

Gorham's Disease or Massive Osteolysis

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[See related article pp. 83-86]

Gorham's disease is a rare disorder characterized by proliferation of vascular channels that results in destruction and resorption of osseous matrix. Since the initial description of the disease by Gorham and colleagues (1954) and by Gorham and Stout (1955), fifty years have elapsed but still the precise etiology of Gorham's disease remains poorly understood and largely unknown. There is no evidence of a malignant, neuropathic, or infectious component involved in the causation of this disorder. The mechanism of bone resorption is unclear.

The clinical presentation of Gorham's disease is variable and depends on the site of involvement. It often takes many months or years before the offending lesion is correctly diagnosed. A high index of clinical suspicion is needed to arrive at an early, accurate diagnosis. Patients with Gorham's disease may complain of dull aching pain or insidious onset of progressive weakness. In some cases, pathologic fracture often leads to its discovery. Gorham's disease is progressive in most patients; however, in some cases, the disease process is self-limiting. The clinical course is generally protracted but rarely fatal, with eventual stabilization of the affected bone being the most common sequelae. Chylous pericardial and pleural effusions may occur due to mediastinal extension of the disease process from the involved vertebra, scapula, rib or sternum, and can be life threatening. A high morbidity and mortality is seen in patients with spinal and/or visceral involvement.

The medical treatment for Gorham's disease includes radiation therapy, anti-osteoclastic medications (bisphosphonates), and alpha-2b interferon. Surgical treatment options include resection of the lesion and reconstruction using bone grafts and/or prostheses. In most cases, bone grafts tend to undergo resorption and are not helpful. Surgical reconstruction and/or radiation therapy are used for management of patients who have large, symptomatic lesions with long-standing, disabling functional instability. Surgical stabilization may be required for unstable spinal lesions. Various treatment options, including pleurectomy, pleurodesis, thoracic duct ligation, radiation therapy, interferon therapy, and bleomycin, have been used for management of patients with Gorham's disease presenting with chylothorax. In general, no single treatment modality has proven effective in arresting the disease.

Keywords: Essential Osteolysis; Bone diseases; Bone resorption

A diverse group of primary or idiopathic disorders can lead to significant lysis of the skeleton. These osteolytic syndromes (table 1) differ in the presence or absence of genetic transmission, the associated clinical features, and the major locations of osteolysis. However, a detailed discussion of all these osteolytic disorders is beyond the scope of this overview and will, therefore, focus only on Gorham's disease or massive osteolysis.

Gorham's disease, fortunately, is an extremely rare disorder of the musculoskeletal system. In 1954, Gorham and colleagues¹ reported on two patients with massive osteolysis of the bone. Of the two cases, one was a boy, 16 years of age, with right clavicle and scapula involvement. This patient eventually developed chylothorax and expired. The other was a male, 44 years of age, who also had involvement of the right clavicle and scapula. In addition, these authors provided a brief review of 16 reported cases from the literature.

In 1955, Gorham and Stout² provided a more comprehensive report on this subject. Based on their experience and the available case reports from the literature, they found that "Gorham's disease is usually associated with an angiomatosis of blood vessels and sometimes of lymphatic vessels, which seemingly are responsible for it". In the past 50 years, numerous papers³⁻¹⁴⁷ have been published in medicine, orthopaedic surgery, general surgery, neurosurgery, otolaryngorhinology, plastic surgery, maxillo-facial, and dental literature. On detailed review of the literature, it is evident that various eponyms (table 2) have been used to describe this mysterious disorder of the musculoskeletal system. The purpose of this review is to make the medical community aware of this rare entity, and to discuss the etiopathology, clinical presentation, radiographic findings, differential diagnoses, and treatment options for patients with Gorham's disease.

Etiopathology

To date, the etiology and pathophysiology of this poorly understood disease remains undetermined. The pathological process is the replacement of normal bone by an aggressively expanding but non-neoplastic vascular tissue,^{57,97,113,116} similar to a hemangioma or lymphangioma. Wildly proliferating neovascular tissue causes massive bone loss. In the early stage of the lesion, the bone undergoes resorption, and is replaced by hypervascular fibrous connective tissue and angiomatous tissue. Histologically, involved bones show a non-malignant proliferation of thin-walled vessels; the proliferative vessels may be capillary, sinusoidal or cavernous. In late stages, there is progressive dissolution of the bone leading to massive osteolysis, with the osseous tissue being replaced by fibrous tissue. The stimulus that generates this change in the bone is unknown.⁹⁷

Table 1. Differential Diagnoses of Osteolysis Syndromes.

Massive osteolysis (Gorham's disease)
Acro-osteolysis of Hajdu and Cheney
Idiopathic multicentric osteolysis (carpal-tarsal osteolysis)
Multicentric osteolysis with nephropathy
Hereditary multicentric osteolysis
Neurogenic osteolysis
Acro-osteolysis of Joseph
Acro-osteolysis of Shinz
Farber's disease
Winchester's syndrome
Osteolysis with detritic synovitis

Adapted from Resnick D. Osteolysis and chondrolysis. In: Resnick D, ed. Diagnosis of bone and joint disorders. 4th Ed. Philadelphia, PA: W.B. Saunders Co.; 2002. 4920-4944.

Table 2. Eponyms for Gorham's Disease.

Gorham's Syndrome
Gorham-Stout Syndrome
Morbus Gorham-Stout Disease
Massive Osteolysis
Idiopathic Massive Osteolysis
Progressive Massive Osteolysis
Massive Gorham Osteolysis
Disappearing Bone Disease
Vanishing Bone Disease
Phantom Bone Disease

One main structural feature of the lesion is the presence of unusually wide capillary-like vessels and, therefore, it is likely that the blood flow through these vessels is slow. It has been suggested that the slow circulation produces local hypoxia and lowering of the pH, favoring the activity of various hydrolytic enzymes.²¹ Heyden and colleagues²¹ observed strong activity of both acid phosphatase and leucine aminopeptidase in mononuclear perivascular cells that were in contact with remaining bone, perhaps indicating that these cells are important in the process of osseous resorption.

The exact nature of the disease process is unknown. The resemblance of the pathologic characteristics to those of hemangiomas, coupled with the presence of soft tissue hemangiomatous or lymphangiomatous tissue, has suggested to some investigators, including Gorham and Stout,² that massive osteolysis represents a vascular derangement or a

diffuse hemangiomas. Gorham and Stout² maintained that active hyperemia, changes in local pH, and mechanical forces promote bone resorption. They hypothesized that trauma may trigger the process by stimulating the production of vascular granulation tissue, and that “osteoclastosis” is not necessary. In contrast, Devlin and colleagues⁹⁷ have suggested that bone resorption in patients with Gorham’s disease is due to enhanced osteoclast activity, and that interleukin-6 (IL-6) may play a role in the increased resorption of bone. Moller and associates¹²⁵ reported six cases of Gorham-Stout syndrome with histopathological findings and presented evidence that osteolysis is due to an increased number of stimulated osteoclasts.

Dickson and colleagues⁴⁶ have reported on cytochemical investigation of vanishing bone disease (Gorham’s disease). The ultrastructural localization of non-specific alkaline phosphatase, and of specific and non-specific acid phosphatase activity was studied in slices of tissue removed from a patient with Gorham’s disease. Alkaline phosphatase was present around the plasma membranes of osteoblasts and associated with extracellular matrix vesicles in new woven bone. Concentrations of specific secretory acid phosphatase reaction product in the cytoplasm of degenerating osteoblasts may contribute to the imbalance between bone formation and resorption. Osteoclasts, while few in number, showed non-specific and specific acid phosphatase activity. The Golgi apparatus and heterophagic lysosomes of mononuclear phagocytes were rich in non-specific acid phosphatase. This was also present in the Golgi lamellae and lysosomes of endothelial cells. Acid phosphatase cytochemistry suggests that mononuclear phagocytes, multinuclear osteoclasts, and the vascular endothelium are involved in the process of bone resorption in patients with Gorham’s disease.

Hirayama and colleagues¹³⁰ have reported on the cellular and humoral mechanisms of osteoclast formation and bone resorption in patients with Gorham-Stout syndrome. These authors suggested that the increase in osteoclast formation in Gorham-Stout syndrome is not due to an increase in the number of circulating osteoclast precursors, but rather to an increase in the sensitivity of these precursors to humoral factors which promote osteoclast formation and bone resorption. It has also been suggested that thyroid C cells and calcitonin may play an important role in the pathogenesis of Gorham’s disease.¹²⁰

Clinical Features

Gorham’s disease can involve men or women and any age group, although most cases are discovered before the age of 40 years. No familial predisposition has been found. The process may affect the appendicular or the axial skeleton. The shoulder^{121,123,126,131} and the pelvis^{48,61,95,103,118,145} are the most common sites of involvement, however, various locations such as the humerus,^{5,17,63} scapula,^{1,22,59,68} clavicle,^{1,29,47,59} ribs,^{22,56,71,110,143} sternum, pelvis^{48,61,95,103,118,145} and femur^{55,89,95} can be affected by Gorham’s disease. The disorder is also known to occur at other sites such as the skull,^{18,26,27,51,92,}

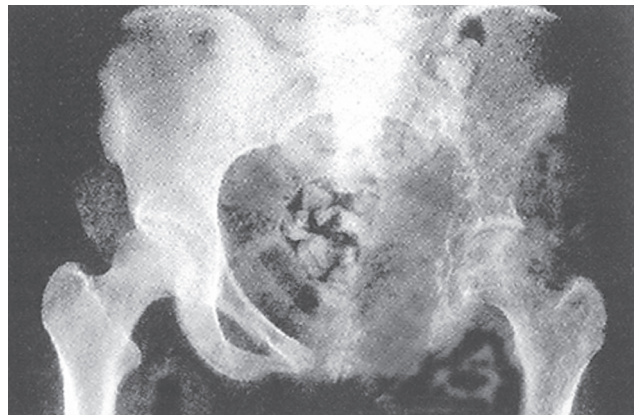


Figure 1. Antero-posterior radiograph of the pelvis in a patient with Gorham’s disease showing osteolysis involving the left ilium. Note the osseous resorption involving the proximal aspect of the left femur. (Reproduced with permission from Elsevier. In: Peter Bullough, ed. Orthopaedic Pathology. 4th Ed. Philadelphia, PA: Mosby; 2004. Figure 7.58, p. 196. Copyright 2004 Elsevier. All rights reserved).

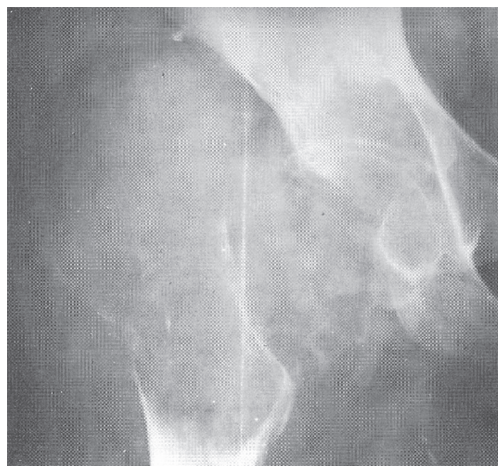


Figure 2. Plain radiograph of the pelvis of a man, 24 years of age, showing a large, expansile osteolytic lesion and a soft-tissue mass involving the right proximal femur. A diagnosis of aneurysmal bone cyst was made after biopsy of the lesion (Reproduced with permission. In: Peter Renton, ed. Orthopaedic Radiology: Pattern Recognition and Differential Diagnosis. 1st Ed. London, UK: Martin Dunitz Ltd.; 1990. Figure 3.43b, p. 170. Copyright 1990 Taylor & Francis. All rights reserved).

98,108,112,128,135 mandible,^{11,12,19,43,66,91, 128,147} maxillofacial skeleton,^{33,54,58,62,92,98,99,127,128} spine,^{30,32,71,78,88,100,106,110, 112,119,122,131,143} hand,^{39,44,114,144} and foot.⁹⁰ Disease of the ribs, scapula, or thoracic vertebrae may lead to the development of chylothorax from direct extension of lymphangiectasia into the pleural cavity or via invasion of the thoracic duct.⁸⁵ Without surgical intervention, patients with Gorham’s disease who develop chylothorax have a high rate of morbidity and mortality.

Clinical manifestations vary and depend on the affected site. Some patients present with a relatively abrupt onset of pain



Figure 3. Plain radiograph in a male, 33 years of age, showing diffuse infiltration along the humeral shaft and osteolysis. There is some reactive sclerosis, no new bone formation and very little evidence of soft-tissue mass. A diagnosis of reticulum cell sarcoma was established on biopsy of the lesion (Reproduced with permission. In: Peter Renton, ed. *Orthopaedic Radiology: Pattern Recognition and Differential Diagnosis*. 1st Ed. London, UK: Martin Dunitz Ltd.; 1990. Figure 3.76, p. 198. Copyright 1990 Taylor & Francis. All rights reserved).

and swelling in the affected extremity, whereas others present with history of insidious onset of pain, limitation of motion, and progressive weakness in the involved limb. This may be accompanied with soft-tissue weakness and/or atrophy. In some cases, history of significant trauma makes the limb painful, forcing the patients to report their symptoms to their family physician and providing for an early diagnosis of Gorham's disease.

Although the degree of osseous deformity in patients with Gorham's disease may become severe, serious complications are infrequent. Paraplegia related to spinal cord involvement may occur in patients who have involvement of vertebrae with resultant osteolysis.⁴ Thoracic cage, pulmonary, or pleural involvement can lead to compromise of respiratory function and death can ensue. Infection of bone and septic shock, although rare, have also been reported.⁸

Investigations

The standard laboratory blood tests are usually within normal limits, and are not helpful to make a diagnosis of Gorham's disease. The serum alkaline phosphatase level may be slightly elevated.

A variety of imaging methods can be used in evaluating patients suspected of having Gorham's disease. Plain

radiographs,^{6,28,36,71,77,79,116,136,143} radioisotope bone scans,^{50,79,81,111,116,143} computed tomography (CT),^{71,76,77,79,87,106,143} and magnetic resonance imaging (MRI)^{76,77,87,106,116,138,143} have all been used in such evaluations.

The most dramatic aspect of Gorham's massive osteolysis is its radiographic appearance. Radiographic findings in patients with Gorham's disease were described by Resnick.¹³⁶ During the initial stage of the lesion, radiolucent foci appear in the intramedullary or subcortical regions, resembling findings seen in patchy osteoporosis. Subsequently, slowly progressive atrophy, dissolution, fracture, fragmentation, and disappearance of a portion of the bone occurs with tapering or "pointing" of the remaining osseous tissue and atrophy of soft tissues. The disease process can extend to contiguous bones; the intervening joints afford no protection to extension of the disease. Thus, osteolysis of ilium may be associated with resorption of the proximal portion of the femur (figure 1), whereas changes in the scapula may later be combined with osteolysis of the proximal aspect of the humerus, clavicle, and ribs. Such patterns of regional osseous destruction should enable physicians to make an accurate diagnosis. The degree of osseous destruction generally increases relentlessly over a period of years and may, eventually, stabilize spontaneously. Some reports of massive osteolysis describe spontaneous recovery of some of the lost osseous tissue¹⁷ or clinical and radiographic improvement after radiation therapy.³⁹

Radioisotope bone scan may demonstrate increased vascularity on initial images and, subsequently, an area of decreased uptake corresponding to the site of diminished or absent osseous tissue. However, these results have been variable.¹¹⁶ The reported MRI findings of Gorham's osteolysis have also been variable. T1-weighted-spin echo MRIs show uniformly low signal intensity in the involved bones, whereas an increased signal intensity generally is observed in T2-weighted-spin echo images. Enhancement of the lesions is usually seen after intravenous administration of gadolinium.

Differential Diagnoses

It is worth emphasizing that for all patients who present with skeletal osteolysis, a thorough history and meticulous physical examination should be undertaken first. Appropriate blood tests and radiographic studies should be requested to rule out other common (in contrast to the extremely rare Gorham's disease) underlying causes of osteolysis such as infection, cancer (primary or metastatic), inflammatory or endocrine disorders. The diagnosis of Gorham-Stout syndrome should be suspected or made only after excluding these aforementioned conditions. Figure 2 through figure 5 show examples of patients who have benign or malignant (primary or metastatic) bone lesions. It should be noted that radiographic findings of these patients might resemble those of patients with Gorham's massive osteolysis. Gorham's disease can also mimic various osteolytic syndromes

(table 1). Readers are encouraged to refer to major textbooks on radiology of musculoskeletal disorders for details of other primary or idiopathic osteolytic syndromes.

Treatment

Due to the rarity of this disease entity, there is no standard therapy available. The medical treatment for Gorham's disease includes radiation therapy,^{10,21,39,44,60,69,101,112,139,140} anti-osteoclastic medication (bisphosphonates),^{109,146} and alpha-2b interferon.¹⁰⁹

The principal treatment modalities are surgery and radiation therapy. Surgical options include resection of the lesion, and reconstruction using bone grafts and/or prostheses. Definitive radiation therapy in moderate doses (40-45 Gy in 2 Gy fractions) appears to result in a good clinical outcome with few long-term complications.⁶⁹ The prognosis for patients with Gorham's disease is generally good unless vital structures are involved.

A particularly dangerous form of the disease affects the thorax resulting in pleural effusion^{29,47,70,71,83,86,93,101,107} and chylothorax.^{9,20,41,48,56,78,85,96,104,122,129,132-134,137,142} Various treatment modalities have been employed for the management of chylothorax in patients with Gorham's disease, including pleurectomy,^{35,134} pleurodesis,^{20,29,48,133,142} thoracic duct ligation,⁸⁵ radiation therapy,^{101,133,139,142} interferon therapy and oral clodronate,¹⁰⁹ and bleomycin.⁹⁶

Tie and colleagues⁸⁵ have reported some success using thoracic duct ligation to treat chylothorax in patients with Gorham's disease. Of the eleven cases they reviewed, seven patients underwent successful thoracic duct ligation and survived, while four patients died following failed attempts to localize the thoracic duct during surgery. It is worth emphasizing that thoracic duct ligation does not always produce a lasting resolution of chylothorax.^{45,132}

Radiation therapy^{101,133,139,142} can be employed for the management of chylothorax in patients who may not be suitable candidates for an extensive surgical procedure due to their poor general health, and for those who have failed surgical treatment. The disadvantages of radiation therapy include the possibility of acute side effects such as gastrointestinal tract irritation with resultant nausea and/or vomiting, and radiation-induced pneumonia. Furthermore, in children and adolescents who receive high-dose radiation therapy, the potential for secondary malignancy and growth restriction exists and should be considered before embarking on this mode of treatment.

Discussion

Gorham's disease is a very rare disorder characterized by uncontrolled, destructive proliferation of vascular or lymphatic capillaries within bone and surrounding soft tissue.² Most cases occur in children and young adults (usually less than 40 years of age) and no definite inheritance



Figure 4. Plain radiograph of the distal femur of a male, 18 years of age, showing osteolytic lesion with a soft-tissue mass. A diagnosis of osteosarcoma was confirmed on biopsy of the lesion (Reproduced with permission. In: Peter Renton, ed. *Orthopaedic Radiology: Pattern Recognition and Differential Diagnosis*. 1st Ed. London, UK: Martin Dunitz Ltd.; 1990. Figure 3.68a, p. 190. Copyright 1990 Taylor & Francis. All rights reserved).



Figure 5. Plain radiograph of the pelvis of a female patient who has extensive metastatic bone disease secondary to carcinoma of the breast. Note the widespread areas of osteolysis throughout the pelvis and proximal femora. There is also some reactive sclerosis. (Reproduced with permission. In: Peter Renton, ed. *Orthopaedic Radiology: Pattern Recognition and Differential Diagnosis*. 1st Ed. London, UK: Martin Dunitz Ltd.; 1990. Figure 2.13, p. 86. Copyright 1990 Taylor & Francis. All rights reserved).

pattern has been reported. Diagnosis is often delayed in most cases as laboratory studies are usually within normal limits. A high index of clinical suspicion together with characteristic radiographic and histopathological findings are helpful for making an early accurate diagnosis.

The natural history of Gorham's disease is unpredictable and, in some cases, spontaneous regression has been reported.^{17,45} Campbell and colleagues¹⁷ reported a case of an elderly woman who presented with a pathological fracture

of the right humerus. In this case, progressive dissolution of the shaft of humerus occurred over a period of six months. No cause could be established and the patient refused biopsy. The pathologic humerus was treated with splinting and the humeral shaft gradually reformed and re-ossified over a period of next two years. In many other patients, Gorham's disease is relentlessly progressive and involvement of vital structures can occur leading to high morbidity and mortality. Extension of the disease from the scapula, ribs or thoracic vertebra can result in pericardial and pleural effusions, and chylothorax. In general, visceral and spinal involvement is usually associated with a poor prognosis.

Several therapeutic modalities have been used in the management of Gorham's disease. The non-operative options include radiation therapy,^{10,21,39,44,60,69,101,112,139,140} anti-osteoclastic medication (bisphosphonates),^{109,146} and alpha-2b interferon.¹⁰⁹ The operative options include surgical resection,^{10,29,63,69} reconstruction using a bone graft,^{30,63} or a prosthesis.^{5,42} It is worth noting that the success rate after the use of a bone graft is low. Most surgeons, based on their personal experience, have observed that the bone graft undergoes dissolution. In recent years, most patients have been treated with surgery and/or radiation therapy.

Turra and associates⁶³ have reported a 20-year follow-up of a case of surgically treated massive osteolysis of the humerus that occurred in a male, 19 years of age. The lesion was successfully treated with an autogenous fibular shaft transplant. During the 20-year follow-up period, the function of the humerus was restored. Plain radiographs showed incorporation of the fibular graft without any recurrence of the disease. This report supports the contention that only predominantly cortical autogenous bone grafting may be successful. It seems that the cortical bone (compared to the cancellous bone) shows greater resistance to erosion to the offending lymphangiomatous osteolytic tissue.

Rauh and Gross¹¹⁴ reported a 48-year follow-up of Gorham-Stout disease involving the right hand of a 12-year-old patient. The osteolysis progressed until the age of 21 years and was then stable until the age of 59 years when the patient died from metastatic colon cancer. This case report supports the common belief that Gorham's disease undergoes spontaneous resolution.

Boyer and colleagues¹⁴⁵ have recently reported a 50-year clinical and radiographic follow-up of Gorham-Stout syndrome of the pelvis in a man who has never been treated. To date, this is the longest documented case report of Gorham's disease and its natural history. This case-report demonstrates that after a variable time of evolution, the massive osteolysis is able to undergo spontaneous arrest and that the lesions may remain stable during several decades. No reossification was observed even after 37 years of disease quiescence.

Conclusions

Gorham's disease is a rare musculoskeletal disorder. Its diagnosis is usually delayed and often missed as not many physicians have opportunity to treat this rare disease entity in their clinical practice. Review of the published literature on this subject, shows that this disease is described and discussed under a number of eponyms (table 2).

Gorham's disease is a rare, peculiar musculoskeletal disorder in which the affected bone virtually disintegrates and is replaced by vascular fibrous connective tissue. The etiology of Gorham's disease is still speculative. Its clinical presentation is variable, largely depending upon the site of skeletal involvement. The natural history and prognosis of this disease are unpredictable and no effective therapy is known. In recent years, most patients have been treated with surgery and/or radiation therapy.

Physicians must take a thorough history and perform a complete physical examination for all patients who present with osteolysis of the shoulder or pelvic girdle, long bones, or vertebrae. Other diagnoses, such as infection and cancer, must be ruled out by appropriate blood tests and radiographic studies. A definitive diagnosis must be established by performing a biopsy of the offending lesion. The diagnosis of Gorham's disease should be made only after carefully eliminating the aforementioned causes of osteolysis.

In this issue of *Clinical Medicine & Research*, Duffy and colleagues¹⁴⁸ report a case of Gorham's disease with chylothorax that was successfully treated with radiation therapy. The authors should be congratulated for bringing such a rare case to the attention of the medical community and helping to expand upon our poor existing knowledge of this ailment. Awareness of this disease entity should enhance our clinical acumen and allow for better evaluation and management of this fascinating and rare disorder.

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