European Journal of Musculoskeletal Diseases
ISSN 2038-4106/2021

Letter to the Editor

GORHAM-STOUT SYNDROME

G. Carnevali[1] and L. Mavriqi[2]

[1]University of Ferrara, Italy
[2]University of Albania University, Albania

Correspondence to:
Giulia Carnevali, MD, DDS,
University of Ferrara, Ferrara, Italy
e-mail: giulia.carnevali84@gmail.com

ABSTRACT

Gorham-Stout syndrome (GSS) is a relatively rare condition with no known cause. It is distinguished by the breakdown of osseous matrices and the growth of vascular structures, leading to bone loss and subsequent fractures. Even though there has been much research on the disease's pathogenetic pathways, its aetiology is still unclear, and there are a few different views about what caused it. The disease can affect the patient's head, lower and upper extremities, vertebrae, and pelvis to varying degrees. The syndrome can also affect numerous bones at the same time. Pain, impaired functioning, and inflammation of the affected region are the hallmarks of a patient's clinical picture of GSS. However, asymptomatic cases have been described, as have cases in which the diagnosis was confirmed after pathologic fractures. In this concise review, we will discuss the hypotheses concerning the disease's origin, the clinical manifestations, the diagnostic strategy, and the therapy choices available for this extremely uncommon condition.

KEYWORDS: *lymphatic, osteolysis, bone, resorption, vanishing disease*

INTRODUCTION

A rare ailment distinguished by spontaneous and increasing bone resorption is referred to as Gorham-Stout syndrome (GSS), enormous osteolysis, phantom bone disease, and vanishing disease. Each of these terms is a synonym for the other. It has not been determined what causes the condition, despite the significant research that has been done on the disease's pathogenetic pathways. Jackson, in the year 1838, was the first person to describe this phenomenon. He did so in the context of a case involving a young man whose humerus was slowly wasting away (1). In addition, Gorham and Stout authored a study in 1955 that associated the severe osteolysis observed in the condition with hemangiomatosis. This paper appears to have played a significant part in vanishing bone disease, also known as "Gorham-Stout syndrome" (2).

It is a sickness that has an unpredictable progression and might lead to serious problems. There is no connection between gender, ethnic background, environmental elements, or contagious or environmental health conditions. It is not known what causes the pathophysiology. One of the hypotheses claimed that osteoclasts play a significant role as well as endothelial cells (3). In a systematic review, Faruqi T. et al. (3) reported that TNFα and IL-6 are implicated in GSS since

Received: 02 September 2021
Accepted: 06 November 2021

ISSN: 2038-4106

they stimulate osteoclast formation with excessive osteolysis. Macrophages also produce VEGF, which stimulates the proliferation of endothelial cells. Furthermore, the levels of IL-6 were significantly higher in the serum of GSS patients.

Clinically GSS could manifest itself in several bones, most frequently those in the craniofacial region and the upper arms, but any bone can be affected. The location of the affected area is directly related to the complaints. In most cases, the disease manifests with swelling, discomfort, and a restriction in the affected region's functional capacity. However, the condition can sometimes be asymptomatic unless a pathological fracture occurs (4).

According to Hardegger et al. (5), of the five kinds of osteolysis, this illness is classified as type IV: Type I is a monocentric illness with autosomal dominant inheritance, Type II is a monocentric disease with autosomal recessive inheritance, Type III is nonhereditary multicentric osteolysis with nephropathy, and Type V is Winchester syndrome. Osteolysis and increasing bone resorption are both characteristics that are indicative of the condition. Ribs, vertebrae, pelvis, cerebral vault, clavicle, and mandibular are some typical sites impacted by this condition. In normal circumstances, the bones involved are more likely to have osteopenia and fractures, in addition to swelling and pain. Depending on the degree of the condition, patients might anticipate experiencing both disfigurement and impaired functioning. Most diagnoses are made in patients under 40, and the symptoms and complications can range from moderate to life-threatening. The prognosis is difficult to predict, and GSS can sometimes be accompanied by several catastrophic complications (6).

Etiopathology

In 1987, Dickson et al. (7), after researching the cytochemistry of both alkaline and acid phosphatase, concluded that mononuclear phagocytes, multinuclear osteoclasts, and the vascular endothelium are all involved in bone resorption in this condition. Furthermore, in 1996, Devlin et al. (8) attributed this massive osteolysis to the increased activity of the osteoclasts. In this process, interleukin-6 plays a critical role, as its levels are elevated in the serum of patients suffering from GSS in early stages (8). In addition, an interesting finding made by Korsi et al. in 1998 was that the disease manifested itself in a patient who lacked calcitonin, a hormone that possesses antiosteoclastic activity; this was a consequence of the absence of C-cells in the thyroid gland that the patient possessed (9). On the other hand, Moller et al. (10) mentioned the unprecedented frequency of stimulated osteoclasts as a factor responsible for the development of GSS. At the same time, Hirayama et al. (11) concluded that the increased number of circulating osteoclasts is the repercussion of the heightened susceptibility of their precursors to humoral factors that contribute to osteoclast formation.

Clinical features

Patients, whose age ranges from 1 month to 75 years, can have the condition in one or more of their bones (12). The disease typically affects people under 40 (13), and there does not appear to be an epidemiologic association between race, gender, or geography (14). However, they found that men had a "predilection" for the illness (14). Although GSS can affect many bones, most case reports focus on the upper extremity and the craniofacial region (15). The femur, however, was the primary damaged bone in a case series (14). Initial x-rays show radiological alterations that resemble patchy osteoporosis. Later, an appendicular skeleton in the upper and lower limbs experiences concentric shrinking and bone mass loss, resulting in bone deformity. Eventually, the bone begins to resorb almost entirely, giving rise to the known "vanishing bone" disease (16).

The most common symptoms of vanishing bone disease among patients are pain, impaired functioning, and swelling in the affected area, while asymptomatic cases and situations in which the diagnosis was confirmed after a pathological fracture have also been reported (14). Furthermore, the syndrome's complications risk being fatal, especially when chest complications arise. Pulmonary oedema and chylothorax, which are complications of GSS in a proportion as high as 17%, are two conditions that can significantly affect respiratory function. Chylothorax can happen due to the afflicted thoracic bone intrusion of the thoracic duct or by the extension of lymphangiectasia into the pleural cavity (17). Additionally, there have been few reports, bone infections leading to septic shock (18), spinal cord participation and paraplegia from vertebral lesions, cerebrospinal fluid leaking, and meningitis from damaged skull bones (19).

Diagnosis

The syndrome is difficult to diagnose and requires the assistance of multiple diagnostic examinations. A diagnosis cannot be made based on blood tests because they are typically normal, except for alkaline phosphatase, which may have a modest elevation (17).

Plain radiographs, bone scans, computed tomography (20), and magnetic resonance imaging (i.e. MRI) may also contribute to the diagnostic process. In the beginning, plain X-rays show radiolucent foci in the intramedullary or

subcortical regions. Later, a slowly progressive dissolution, fracture, fragmentation, and disappearance of a portion of a bone become visible, along with constriction or "pointing" of the surviving osseous tissue. CT and MRIs better define the extension of lesions (21).

The histological evaluation affirms the disease, and the biopsy reveals nonmalignant overexpression of small vessels. Heffez et al. proposed the eight diagnostic criteria of GSS: (A) presence of angiomatous tissue; (B) absence of atypia; (C) lack of dystrophic calcifications; (D) indication of local bone progressive remineralization; (E) nonexpansive, non-ulcerative lesion; (F) loss of visceral involvement; (G) osteolytic computed tomography pattern; and (H) lack of hereditary, energy metabolism, neoplastic, autoimmune, and contagious pattern. The diagnosis of GSS should only be considered after other possible reasons for osteolysis, such as infection, malignancy, inflammatory and endocrine problems, have been ruled out (22, 23).

Hereditary multicentric osteolysis, osteolysis with nephrotic syndrome, osteomyelitis, rheumatoid, osteolysis due to eosinophilic granuloma, intracoronary malignancies, hyperparathyroidism, and osteolysis due to disorders affecting the central nervous system, such as syringomyelia and tabes dorsalis are all included in the differential diagnosis of the disease (24).

Treatment

Numerous therapeutic options have been proposed, the effectiveness of which varies depending on the aetiology of the condition, which is why treatment is still a matter of research. Three primary approaches can be used to treat the syndrome: medical therapy, radiation therapy, and surgical procedures (25, 26).

In the first area, bisphosphonates, which have an antiosteolytic action, have been employed to treat the illness (27). In addition, some additional pharmacologic drugs, such as vitamin D, calcium, interferon, adrenal extracts, and androgens, have been proposed.

Patients with substantial symptomatic lesions with chronic debilitating functional instabilities are preferable candidates for radiation therapy and surgical intervention. The use of radiotherapy in therapeutic doses considered on the lower end of the spectrum appears to produce excellent results, with only a limited number of long-term problems (23). However, radiation may cause major adverse effects, such as secondary malignancies and growth limitations in children and adolescents who get high-dose radiation treatments. Therefore, in the final stage, especially when fractures arise, orthopedic and maxillofacial surgery is needed, the lesion is removed, and then bone grafts and/or prostheses are used to reconstruct the affected area. Also, general surgeons are involved, especially for chest drainage, thorax duct conjugation, and pleural treatment (28).

CONCLUSION

GSS is an extremely uncommon condition that can grow in ways that are difficult to anticipate and can cause serious problems. At this time, their osteoclast activation and endothelial cell proliferation are the main targets of current studies on the onset of GSS. The exclusion of other causes is the main axis to reach the diagnosis. In addition, there is no established treatment protocol, and research is still ongoing in this area.

REFERENCES

1. Deveci M, Inan N, Corapçıoğlu F, Ekingen G. Gorham-Stout syndrome with chylothorax in a six-year-old boy. *Indian Journal of Pediatrics*. 2011;78(6):737-739. doi:10.1007/s12098-010-0328-2
2. Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone); its relation to hemangiomatosis. *The Journal of Bone and Joint Surgery American Volume*. 1955;37-A(5):985-1004.
3. Faruqi T, Dhawan N, Bahl J, et al. Molecular, Phenotypic Aspects and Therapeutic Horizons of Rare Genetic Bone Disorders. *BioMed Research International*. 2014;2014:1-16. doi:10.1155/2014/670842
4. 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. *Archives of Otolaryngology–Head & Neck Surgery*. 2003;129(12):1340-1343. doi:10.1001/archotol.129.12.1340
5. Hardegger F, Simpson LA, Segmueller G. The syndrome of idiopathic osteolysis. Classification, review, and case report. *The*

Journal of Bone and Joint Surgery British Volume. 1985;67(1):88-93. doi:10.1302/0301-620X.67B1.3968152

6. Liu Y, Zhong DR, Zhou PR, et al. Gorham-Stout disease: radiological, histological, and clinical features of 12 cases and review of literature. *Clinical Rheumatology*. 2014;35(3):813-823. doi:10.1007/s10067-014-2780-2
7. Dickson GR, Mollan RAB, Carr KE. Cytochemical localization of alkaline and acid phosphatase in human vanishing bone disease. *Histochemistry*. 1987;87(6):569-572. doi:10.1007/bf00492472
8. Devlin RD, Bone HG, Roodman GD. Interleukin-6: a potential mediator of the massive osteolysis in patients with Gorham-Stout disease. *The Journal of Clinical Endocrinology and Metabolism*. 1996;81(5):1893-1897. doi:10.1210/jcem.81.5.8626854
9. Korsić M, Jelasić D, Potocki K, Giljević Z, Aganović I. Massive osteolysis in a girl with agenesis of thyroid C cells. *Skeletal Radiology*. 1998;27(9):525-528. doi:10.1007/s002560050433
10. 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. *The Journal of Bone and Joint Surgery British Volume*. 1999;81(3):501-506. doi:10.1302/0301-620x.81b3.9468
11. Hirayama T, Sabokbar A, Itonaga I, Watt-Smith S, Athanasou NA. Cellular and humoral mechanisms of osteoclast formation and bone resorption in Gorham-Stout disease. *The Journal of Pathology*. 2001;195(5):624-630. doi:10.1002/path.989
12. Vinée P, Tanyü MO, Hauenstein KH, Sigmund G, Stöver B, Adler CP. CT and MRI of Gorham syndrome. *Journal of Computer Assisted Tomography*. 1994;18(6):985-989. doi:10.1097/00004728-199411000-00028
13. Kiran D, Anupama A. Vanishing bone disease: a review. *Journal of Oral and Maxillofacial Surgery*. 2011;69(1):199-203. doi:10.1016/j.joms.2010.05.088
14. Hu P, Yuan X, Hu X, Shen F, Wang J. Gorham-Stout syndrome in mainland China: a case series of 67 patients and review of the literature. *Journal of Zhejiang University Science B*. 2013;14(8):729-735. doi:10.1631/jzus.B1200308
15. Chrcanovic BR, Gomez RS. Gorham–Stout disease with involvement of the jaws: a systematic review. *International Journal of Oral and Maxillofacial Surgery*. 2019;48(8):1015-1021. doi:10.1016/j.ijom.2019.03.002
16. Ross JL, Schinella R, Shenkman L. Massive osteolysis. An unusual cause of bone destruction. *The American Journal of Medicine*. 1978;65(2):367-372. doi:10.1016/0002-9343(78)90834-3
17. Patel DV. Gorham's Disease or Massive Osteolysis. *Clinical Medicine and Research*. 2005;3(2):65-74.
18. Kery L, Wouterst HW. Massive osteolysis: report of two cases. *The Journal of Bone and Joint Surgery British volume*. 1970;52-B(3):452-459. doi:10.1302/0301-620x.52b3.452
19. Iyer GV. Cerebrospinal fluid rhinorrhoea from massive osteolysis of the skull. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1979;42(8):767-769. doi:10.1136/jnnp.42.8.767
20. Marymont JV. Comparative imaging. Massive osteolysis (Gorham's syndrome, disappearing bone disease). *Clinical Nuclear Medicine*. 1987;12(2):153-154.
21. Resnick D, Niwayama G. Osteolysis and chondrolysis. Diagnosis of bone and joint disorders. *The Journal of Bone and Joint Surgery British volume*. 2003;85-B(5):779-779. doi:10.1302/0301-620x.85b5.0850779a
22. Heffez L, Doku HChris, Carter BL, Feeney JE. Perspectives on massive osteolysis. *Oral Surgery, Oral Medicine, Oral Pathology*. 1983;55(4):331-343. doi:10.1016/0030-4220(83)90185-8
23. Raghuveer H, Jayalekshmy R. Gorham's massive osteolysis of the mandible – a progressive radiographic presentation. *Dentomaxillofacial Radiology*. 2009;38(5):292-295. doi:10.1259/dmfr/73198793
24. Ozbayrak M, Yilmaz MH, Kantarci F, et al. A Case of an Idiopathic Massive Osteolysis with Skip Lesions. *Korean Journal of Radiology*. 2013;14(6):946-950. doi:10.3348/kjr.2013.14.6.946
25. Dunbar SF, Rosenberg A, Mankin H, Rosenthal D, Suit HD. Gorham's massive osteolysis: The role of radiation therapy and a review of the literature. *International Journal of Radiation, Oncology, Biology, Physics*. 1993;26(3):491-497. doi:10.1016/0360-3016(93)90968-2
26. Szabo C, Habre W. Gorham syndrome: anaesthetic management. *Anaesthesia*. 2000;55(2):157-159. doi:10.1046/j.1365-2044.2000.055002157.x

27. Hammer F, Kenn W, Wesselmann U, et al. Gorham-Stout Disease-Stabilization During Bisphosphonate Treatment. *Journal of Bone and Mineral Research*. 2004;20(2):350-353. doi:10.1359/jbmr.041113
28. Aizawa T, Sato T, Kokubun S. Gorham disease of the spine: a case report and treatment strategies for this enigmatic bone disease. *The Tohoku Journal of Experimental Medicine*. 2005;205(2):187-196. doi:10.1620/tjem.205.187