

Mandibular Gorham–Stout disease

A case report and literature review

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Abstract

Rationale: Gorham–Stout disease (GSD) is characterized by aggressive bone resorption, proliferation of vascular or lymphatic vessels, and soft-tissue swelling. Bones that initially appear normal start to resorb, partially or completely. However, the etiology of GSD is unknown.

Patient concerns: A 29-year-old man with a chief complaint of toothache and mobility in the lower right mandible for the previous 1 year.

Diagnoses: Gorham–Stout disease (GSD).

Interventions: The RANK-ligand inhibitor denosumab was suggested to use to inhibit the development of osteoclasts and slow mandibular resorption. In addition, we proposed resection of the remaining mandible and reconstruction via vascularized bone graft, after resorption of the mandible had become stationary.

Outcomes: Regular follow-ups were advised to this patient to monitor the stability of bone resorption prior to any surgical intervention.

Lessons: We strongly recommend that every attempt should be made for early diagnosis and prompt effective medical and surgical management. The failure to do so results in further complications and poor prognosis.

Abbreviations: GSD = Gorham–Stout disease, RANK = receptor activator of nuclear factor κ B.

Keywords: Gorham disease, mandible, massive osteolysis, prognosis

1. Introduction

Gorham–Stout disease (GSD), also known as vanishing or phantom bone disease, is a very rare condition of progressive massive osteolysis.^[1] The osteolysis results from elevated localized osteoclastic activity and can be observed through radiographic examination. In addition to massive osteolysis, GSD appears on pathology as lack of bone formation and proliferation of vascular and lymphatic vessels. This, and localized tissue changes, lead to formation of fibrous tissues. Although a number of GSD cases have been reported, the etiology is not understood well.

Evidence suggests that in GSD proliferation of blood vessels may result in an increased vascularity of the affected bone, a high

rate of oxygen consumption, and altered tissue acidity.^[2] Several lymphangiogenic pathways that may be relevant to Gorham disease have been suggested, such as platelet-derived growth factor, interleukin-6, and vascular endothelial growth factor.^[3] Some researchers have also proposed involvement by the RANK-ligand/RANK system,^[4] and a variety of bone diseases such as postmenopausal osteoporosis^[5] and inflammatory bone loss.^[6] It has been suggested that the main contributory factors are increased localized osteoclastic activity and interleukin-6.^[7]

GSD is not restricted to gender, age, or race. It may involve any part of the body, although it commonly affects the pelvis, shoulders, and craniofacial area. About 30% of cases are reported in the maxillofacial region, mainly involving the lower jaw.^[7] The disease is without symptoms during the initial stage and is usually diagnosed by routine radiographs. Absorption of bone tissue is spontaneous and progressive until the entire bone is involved, and even adjacent soft tissue may be invaded.^[8] Therefore, patients suffering from maxillofacial GSD in the advanced stages may present with facial asymmetry, tooth mobility, impaired occlusal function, pathological fracture, occlusal disorders, dysfunctional mouth opening, and other symptoms. In some cases, although the patient has a history of toothache, there is no inflammatory response. On the other hand, some patients with self-limiting osteoporosis may experience a quiescent period, during which bone resorption is stable and does not progress.^[2]

Because there is so little knowledge concerning GSD, no standard treatment has been determined for its management. Conventional therapy involves inhibition of local osteolysis with drugs such as bisphosphonates and calcitonin. Pathological fractures that occur due to massive bone resorption are treated surgically.^[1]

The prognosis of GSD is variable and depends on multiple factors such as the extent and location of the affected bones. The

Editor: Li Wu Zheng.

ML and WL contributed equally to this work.

Funding/support: This study was supported by the National Natural Science Foundation of China (Project approval number 81602377).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:42(e8184)

Received: 3 July 2017 / Received in final form: 4 September 2017 / Accepted: 6 September 2017

<http://dx.doi.org/10.1097/MD.00000000000008184>



Figure 1. Panoramic radiograph of the patient showing a large area of left mandibular destruction and symmetric defects.

disease can be divided into an early stage with proliferation of intramedullary and cortical vessels, and a later stage characterized by destruction and resorption of bone.^[9] The disease may be self-limiting over time or may lead to mortality if tissues such as craniofacial bones (cerebrospinal fluid leakage) or ribs (chylothorax) are involved.^[11] This article describes a rare case of mandibular GSD. Of note, the osteolysis in 2 quadrants of the mandible was inversely directed (from top to bottom on the right, and bottom to top on the left). A review of the relevant literature has also been included.

2. Case report

The study was approved by the Ethics Committee of Jilin University. Informed consent was obtained from the individual participant included in the study.

In February 2016, a 29-year-old man visited the Hospital of Stomatology, Jilin University with a chief complaint of toothache and mobility in the lower right mandible for the previous 1 year. A previous radiographic examination (dated February 2015–February 2016), revealed an area of bone destruction in the right side of the mandible (Fig. 1A). The patient reported a sense of floating teeth upon biting and occlusal disorder. There was no history of trauma, numbness in the lower lip, weight loss, paresthesia, or obvious lymph nodes. The patient used self-medication (antibiotics) that resulted in no obvious improvement.

During the extraoral examination, facial asymmetry and a slightly swollen left cheek were noted. The inferior border of the left mandible felt diminished upon palpation and was not tender. The intraoral examination revealed that the teeth and alveolar bone of the right mandible were floating. The patient had lost a number of teeth (31, 38, 41, 47, and 48). Multiple teeth (32, 42, 43, 44, 45, and 46) were mobile on clinical examination. The patient had signs of malocclusion.

Further laboratory investigations such as routine blood examination, immune-detection, and biochemistry of parathyroid hormones were performed.

2.1. Radiographic examination

The panoramic radiograph and 3D-computed tomography (CT) scan revealed a large bilateral mandibular bone destructive lesion with undefined margins (Fig. 2). The bony destructions were characteristically honeycomb-like, coupled with floating teeth (32, 42, 43, 44, 45, and 46). The extent of bone destruction was significantly more than the bone resorption shown radiographically 4 months previously (Fig. 1). There were no other skeletal abnormalities in the craniofacial bones.

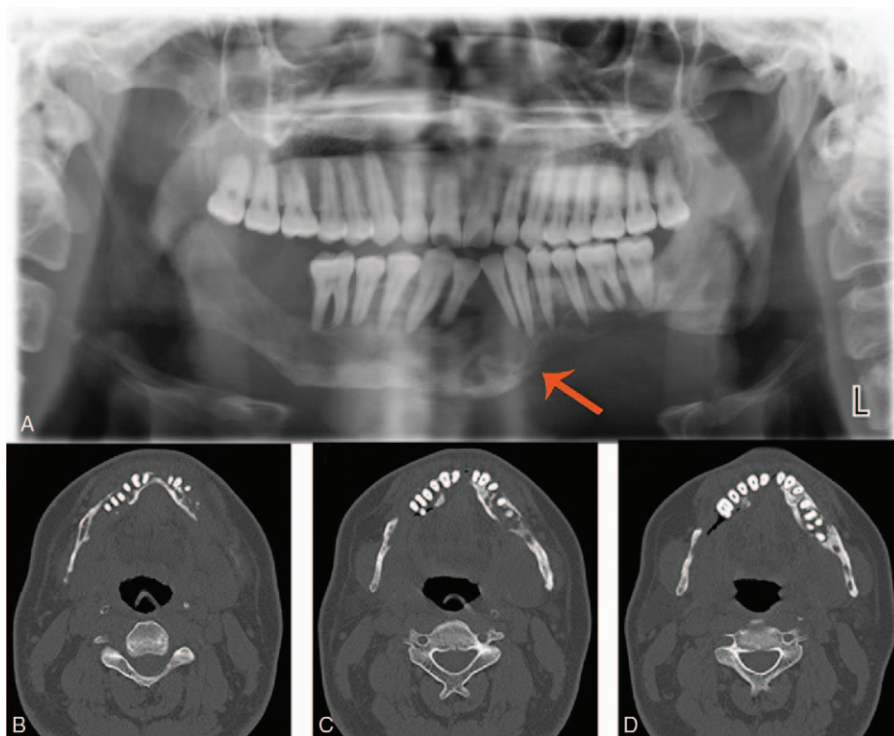


Figure 2. Images of panoramic radiograph and computed tomography (CT) scan. (A) Panoramic radiograph showing a large area of bilateral mandibular bone destruction with unclear margin and local bony defects. (B–D) CT scans showing the destruction of the alveolar bone in the mandible with no clear margins. The destruction was honeycomb-like (arrow), coupled with floating teeth.

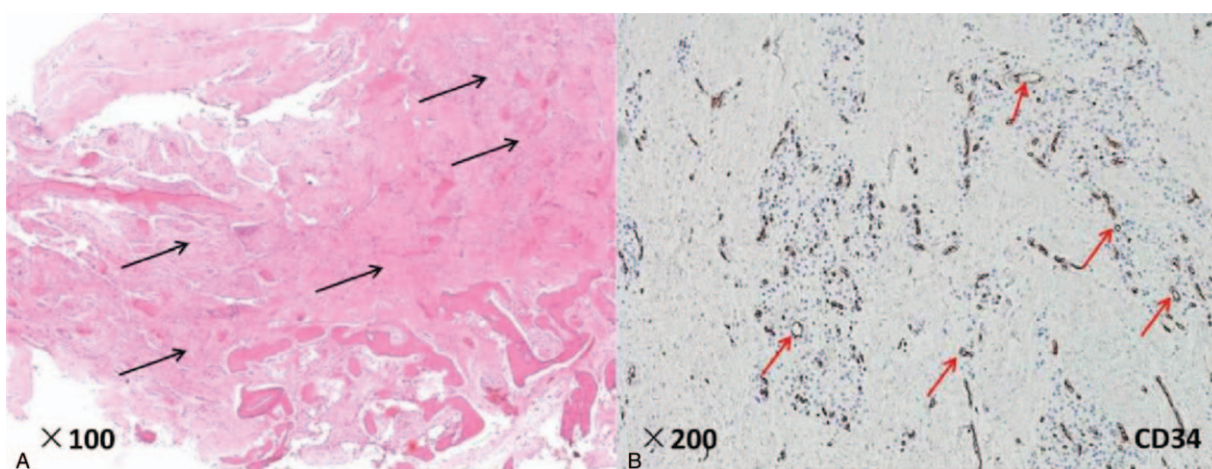


Figure 3. Histopathology of tissues. (A) Thin-walled congestive vascular proliferates intermixed with fibrous connective tissue, with mild infiltration of lymphocytes and plasma cells in the connective tissue. (B) Positive staining for CD34 indicating vascular endothelial cellular activity.

2.2. Differential diagnosis

There are several diseases that may be relevant to the present symptoms and clinical scenario: malignant neoplasm, osteomyelitis, and GSD. Malignant neoplasm includes squamous cell carcinoma, which is the most common neoplasm in the maxillofacial region. However, in our present case there were no associated symptoms such as local bone ache or numbness of the lower lip. Rather, the radiographic examination revealed irregular vermiform destruction of the bone, which did not indicate malignant tumor. Thus, malignant neoplasm as a diagnosis was eliminated.

Osteomyelitis (and other infectious conditions) is caused by bacteria and characterized by inflammation. Our patient presented with facial swelling, toothache, tooth mobility, and no numbness of the lower lip. Although the patient had a massive bone resorption, there were no symptoms of obvious inflammation.

GSD was considered, as the patient had bony destruction without numbness of the lower lip and no history of osteomyelitis (infection) of the mandible. Therefore, the patient was likely suffering from GSD, a rare condition that needed further investigations to confirm. The laboratory investigations were within normal limits, including parathyroid hormones, calcitonin, and alkaline phosphatase levels. The patient underwent an incisional biopsy. The histopathological examination revealed progressive bone resorption and lack of new bone formation (Fig. 3). Osteoclasts were not conspicuous on the surface of the destroyed bone. Varying degrees of hemorrhage were observed on the residual bone tissues. In addition, there were thin-walled congestive vascular proliferates intermixed with fibrous connective tissues. Mild infiltration of lymphocytes and plasma cells in the connective tissue were observed, and positive staining for CD34. There were no indications of cancerous tissues. Based on the above clinical manifestations and radiographic and histopathological findings that indicated large bone dissolution, GSD of the mandible was the diagnosis.

2.3. Management of GSD

Because the patient was undergoing persistent progressive bone dissolution, the RANK-ligand inhibitor denosumab was

prescribed (60 mg, administered as a single subcutaneous injection every 6 months). The drug inhibits the development of osteoclasts and was considered likely to slow mandibular resorption.

In addition, we proposed resection of the remaining mandible and reconstruction via vascularized bone graft, after resorption of the mandible had become stationary. Regular follow-ups were advised to this patient to monitor the stability of bone resorption prior to any surgical intervention.

3. Discussion

GSD was first described in detail by Gorham and Stout in 1955. The bones that are most involved are the pelvis, shoulder, scapula, skull, and clavicle. GSD can occur in any age group, but has mainly been reported in children and young adults.

Although active osteolysis characterizes GSD, the etiopathology is not clearly understood. Several explanations have been proposed. GSD has been associated with posttraumatic hyperemia, growth of unrestricted granulation tissue, hemangiomas, or lymphangiomas.

Soft tissue lesions are present in ~60% of GSD patients. Angiomas can be observed in the affected bones or adjacent soft tissues, and progressive osteolysis is usually associated with angiomas of blood and lymphatic vessels. Heyden et al^[10] suggested that angiomas may alter the local environment with increased hypoxia and acidosis, activating hydrolytic enzymes, which results in osteolysis and resorption of affected bones. Therefore, it is speculated that GSD is a disease of disordered lymphangiogenesis and angiogenesis. A further study^[11] of the cellular and humoral mechanisms of osteoclast formation in GSD revealed that an increase in the sensitivity of osteoclast precursors to humoral factors promoted osteoclast formation and bone resorption, rather than increasing the number of circulating osteoclast precursors.

In the present case, there was a tumor-like hyperplasia of vascular tissues and fibrous tissues. Although there was no inflammation in oral tissues, local bone resorption was seen. Features characteristic of GSD included bone resorption and formation of fibrous and granulation tissues.

The clinical presentation of GSD is highly variable depending on the structures involved, and the progression of osteolysis is

generally unpredictable. In the majority of patients, osteolysis progresses until the entire bone has disappeared. However, in a few patients progression may be self-limiting and reach remission.

In the current case, aggressive osteolysis progressed quickly, with irregular vermiform destruction of the bone. Radiographs and CT images indicated a large area of bony involvement. Some tests for endocrine and autoimmune markers were unremarkable, for example, parathyroid hormones, calcitonin, and alkaline phosphatase were all within normal range.

The routine histological examination of the present case revealed the presence of small fragments of destructed trabeculae and the proliferation of some thin-walled vessels. These findings were consistent with the formation of fibrous tissues replacing the resorbed bone. The presence of CD31 and CD34 indicated vascular endothelial cell activity, leading to the proliferation of vessels and lymphatic ducts. The immunohistochemical examination showed endothelium staining positive for CD-40 and D2-40 that is specific for lymphatic endothelium.^[12] The KI67 probe was also observed in peripheral epithelial cells, confirming that there was no central cellular proliferation or malignant cells.

GSD in anatomical locations such as the ribs, scapula, or thoracic vertebrae may cause further complications, including involvement of the pleura (chylothorax) and nerve root compression, resulting in poor prognosis. Chylothorax is a very rare complication of GSD that is usually fatal, owing to progressive hypoproteinemia, malnutrition, and immunosuppression with lymphocytopenia. In addition, thoracic cage, pulmonary, or pleural involvement may lead to incapacitation of respiratory functions and death. Infection of relevant bones and septic shock is another rare complication of GSD that has been reported.^[13] Therefore, GSD can be occasionally fatal, mainly because of complications. A previous study reported a 10-year-old boy with GSD accompanied by aggressive lymphatic malformation, who died of complications.^[14]

To date, the treatment of massive osteolysis has been controversial. A variety of treatment modalities targeting control of progressive osteolytic activity have been assessed. Takahashi et al^[15] suggested that a local injection of OK-432 (a low-virulence strain of group-A human *Streptococcus pyogenes* incubated with penicillin) has an antiangiogenic action. Klinische Einheit injected locally (once every 6 weeks) into the tibial osteolytic region was useful for femoral lesions and remission of chylothorax.^[16]

It has been suggested that massive osteolysis is due to an increased number of stimulated osteoclasts. The inhibition of local osteolysis using bisphosphonates and calcitonin is usually helpful to prevent local progressive osteolysis. Bisphosphonates such as zoledronate and alendronate have been reported to reduce the resorption of mineralized tissues in animals (dogs and monkeys).^[17] Likewise, we should consider the side effects of medical therapies, such as gastro-intestinal irritation, osteonecrosis of the jaw, and ocular inflammation.

Surgical interventions in GSD are the best choice for healing, including resection of the destructed bone and reconstruction using bone grafts or prostheses. The implanted bones may be resorbed in a few weeks. Distraction osteogenesis has been reported as another effective reconstruction method for managing osseous defects.^[18] Surprisingly, prognosis of GSD is highly variable, and some patients experience spontaneous remission.

For the current case, we applied comprehensive treatment. The patient was first treated by medication (diphosphonates) to stabilize the osteolysis. Resection of the affected mandible was then performed. The vascularized bone (for instance, fibular) was

used to construct the mandibular defect after a stationary phase was reached.

In conclusion, GSD is rare and well known for its challenging diagnosis. Herein, we reported a rare case of GSD to make physicians aware of the clinical picture and management. To halt the resorption of affected bones and achieve complete healing, we strongly recommend that every attempt should be made for an early diagnosis and prompt medical and surgical management. The failure to do so results in further complications and drastically affects prognosis.

Acknowledgement

The authors thank the National Natural Science Foundation of China (Project approval number 81602377) for the support. The authors also thank Medjaden Bioscience Limited for assisting in the preparation of this manuscript.

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