Gorham Disease

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Abstract

Gorham disease, a rare condition of unknown etiology, presents as skeletal lucency on radiographs, prompting the classic eponym of *vanishing bone disease*. Initial clinical presentation varies considerably but typically involves prolonged soreness in the affected region and, rarely, acute pathologic fracture. The nonspecific nature of complaints, lack of markers of systemic illness, and rarity of the disease contribute to delayed diagnosis. Several imaging studies (eg, plain radiographs, computed tomography, magnetic resonance imaging, nuclear studies) provide nonspecific findings, but frank cortical destruction and true "disappearance" of bone with extensive soft-tissue edema are evident. Diagnosis can be rendered only after exclusion of neoplastic and infectious etiologies through clinical and laboratory work-up, imaging studies, and tissue sampling. Although no single or combined treatment modality is considered the gold standard, management generally centers on radiation therapy for local control of large and painful lesions, and on surgical intervention for pathologic progression that would otherwise result in substantial functional limitations. Antiosteoclastic medications, a combination of interferon alpha-2b and low-molecular-weight heparin, and propranolol reportedly have been of some benefit.

Gorham disease, a rare condition of unknown etiology, manifests as acute, spontaneous osteolysis associated with benign hemangiomatosis or lymphangiomatosis, which presents as skeletal lucency on radiographs, prompting the classic eponym of *vanishing bone disease*.[1-6] There is no evidence supporting the idea that osteoclasts are present in any meaningful amount in the resorption areas or that local reparative osteogenesis occurs.[4,6]

Jackson and colleagues first described idiopathic osteolysis in 1838,[1,2] and Gorham and Stout[3] introduced the syndrome to the orthopedic community in 1955. Since then, few strides have been made in identifying the disease origin.[1,2,4] Diagnosis is possible only after meticulous work-up has excluded neoplastic and infectious etiologies.[7,8]

Clinical Presentation

Gorham disease affects patients ranging widely in age, from 2 months to 78 years, but typically presents in those under 40 years. There is a questionable predilection for males but no correlation with ethnicity or geographic region. There is no clear hereditary pattern of transmission.[7] Although the bones of the head, neck, and upper extremities are involved in most cases, bone of any type or location can be affected.[6] Pelvic bones seem to be involved least often.[6,7]

Initial clinical presentation varies considerably but typically involves prolonged soreness in the affected region and, rarely, acute pathologic fracture.[1,2,4] The nonspecific nature of complaints, lack of markers of systemic illness, and rarity of the disease contribute to delayed diagnosis.[1,2]

Imaging

Plain radiographs show permeative osteolysis involving the subcortical and intramedullary regions and typically affecting regional, contiguous bones, without adjacent sclerosis, and somewhat resembling heterogeneous osteoporosis (**Figure 1**).[8-10]

Computed tomography (CT) better defines the severity and extent of these changes. Progression can result in osseous tapering, or "pointing" at lytic margins, forming cone-shaped spicules. In progressive cases, there is an "extraosseous" stage characterized by frank cortical destruction and true "disappearance" of bone, with extensive soft-tissue edema[8-10] (**Figures 2A, 2B**).

Magnetic resonance imaging shows an infiltrative and irregular T2 hyperintense signal throughout regions of bone affected by osteolysis, but this finding is not characteristic. There is heterogeneous enhancement on postcontrast sequences, and, though masslike enhancement is absent,

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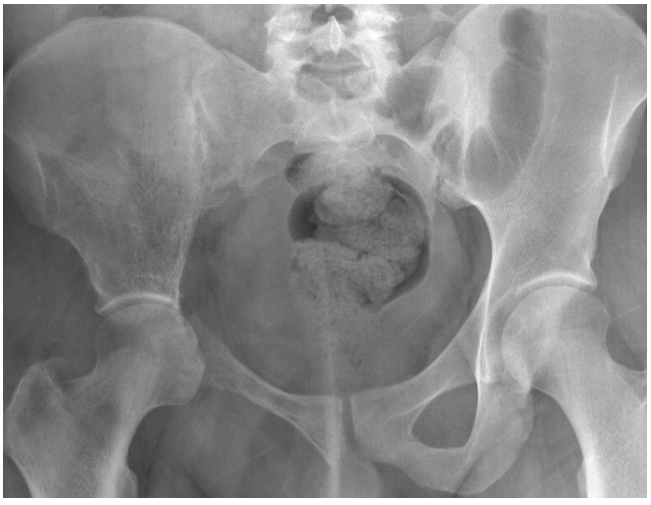

Figure 1. Anteroposterior radiograph of the pelvis shows complete destruction of the right ischium, medial acetabular wall, and the inferior pubic ramus, with permeative osteolysis also involving the right superior pubic ramus and the iliac wing, as well as the right sacrum. Subtle lucency in the right femoral head and the intertrochanteric region also indicates site involvement.

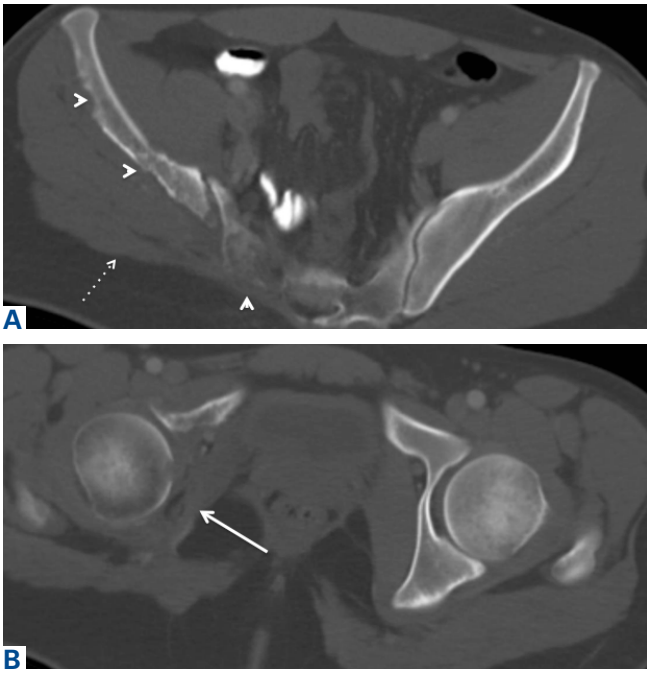

Figure 2. (A) Contrast-enhanced axial computed tomography (CT) shows extensive permeative osteolysis of the right sacrum and the right iliac bone (white arrowheads), which is destroyed posteriorly, and asymmetric atrophy of the right vs left gluteal muscles (white dashed arrow). (B) Axial CT more inferiorly shows obliteration of the right medial acetabular wall (white arrow).

signal abnormalities may extend into adjacent soft tissues. These changes indicate inflammation and hemorrhage of various degrees interspersed with scant fibrous tissue[8-10] (**Figures 3A, 3B**).

Bone scintigraphy using technetium-99m is similarly nonspecific, typically revealing radiotracer uptake that is consistent with bony reaction to an underlying osteolytic process (**Figure 4**) but turning negative with ongoing resorption. In some cases of Gorham disease, bone scintigraphy did not reveal a significant increase in activity, such as would be expected in a vascular malformation or purely angiomatous neoplasm. Similar findings could be attributed to a variety of pathologies, including primary bone tumor, metastasis, or even osteomyelitis.[8-10]

Positron emission tomography/CT typically shows foci of increased metabolic activity in the areas of osteolysis.[10]

Diagnosis

There have been 8 histologic and clinical criteria described to diagnose Gorham disease: (1) biopsy positive for presence of angiomatous tissue, (2) complete absence of any cellular atypia, (3) lack of osteoclastic response and lack of dystrophic calcifications, (4) evidence of progressive resorption of native bone, (5) no evidence of expansive or ulcerative lesion, (6) lack of visceral involvement, (7) osteolytic radiographic pattern, and (8) no concrete diagnosis after hereditary, metabolic, neoplastic, immunologic, and infectious work-up.[4-6] These

Take-Home Points

- Gorham disease is a rare condition that manifests as an acute, spontaneous osteolysis.
- There is no clear hereditary pattern of transmission. Bones of any type or location can be affected.
- Imaging studies are nonspecific, but show permeative osteolysis involving the subcortical and intramedullary regions and typically affect regional, contiguous bones, without adjacent sclerosis, somewhat resembling osteoporosis.
- Tissue biopsy is indicated to rule out other potential etiologies of osteolysis, and the histologic findings help confirm a diagnosis of Gorham disease.
- There is no single or combined treatment modality that is considered as the gold standard. Surgical treatment includes resection of the lesion and reconstruction. Also, antiosteoclastic medication can be used.

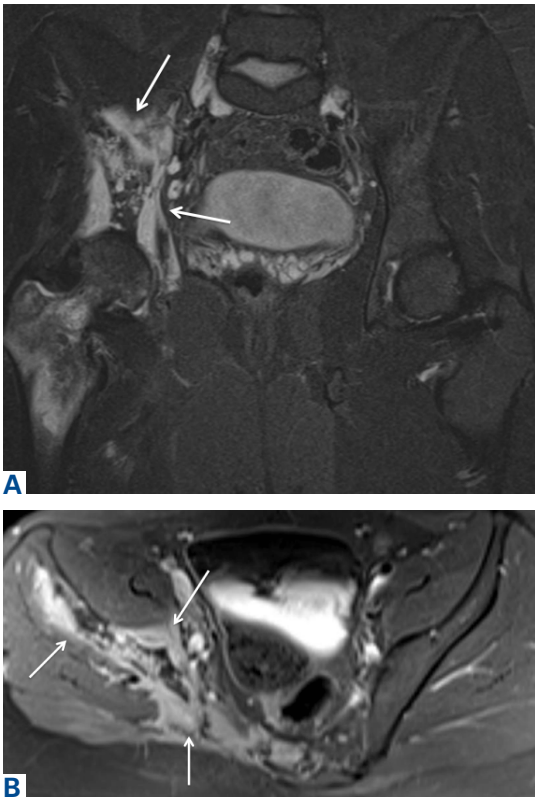

Figure 3. (A) T2-weighted fat-suppressed coronal magnetic resonance imaging (MRI) shows extensive soft-tissue edema enveloping the right iliac bone (white arrows) with pronounced underlying bone marrow edema pattern in the right iliac bone and the proximal femur. (B) Contrast-enhanced MRI shows enhancing soft-tissue surrounding iliac bone laterally, anteriorly, and posteriorly (white arrows), infiltrating the marrow and resulting in osseous destruction of bone around the right sacroiliac joint, as seen on computed tomography (CT). Material from this area was subsequently aspirated under CT guidance and found to be serosanguinous; cultures of the aspirate were negative for bacteria and atypical organisms.

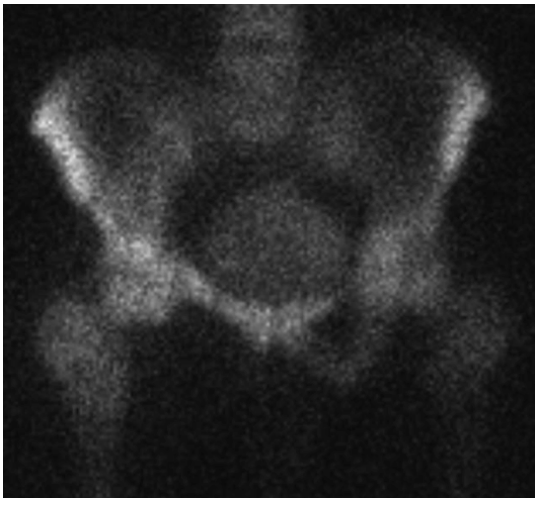

Figure 4. Technetium 99–methyl diphosphonate bone scan in the frontal projection shows the absence of radiotracer uptake in the right ischium, the inferior pubic ramus and subtle increased uptake in the proximal right femur. These findings represent different stages of disease; complete osseous destruction results in areas of photopenia, areas of ongoing osteolysis, and attempted remodeling in the femur manifest as increased radiotracer uptake.

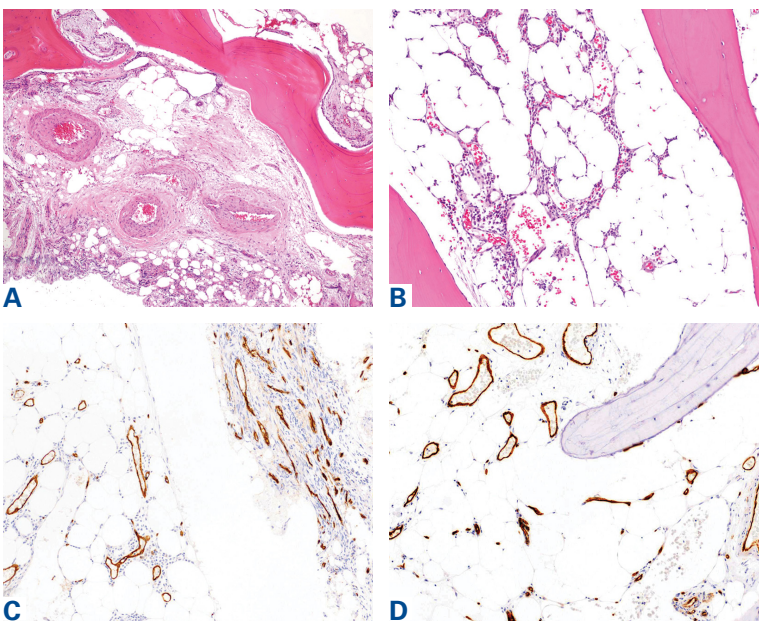

Figure 5. (A) Surgically resected specimen with a proliferating, well-developed, varying-caliber, cytologically benign vessels, characteristic of Gorham disease (hematoxylin-eosin). (B) A needle biopsy reveals a collection of small, thin-walled vessels between bony trabeculae (hematoxylin-eosin). Immunohistochemistry may be useful particularly for this and other small biopsy specimens. Vasculature is highlighted by the (C) vascular endothelial marker CD34 and the (D) lymphatic endothelial marker D2-40 (each with immunohistochemical stain).

criteria confirm that the diagnosis can be rendered only after exclusion of neoplastic and infectious etiologies through clinical and laboratory work-up, imaging studies, and tissue sampling.

Tissue biopsy is indicated to rule out other potential etiologies of osteolysis, and the histologic findings help confirm a diagnosis of Gorham disease. Biopsies typically show a progressive osteolysis that is consistently associated with a benign but abnormal vascular proliferation that in many cases has characteristics of lymphatic endothelium. The apparent bony destruction is largely attributed to this process (**Figures 5A-5D**).[11,12]

The differential diagnosis includes infection (osteomyelitis, Brodie abscess), benign tumors (eosinophilic granuloma/Langerhans cell histiocytosis), malignant tumors (Ewing sarcoma and angiosarcoma), inflammatory conditions (eg, apatite-

Table. **Articles on Different Treatment Modalities for Different Presentations of Gorham Disease**

Article	History/Manifestation	Recommendation/Treatment	Outcome
Fontanesi[15]	History of Noonan syndrome	Radiation	Resolution at 6 mo
Nir et al[14]	Osseous disease with visceral extension	Propranolol	Near resolution at 15 mo
Paley et al[20]	Isolated osseous disease	Surgery (autograft and prosthetic reconstruction)	Graft resorption at 4 y
Patrick[17]	With chylothorax	Surgery (pleurodesis)	Resolution at 1 y
Pfleger et al[16]	With chylothorax	Surgery (thoracic duct ligation and pleurodesis), interferon alfa-2b	Various (review of 38 cases)
Lee et al[23]	Mediastinal compromise, recurrent chylothorax	Surgery (radical thoracocervical resection), unspecified chemotherapy and radiation	Death status post 14 y of complications
Hagberg et al[18]	Isolated osseous disease	Interferon alfa-2b, oral clodronate	Resolution at 19-mo follow-up
Takahashi et al[19]	Gorham disease with local soft-tissue extension	Interferon alfa, steroid pulse therapy	Resolution at 10 mo
Brodszki et al[13]	Gorham disease with chylothorax	Interferon alfa-2b, low-molecular-weight heparin (tafoxiparin), surgery, radiation	Resolution (1 of 2 patients required surgery) at 2-6 mo
Avelar et al[21]	Isolated osseous disease	Zoledronic acid	Resolution at 12 mo
Holroyd et al[22]	Isolated osseous disease	Etoposide	Death at 2 y

associated destructive arthritis), endocrine disorders (eg, osteolytic hyperparathyroidism), benign non-neoplastic conditions (venous or venolymphatic malformation), and other syndromes that present with osteolysis.[1,2] Nevertheless, progressive and unusually substantial bone destruction without evidence of repair is almost pathognomonic for Gorham disease.[9]

Treatment

Although no single or combined treatment modality is considered the gold standard (**Table**),[1,2,4,13-23] management of Gorham disease generally centers on radiation therapy for local control of large and painful lesions and on surgical intervention for pathologic progression that would otherwise result in substantial functional limitations.[2] Also described for treatment are antiosteoclastic medications (bisphosphonates), which are often used in conjunction with radiation and/or surgical intervention.[2,4] The newer literature cites some benefit of using various experimental modalities, including a combination of interferon alfa-2b and low-molecular-weight heparin,[13] and even propranolol.[14]

Surgical treatment usually includes lesion resection and subsequent reconstruction using combinations of bone grafts (allogenic) and prostheses. Bone graft alone is quickly resorbed and has not been found to be beneficial.[1,2,4,20]

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References

1. Saify FY, Gosavi SR. Gorham's disease: a diagnostic challenge. *J Oral Maxillofac Pathol.* 2014;18(3):411-414.
2. Patel DV. Gorham's disease or massive osteolysis. *Clin Med Res.* 2005;3(2):65-74.
3. Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone); its relation to hemangiomatosis. *J Bone Joint Surg Am.* 1955;37(5):985-1004.

4. Heffez L, Doku HC, Carter BL, Feeney JE. Perspectives on massive osteolysis. Report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol*. 1983;55(4):331-343.
5. Gulati U, Mohanty S, Dabas J, Chandra N. "Vanishing bone disease" in maxillofacial region: a review and our experience. *J Maxillofac Oral Surg*. 2015;14(3):548-557.
6. Nikolaou VS, Chytas D, Korres D, Efstathopoulos N. Vanishing bone disease (Gorham-Stout syndrome): a review of a rare entity. *World J Orthop*. 2014;5(5):694-698.
7. Möller G, Priemel M, Amling M, Werner M, Kuhlmey AS, Delling G. The Gorham-Stout syndrome (Gorham's massive osteolysis). A report of six cases with histopathological findings. *J Bone Joint Surg Br*. 1999;81(3):501-506.
8. Dominguez R, Washowich TL. Gorham's disease or vanishing bone disease: plain film, CT, and MRI findings of two cases. *Pediatr Radiol*. 1994;24(5):316-318.
9. Kotecha R, Mascarenhas L, Jackson HA, Venkatramani R. Radiological features of Gorham's disease. *Clin Radiol*. 2012;67(8):782-788.
10. Dong A, Bai Y, Wang Y, Zuo C. Bone scan, MRI, and FDG PET/CT findings in composite hemangioendothelioma of the manubrium sterni. *Clin Nucl Med*. 2014;39(2):e180-e183.
11. Baulieu F, De Pinieux G, Maruani A, Vaillant L, Lorette G. Serial lymphoscintigraphic findings in a patient with Gorham's disease with lymphedema. *Lymphology*. 2014;47(3):118-122.
12. Manisali M, Ozaksoy D. Gorham disease: correlation of MR findings with histopathologic changes. *Eur Radiol*. 1998;8(9):1647-1650.
13. Brodszki N, Länsberg JK, Dictor M, et al. A novel treatment approach for paediatric Gorham-Stout syndrome with chylothorax. *Acta Paediatr*. 2011;100(11):1448-1453.
14. Nir V, Guralnik L, Livnat G, et al. Propranolol as a treatment option in Gorham-Stout syndrome: a case report. *Pediatr Pulmonol*. 2014;49(4):417-419.
15. Fontanesi J. Radiation therapy in the treatment of Gorham disease. *J Pediatr Hematol*. 2003;25(10):816-817.
16. Pfleger A, Schwinger W, Maier A, Tauss J, Popper HH, Zach MS. Gorham-Stout syndrome in a male adolescent—case report and review of the literature. *J Pediatr Hematol Oncol*. 2006;28(4):231-233.
17. Patrick JH. Massive osteolysis complicated by chylothorax successfully treated by pleurodesis. *J Bone Joint Surg Br*. 1976;58(3):347-349.
18. Hagberg H, Lamberg K, Åström G. α-2b interferon and oral clodronate for Gorham's disease. *Lancet*. 1997;350(9094):1822-1823.
19. Takahashi A, Ogawa C, Kanazawa T, et al. Remission induced by interferon alfa in a patient with massive osteolysis and extension of lymph-hemangiomatosis: a severe case of Gorham-Stout syndrome. *J Pediatr Surg*. 2005;40(3):E47-E50.
20. Paley MD, Lloyd CJ, Penfold CN. Total mandibular reconstruction for massive osteolysis of the mandible (Gorham-Stout syndrome). *Br J Oral Maxillofac Surg*. 2005;43(2):166-168.
21. Avelar RL, Martins VB, Antunes AA, de Oliveira Neto PJ, de Souza Andrade ES. Use of zoledronic acid in the treatment of Gorham's disease. *Int J Pediatr Otorhinolaryngol*. 2010;74(3):319-322.
22. Holroyd I, Dillon M, Roberts GJ. Gorham's disease: a case (including dental presentation) of vanishing bone disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;89(1):125-129.
23. Lee S, Finn L, Sze RW, Perkins JA, Sie KC. Gorham Stout syndrome (disappearing bone disease): two additional case reports and a review of the literature. *Arch Otolaryngol Head Neck Surg*. 2003;129(12):1340-1343.

This paper will be judged for the Resident Writer's Award.