threatening complications. Unfortunately, the underlying cause of GSD remains unknown and, as a result, the therapeutic options for individuals with GSD are limited. Here we review the latest advances in GSD research and present strategies to address basic and clinical research questions related to GSD.

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Contents

Introduction

Gorham–Stout disease (GSD, also known as massive osteolysis, vanishing bone disease, phantom bone disease, Gorham's disease and Gorham–Stout syndrome) is a rare disease of unknown etiology characterized histologically by the proliferation of endothelial-lined vessels in bone and by the replacement of bone with fibrous tissue [1]. In 1838, J.B.S. Jackson published the first case of GSD [2]. In his paper titled "A

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Boneless Arm", Jackson describes Mr. Brown, a patient whose entire humerus gradually disappeared over a period of several years [2]. Over 100 years would pass before another substantial report on massive osteolysis would be published [3]. In 1954, Gorham and colleagues published a report on the histological changes they observed in a patient with massive osteolysis [3]. They found that several of the affected bones from their patient displayed a dramatic increase in vascularity [3]. This crucial finding, as well as previous reports describing vascular changes accompanying massive osteolysis [4–8], prompted Gorham and Stout to further define the histological and clinical features of massive osteolysis. By evaluating histological samples from 8 previously studied cases, Gorham and Stout were able to firmly establish that massive osteolysis is accompanied by the extensive proliferation of endothelial-lined channels in bone [1]. Furthermore, by reviewing an additional 16 cases from the literature, they were able to provide the first detailed report on the clinical features of this rare disease [1]. Despite advances in clinical and basic science research since Gorham and Stout's publication in 1955, much still remains unknown about the pathology of GSD. This lack of knowledge has hindered the identification of effective therapies for treating this devastating disease. To address this need, the Lymphatic Malformation Institute (LMI) and Lymphangiomatosis & Gorham's Disease Alliance (LGDA) recently sponsored an international scientific conference focused on developing strategies to address many of the basic and clinical research questions related to GSD. In this review we summarize clinical information for 185 previously published cases of GSD, highlight the latest advances in GSD research and address unanswered questions related to GSD.

Clinical features of GSD

GSD can present at any age (age range is from 7 months to 83 years), but is most commonly diagnosed in children and young adults (average age of diagnosis is 25 years; Supplemental Table 1). The disease does not display a clear sex predilection (1.6:1 male-to-female ratio; Supplemental Table 1) or inheritance pattern [9]. Although GSD can affect any bone in the body, it frequently affects the maxilla, mandible, clavicle, ribs, cervical vertebrae, pelvis and femur (Supplemental Table 1). Areas of bone resorption can arise in a single bone or in multiple contiguous bones (Supplemental Table 1). Osteolytic lesions in patients with GSD initially appear as small radiolucent foci in radiographic images [10]. These foci enlarge and coalesce as the disease progresses [10]. Additionally, tubular bones undergo concentric shrinkage causing them to have a "sucked candy" appearance. In severe cases, this process continues until the entire bone is resorbed and replaced by fibrous tissue. Eventually, for reasons that are not entirely clear, the disease can spontaneously arrest and stabilize. Importantly, new bone does not form to a notable extent after the disease has stabilized [1].

The symptoms of GSD vary and depend on which sites in the body are affected. The most common symptom is localized pain (Supplemental Table 1). Other symptoms include swelling, weakness and functional impairment of affected limbs. GSD patients may be asymptomatic until they suffer a bone fracture either spontaneously or following minor trauma. Patients with thoracic involvement may seek medical attention because they have difficulty breathing. This is typically caused by chylothorax, an accumulation of chyle (lymph rich in fat) in the pleural cavity [11]. Approximately 25% of GSD patients develop chylothorax, which can result in respiratory distress and failure (Supplemental Table 1). Additionally, involvement of the vertebrae can cause severe neurological defects, deformity, paralysis, and death.

Histological features of GSD

Gorham and Stout evaluated biopsy specimens from 8 previously reported cases of massive osteolysis to determine whether these patients displayed similar histopathological alterations in their affected tissues. They observed that the affected bone, and the fibrous tissue that had replaced bone, contained numerous dilated endothelial-lined vessels [1]. Numerous other investigators have observed the same changes in sections of affected bones stained with hematoxylin and eosin. However, the identity of the deranged vessels differs from case to case. In some cases, the abnormal channels are reported to be blood vessels [1,3,12–14] whereas in other cases they are reported to be lymphatic vessels [4,15–17]. The emergence of immunohistochemical markers of lymphatic endothelial cells has greatly facilitated the characterization of the abnormal vessels in GSD. Two commonly used molecular markers of lymphatic endothelial cells are LYVE-1, a receptor for the glycosaminoglycan hyaluronan, and podoplanin, a transmembrane glycoprotein recognized by the antibody D2-40 [18,19]. These markers have revealed that lymphatic vessels are not present in normal bones [20], but are present in medullary and cortical regions of bones in patients with GSD [20–25]. Affected soft tissues in GSD patients also display abnormal lymphatic vessels [26,27]. Although numerous lymphatic vessels are present in affected tissues in GSD, they are not widely labeled by MIB-1, a monoclonal antibody against the proliferation marker Ki-67 [21,28]. Therefore, according to the International Society for the Study of Vascular Anomalies (ISSVA) classification system, the lymphatic anomaly in GSD is a malformation rather than a tumor [21]. Together, these observations suggest that lymphatic vessels rather than blood vessels are primarily affected in GSD.

Etiology of GSD

The cause of excessive bone resorption in GSD is unclear. In the following sections we discuss the potential role of endothelial cells, osteoclasts and osteoblasts in the pathogenesis of GSD (Fig. 1).

Endothelial cells

Several investigators have proposed that the abnormal endothelial-lined channels in osteolytic zones promote bone resorption. Gorham and Stout believed that the local proliferation of endothelial-lined vessels could promote bone loss by increasing blood flow, changing local pH, or by exerting mechanical force [1]. Heyden et al. proposed that sluggish blood flow in osteolytic areas might cause local hypoxia, which could lower tissue pH and favor the activity of hydrolytic enzymes [29]. Importantly, these ideas attempt to explain how blood vessels could promote bone loss in GSD. However, there is mounting evidence that lymphatic vessels are primarily affected in GSD. The uncontrolled growth of fluid-filled lymphatic vessels could cause osteolysis by compressing bone. Alternatively, lymphatic endothelial cells may secrete factors that influence the activity of osteoclasts and/or osteoblasts.

Lymphangiogenesis, which is the sprouting of new lymphatic vessels from pre-existing vessels, occurs in an uncontrolled fashion in GSD. This process is driven, in part, by growth factors in the microenvironment that activate receptors on the surface of lymphatic endothelial cells. Members of the vascular endothelial growth factor (VEGF) family are thought to be the most important factors that drive lymphangiogenesis [30–32]. One prominent lymphangiogenic member of this family is VEGF-C, a ligand of the receptor tyrosine kinases VEGFR2 and VEGFR3 [33,34]. Although the signaling pathways stimulating lymphangiogenesis in many pathological settings have been characterized, the pathways driving lymphangiogenesis in GSD have not been defined. It is possible that a local increase in the level of VEGF-C or of another pro-lymphangiogenic factor (VEGF-A, -D, Ang-1, -2, etc.) could stimulate lymphangiogenesis in GSD [35–38]. Indeed, VEGF-C has been found to be elevated in the serum of one GSD patient [27] and VEGF-A has been found to be elevated in the serum of three GSD patients [27,39] and in the plasma of another patient [40] (Table 1). Alternatively, a decrease in the level of an anti-lymphangiogenic factor (sVEGFR2 [41], TGF-β [42], IFN-γ [43], etc.) could promote the uncontrolled growth of lymphatic vessels in the bones of patients with GSD.

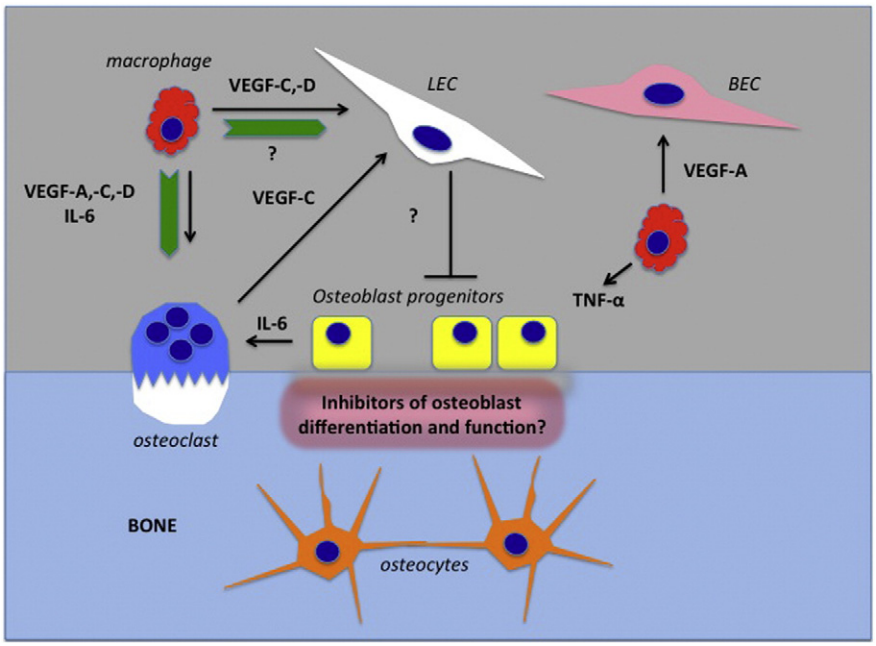

Fig. 1. Diagram illustrating cells and interactions that likely contribute to the disease mechanism in GSD. The proliferation of lymphatic endothelial cells (LECs) and blood endothelial cells (BECs) could be stimulated by increased levels of VEGF-C, and -D and macrophage-derived VEGF-A. Macrophages may also contribute to the formation of LECs and are the progenitors of osteoclasts (block arrows). In addition, they produce VEGF-A, -C, and -D and interleukin 6 (IL-6); all stimulate osteoclast differentiation. Osteoblast progenitor cells may be inhibited in their differentiation and function by factors secreted by LECs and by factors produced by osteocytes, including sclerostin, and Dickkopf- and soluble frizzled-related proteins. Although low levels of TNF-α can stimulate stromal cell recruitment and osteogenic differentiation [91], high levels of TNF-α produced by macrophages inhibit osteoblast differentiation and enhance osteoclastogenesis by stimulating RANKL production by stromal cells.

Osteoclasts

Osteoclasts are multi-nucleated cells, differentiated from myeloid progenitors, that resorb bone by locally secreting proteolytic enzymes and hydrogen ions [44]. Several growth factors and cytokines regulate their differentiation and activity, including the stimulatory factors CSF-1 (M-CSF), RANKL, IL-6, TNF-α, VEGF-A and VEGF-C and the inhibitory factor osteoprotegerin (OPG). Hyperactive osteoclasts participate in the pathogenesis of several human skeletal disorders in which bone is lost, including cherubism [45], familial expansile osteolysis [46], and juvenile Paget disease (also known as familial hyperphosphatasia) [47]. However, there are conflicting reports on whether osteoclasts are present in osteolytic zones in GSD. In fact, while some investigators have observed osteoclasts in osteolytic zones [12,13,21,48–56], Gorham and Stout, as well as other investigators, have reported that osteoclasts are not present in areas of bone resorption [1,15,29,57,58]. The reason for this discrepancy is unclear, but it has been proposed that it may be due to evaluations being conducted at different phases (active versus stable) of the disease [59].

Whether this explanation is correct is not clear, but studies of some cases of GSD suggest that patient osteoclast progenitor cells may be more sensitive to the osteoclast-inducing factors CSF-1 and RANKL than control cells [51] and that patient serum can induce osteoclast formation in an IL-6-dependent manner [60]. In addition, histochemistry and electron microscopy of tissue isolated from GSD bone lesions indicate the presence of an increased number of pericyte/macrophage-like mononuclear cells with abundant acid phosphatase positive lysosomal bodies [29,61]. These macrophage-like cells may serve as progenitors of osteoclasts in GSD lesions. In addition, macrophages are known to produce VEGF-A, VEGF-C and VEGF-D [62] and all three factors are able to stimulate osteoclast differentiation and lymphangiogenesis [63–65]. Finally, in an inflammatory environment macrophages may even directly contribute to lymphangiogenesis by expressing markers of lymphatic endothelium and forming tube-like structures [66,67].

Table 1
Circulating levels of biomarkers in patients with Gorham–Stout disease.

Protein	Level during active phase of disease	Level during inactive phase of disease	Reported normal value(s)	Reference
VEGF-A	163 pg/ml (Plasma)	25 pg/ml (Plasma)	1–63 pg/ml (Plasma)	Dupond et al. [40]
VEGF-A	277 pg/ml (Serum)	161 pg/ml (Serum)	50 pg/ml (Serum)	Morimoto et al. [39]
VEGF-A	730 pg/ml (Serum)	570 pg/ml (Serum)	62–707 pg/ml (Serum)	Brodszki et al. [27]
VEGF-A	1200 pg/ml (Serum)	370 pg/ml (Serum)	62–707 pg/ml (Serum)	Brodszki et al. [27]
VEGF-A	100 pg/ml (Serum)	N/A	N/A	Hagendoorn et al. [26]
VEGF-C	4050 pg/ml (Serum)	3910 pg/ml (Serum)	2459–6651 pg/ml (Serum)	Brodszki et al. [27]
VEGF-C	6930 pg/ml (Serum)	2260 pg/ml (Serum)	2459–6651 pg/ml (Serum)	Brodszki et al. [27]
PDGF-BB	108 pg/ml (Serum)	N/A	15 pg/ml (Serum)	Hagendoorn et al. [26]
IL-6	7 pg/ml (Serum)	15 pg/ml (Serum)	<8 pg/ml (Serum)	Brodszki et al. [27]
IL-6	6.7 times higher than the upper limit of the normal range	1.9 times higher than the upper limit of the normal range	N/A	Plasswilm et al. [76]
IL-6	8.4 pg/ml (Serum)	<5.4 pg/ml (Serum)	<5.0 pg/ml (Serum)	Hammer et al. [50]
IL-6	7 times higher than the upper limit of the normal range	1.75 times higher than the upper limit of the normal range	N/A	Devlin et al. [60]
IL-6	71.1 pg/ml (Serum)	N/A	<4.0 pg/ml (Serum)	Fujiu et al. [15]

Osteoblasts

A remarkable aspect of the osteolytic process in GSD is the absence of evidence for increased osteoblast activity along surfaces of remaining bone fragments in sections of affected tissues [61]. This is quite different from other skeletal disorders with bone loss due to increased differentiation and activity of osteoclasts. For example, the massive loss of maxillary and mandibular bones in cherubism, caused by mutations that result in increased sensitivity of myeloid cells to macrophage- and osteoclast-inducing signals [45], is associated with a robust increase in osteoblast activity. In active GSD lesions the disappearing bone is replaced by fibrovascular tissue rather than newly formed woven repair bone. Particularly striking are observations that osteoblastic cells within active lesions exhibit ultrastructural features suggesting that they have either decreased synthetic activity or are degenerating [61]. Finally, osteocytes within bone tissue close to the lesions have been reported to having pyknotic nuclei and occupying enlarged lacunae [29,61].

This lack of an osteoblastic repair response in GSD lesions is particularly puzzling in view of the high circulating levels of VEGF-A reported for many GSD patients [27,40,68] and the strong evidence that VEGF-A stimulates bone repair by promoting angiogenesis and bone turnover [69]. Also puzzling is that this loss of an osteoblastic response is restricted to the vanishing bone(s), while bone homeostasis appears to be relatively unaffected in other parts of the skeleton. This suggests that the pathophysiological events causing osteolysis in GSD are localized and that factors produced in the process might stimulate mesenchymal progenitors to differentiate along the fibroblastic, rather than osteoblastic lineage. The role of osteocytes in regulating osteoblast differentiation and activity may be important in this context. Osteocytes release factors that stimulate osteoblast differentiation [70,71] and recruitment of mesenchymal stem cells to bone fracture sites [72] and they inhibit osteoblast differentiation by producing Wnt signaling inhibitors such as sclerostin, Dickkopf-related proteins and soluble frizzled-related proteins [73]. Thus, it is possible that changes in such osteocyte-produced factors may contribute to the lack of osteoblastic repair responses in GSD.

Genetics and GSD

GSD is a sporadic disease potentially caused by specific genetic risk factors or by mosaicism for a somatic mutation. Approaches that have been used to identify the genetic basis of other sporadic diseases could be used to search for mutations that may be contributing to GSD. For example, Proteus and CLOVES are two sporadic overgrowth syndromes caused by somatic activating mutations in *AKT1* and *PIK3CA*, respectively [74,75]. These mutations were found by sequencing DNA purified from affected tissues. Importantly, the disease causing mutations were not present in DNA isolated from the blood or saliva of patients. Therefore, it has been suggested that DNA purified from affected tissues, rather than blood or saliva, be analyzed to search for the potential genetic underpinnings of GSD. Unfortunately, affected bones from GSD patients are frequently fixed, decalcified with acid, and embedded in paraffin, which makes exome sequencing technically challenging. To overcome this obstacle, it has been recommended that DNA from fresh tissues or from cell lines derived from affected tissues be used in exome sequencing experiments. Identification of mutations associated with GSD would help direct the development of animal models and the search for therapeutic strategies.

Biomarkers for monitoring the activity of GSD

The clinical course of GSD is unpredictable. In some patients the disease progresses slowly whereas in others it progresses rapidly and causes severe disability. A current challenge in the clinic is identifying which patients fall into the latter category and require close monitoring and aggressive treatment. To address this problem, several studies have examined whether lymphangiogenic and osteoclastogenic factors could serve as biomarkers of disease activity in GSD. Most of these reports have centered on the growth factor VEGF-A [27,39,40] and the cytokine IL-6 [15,50,60,76]. These studies have shown that VEGF-A and IL-6 can be elevated in the circulation of patients with GSD and that the level of these factors can decrease following treatment with various therapies (Table 1). However, VEGF-A [26] and IL-6 [27] are not elevated in all GSD patients. Therefore, additional factors are being analyzed with the hope of finding additional biomarkers. Other factors evaluated in the circulation of GSD patients include VEGF-C [27], PDGF-BB [26], sRANKL [50], and osteoprotegerin [50] (Table 1). While the clinical diversity of GSD makes it unlikely that a single biomarker for all GSD patients can be found, a universal set of biomarkers to monitor disease activity could provide diagnostic, prognostic or predictive information.

Therapies for treating GSD

Depending on the severity of the disease, the extent of organ-involvement and other signs, different strategies are used to treat GSD. These strategies include surgery, radiotherapy and pharmaceuticals (Supplemental Table 1). Surgery for GSD mainly consists of interventions to reduce or halt fluid build-up in the pleural cavity and these interventions include pleurectomy, pleurodesis, thoracentesis, and thoracic duct embolization or ligation [9]. Surgery is also performed to stabilize affected regions of the skeleton once the disease appears to have stabilized [77]. Radiotherapy has been used in cases where surgery is not possible or in combination with surgery [78–80]. Several case reports have described the successful use of radiotherapy, with an overall success rate in the case of local lesions being about 75% [78]. A total of 36–45 Gy, given in 2 Gy portions, appears to provide the most therapeutic benefit [78,79,81,82]. Several pharmaceuticals have also been used to treat patients with GSD [9]. However, since pharmaceuticals are most often used in combination with other therapeutic approaches, it is difficult to assess the benefit of the administered pharmaceutical(s). Moreover, a consensus regarding the effectiveness of specific pharmaceuticals cannot be derived from a review of the available literature. The most commonly prescribed pharmaceuticals to treat GSD are bisphosphonates and interferon alpha 2b [23,26,48,50,83–86]. These have been used as single agents or in combination with one another. Other pharmaceuticals that have been used to treat GSD include the anti-VEGF-A antibody, Bevacizumab [87], propranolol [88], low molecular weight heparin [27], steroids, vitamin D, and calcitonin [9].

Clinical trials are needed to test the efficacy of existing and emerging therapies against GSD. An ongoing clinical trial is testing the efficacy of the mTOR inhibitor rapamycin (Sirolimus) in children and young adults with several different vascular anomalies involving bone, including GSD (www.clinicaltrials.gov; NCT00975819) [89,90]. Preliminary, but promising, findings from this trial were presented at the 1st International Conference on Generalized Lymphatic Anomaly and Gorham–Stout Syndrome held in Bethesda, MD in June 2013 and the final results from the study are expected in mid-2014. In the future, the recently launched Lymphangiomatosis & Gorham's Disease Alliance global patient registry (www.LGDARegistry.org) and Boston Children's Hospital lymphatic anomalies registry (contact the Vascular Anomalies Center at BCH for more information) could help gather patients for new trials.

GSD and generalized lymphatic anomaly

Generalized lymphatic anomaly (GLA, also known as lymphangiomatosis) is a rare disease highly related to GSD. GLA is characterized by the extensive proliferation of lymphatic vessels and frequently affects bone. A retrospective review of 32 GLA and 19 GSD patients in the Vascular Anomalies Center database at Boston Children's Hospital revealed that GLA and GSD patients display differences in bone disease [25]. GLA patients display lytic areas confined to the medullary cavity whereas GSD patients display progressive osteolysis resulting in the loss of cortical bone [25]. GLA patients typically have more bones

involved than GSD patients and the appendicular skeleton is more frequently involved in GLA than GSD patients [25]. Macrocystic lymphatic malformations are also more frequently observed in GLA than GSD patients [25]. Affected bones from GLA and GSD patients display abnormal lymphatic channels and appear similar to one another histologically [25]. Continued study of GLA and GSD will help delineate the clinical, histological, and genetic similarities and differences between these two rare diseases.

Concluding remarks

Our understanding of the features of GSD has increased dramatically since Gorham and Stout's publication in 1955. Case reports and case series have shed light on the disease process, identified potential biomarkers for monitoring disease activity, and pointed towards specific therapies for treating GSD. Despite these advances, much still remains unknown about GSD. The molecular mechanisms driving osteolysis and lymphangiogenesis in GSD remain unclear, a genetic basis of GSD has not been defined, and there are no FDA approved therapies for treating GSD. Importantly, numerous research projects are currently underway to address these and other basic science and clinical research questions. Together, these efforts will lead to a deeper understanding of the etiology of GSD and help identify therapies to treat patients suffering from this insidious disease.

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Conflict of interest

The authors declare no conflict of interest.

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