Gorham-Stout disease with involvement of the jaws: a systematic review

Short title: Gorham-Stout disease of the jaws

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KEYWORDS

Gorham-Stout disease; massive osteolysis; jaw; clinical features; treatment; persistence following treatment

ABSTRACT

The purpose was to systematically review all published cases of Gorham-Stout disease (GSD) involving the jaws, identify the clinic-radiological and histopathological features associated with the persistence of the lesions, and the best treatment options available. An electronic search was undertaken in November/2018. Eligibility criteria included publications having enough information to confirm the diagnosis. Eighty-six publications reporting 89 cases were included. Features observed: symptomatic (51.1%), swelling (34.1%), pathological fracture (31.8%), history of previous trauma (32.1%), high levels of alkaline phosphatase (24.3%), predominance of vascular tissue (72.4%). Nearly 1/4 of the patients were only followed up and no treatment was implemented. Most of treatments consisted of some type of surgery with/without additional therapies (42.0%), drugs (20.5%), and radiotherapy (14.8%). Half of the cases were found to persist after some treatment modality and five patients died. Among the different variables investigated, only the fact of crossing the midline showed association with the persistence of the lesion. There is still a lot to understand about GSD, a rare condition with no clear consensus on the etiopathology, unpredictable clinical course, and no standard treatment. The high percentage of cases that persist after treatment are found to be associated only with the lesion crossing the midline.

KEYWORDS

Gorham-Stout disease; massive osteolysis; jaw; clinical features; treatment; persistence following treatment

INTRODUCTION

Gorham-Stout disease (GSD), also called Gorham disease or vanishing bone disease, among many other names, is an extremely rare bone disease of unknown etiology. The clinical progression and prognosis is unpredictable, and treatment is uncertain. Absorption, initially localized to one bone, often extends to involve those adjacent ¹. The lesions of this condition are histopathologically characterized by extensive loss of bony matrix replaced by a proliferation of thin-walled capillary-sized vascular channels, and at a later stage by fibrous connective tissue ². The first case reported in the literature was in 1838 ³, involving an arm. GSD with involvement of the jaws is considered to be a rare condition, with the first case being reported in the literature in 1924 ⁴. The aim of the present study was to integrate the available data published in the literature on GSD involving the jaws into an updated comprehensive comparative analysis of their features, as well as to identify the clinic-radiological and histopathological features associated with the persistence of the disease. We also performed an analysis of the literature regarding the best treatment options available for this condition.

MATERIALS AND METHODS

This study followed the PRISMA Statement guidelines ⁵.

Search strategies

An electronic search without time restrictions was undertaken in November 2018 in the following databases: PubMed/Medline, Web of Science, Science Direct, J-Stage, and Lilacs. The following terms were used in the search strategies:

("Gorham disease" OR "Gorham's disease" OR "Gorham-Stout disease" OR "Gorham Stout disease" OR "Gorham syndrome" OR "Gorham's syndrome" OR "Gorham-Stout syndrome" OR "Gorham Stout syndrome" OR "massive osteolysis" OR "idiopathic massive osteolysis" OR "disappearing bone disease" OR "vanishing bone disease" OR "vanishing bone disorder" OR "phantom bone disease") AND (mandible OR maxilla OR jaw OR maxillofacial OR face)

Google Scholar was also checked. A manual search of all related oral pathology, maxillofacial and specialist dental and oral journals was performed. The reference list of the identified studies and the relevant reviews on the subject were also checked for possible additional studies. Publications with lesions identified by other authors as being GSD, even not having the term "Gorham disease " in the title of the article, were also re-evaluated by an author (R.S.G.) of the present study.

Inclusion and Exclusion Criteria

Publications reporting cases of patients with GSD with involvement of at least one of the jaws, and with enough information to confirm the diagnosis were included. The criteria listed by Heffez et al. ⁶ with mild modifications were used to diagnose a patient with GSD:

- Biopsy showing angiomatous tissue or fibrous connective tissue;
- Absence of cellular atypia;

- Minimal or no osteoclastic response and absence of dystrophic calcifications;
- Evidence of local bone progressive resorption;
- The lesion is not ulcerative and does not provoke cortical expansion;
- Absence of visceral involvement;
- Osteolytic radiographic pattern;
- Negative hereditary, metabolic, neoplastic, immunologic, and infectious etiology;
- Monocentric occurrence.

Study selection

The titles and abstracts of all reports identified through the electronic searches were read independently by the authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. Disagreements were resolved by discussion between the authors. The clinical and radiological aspects, as well as the histological description of the lesions reported by the publications were thoroughly assessed by one of the authors (R.S.G.) of the present study, an expert in oral pathology, in order to confirm the diagnosis of GSD.

Data extraction

The following data were extracted: patient's sex and age, duration of the lesion previously to treatment, history of previous (local) facial trauma, lesion location (maxilla/mandible), involvement of other/adjacent bones (mono- or polyostotic involvement), pathological fracture of the jaw bones, cortical bone destruction, presence of swelling, clinical symptoms, involvement of skin, levels of alkaline phosphatase in serum, histopathological appearance of the tissue obtained from the last surgery (predominance of either vascular or fibrous tissue), treatment performed, persistence of bone resorption, and follow-up period. Contact with authors for possible missing data was performed.

Analyses

A descriptive analysis was performed based on mean, standard deviation (SD), and percentage values. The Kolmogorov–Smirnov test was used to test the normality of the distribution of variables, and Levene’s test was used to evaluate homoscedasticity. The Student *t*-test or Mann–Whitney test was performed to compare two independent groups, depending on the normality of the data. The Pearson χ^2 test or Fisher’s exact test was used for categorical variables, depending on the expected count of events in a 2×2 contingency table. Whenever possible, the probability of persistence of bone resorption after treatment was calculated using the odds ratio (OR) and 95% confidence interval (95% CI). The level of statistical significance was set at $P < 0.05$. All data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Literature search

The study selection process is summarized in Figure 1. The search strategy in the databases resulted in 376 papers, 9 additional eligible papers were found in Google Scholar, and 10 papers through hand-searching. At the end, a total of 86 publications were included (readers interested in the list should contact the first author for details).

Description of the Studies and Analyses

Table 1 presents demographic and clinical features of all 89 cases of GSD with involvement of at least one of the jaws. The patients had a mean $\pm$ SD of 31.7 $\pm$ 18.4 years of age, and nearly 2/3 of them were male. A number of 33 patients presented polyostotic GSD, in which adjacent bones were involved. Concerning the jaws, in 6 patients the maxilla was the only jaw bone involved, in 64 patients the mandible was the only jaw bone involved, and in 19 cases both jaw bones were involved. In 50% of the cases the lesion crossed the midline of the body. Cortical bone perforation was observed in almost all cases. Half of the patients were symptomatic, about 1/3 presented swelling at the lesion site, about 1/3 presented pathological fracture of the involved jaw during the course of the disease, 1/3 of the patients had a history of previous trauma, and high levels of alkaline phosphatase was observed in 1/4 of the patients. Almost 3/4 of the cases showed a predominance of vascular tissue observed in the histopathological analysis of the samples obtained from the last surgery of the patient.

Besides the fact that nearly 1/4 of the patients were only followed up and no treatment was implemented, there was a great variety of treatments performed, but most of them consisted of some type of surgery with/without additional therapies (42.0%), drugs (20.5%), and radiotherapy (14.8%). Drugs commonly used were bisphosphonates, corticosteroids, calcitonin, chemical compounds containing calcium, alpha interferon, vitamin D, or a combination of these. One case treated with cisplatin + 5-fluorouracil was reported (with no persistence of resorption, followed up for

120 months) and another case treated with denosumab (with no follow-up information). The patients usually had had a relatively long previous history of the disease (mean of 3.5 years) before they looked for professional medical help, and that period reached 17 years in one patient. Patients had a mean follow-up time of 4 years. The rate of persistence of resorption after first treatment was slightly higher than 50%. Table 2 shows the persistence of resorption according to the treatment implemented.

Five cases of death were reported, of which three could be related to the condition. In one case the patient died after spontaneous pathologic fracture of the affected cervical vertebrae with subsequent transection of spinal cord ⁷. In another case the patient died due to hemodynamic instability, cardiac arrest, and brain death – the lesion extended into intracerebral space through foramen magnum ⁸. In the third case ⁹, with the involvement of several facial, skull and vertebral bones, the patient became bedridden due to increasing pain and neck instability. The patient eventually became deaf and dumb and lost her left eyesight. The patient was suspected to have committed suicide, after the tracheal cannula was found to be out of place. For the other two cases, it is not possible to clearly associate the patient's death with the disease. In one case the patient developed acute schizophrenia and suddenly collapsed and died ¹⁰. In the other case the patient died of severe pleural effusion after receiving radiation therapy ¹¹.

Table 3 shows the rate of persistence of resorption for GSD according to different factors. Lesions that crossed the midline was the only factor suggested to have an influence in the persistence of resorption after the first treatment.

DISCUSSION

The aim of the present study was to integrate the available data published in the literature on GSD with involvement of the jaws into an updated comprehensive analysis of their features, as well as the options of treatment and the frequency of recurrence. A review of pathological lesions and conditions is important because it provides information that can improve diagnostic accuracy, allowing pathologists and surgeons to make informed decisions and refine treatment plans to optimize clinical outcomes¹²⁻¹⁶.

Many supposed cases of GSD were excluded in the selection process of the present review. As a reason for that, the team providing treatment to these patients did not perform any biopsy when no surgical treatment was implemented, nor histopathological exams when one or many surgeries were performed. Some of the diseases included in the differential diagnosis can only be ruled out by microscopic examination, which brings a certain degree of uncertainty to the diagnosis, even though the clinical and radiological features of the cases might match those to the patients with GSD.

The differential diagnosis of GSD in the jaws (Table S1 – see Supplemental Appendix) includes infection (osteomyelitis), neoplastic diseases (Langerhans cell histiocytosis, Ewing sarcoma, angiosarcoma), endocrine disorders (e.g., osteolytic hyperparathyroidism)^{17, 18}, and other conditions/syndromes that present with osteolysis, such as Hajdu-Cheney syndrome, generalized lymphatic anomaly, and Paget disease¹⁹. Nevertheless, progressive and unusually substantial bone destruction without evidence of repair is almost pathognomonic for Gorham disease²⁰.

So far, there is no clear consensus on the etiopathogenesis of GSD. Many hypotheses have been raised (Table S2 – see Supplemental Appendix) since Gorham and Stout²¹ proposed that hemangiomatosis would lead to hyperemia causing excessive bone destruction. Hypotheses include local hypoxia/acidosis and endothelial dysplasia^{22, 23}, enhanced osteoclastic activity or increased sensitivity of osteoclast precursors to humoral factors²⁴⁻²⁷, lack of thyroid C cells and calcitonin²⁸, proliferation of lymphatic vessels^{29, 30}, among others. A molecular analysis of a patient with PTEN

hamartoma tumor syndrome and GSD suggested that *PTEN* mutation could be the first of two or more steps in the development of GSD ³¹. More recently, the whole genome signature was investigated in the lesions and healthy tissues of a patient with GSD ³². After filtering for the mutated genes related to osteogenesis or osteolysis they suggested that *TNFRSF11A* and *TREM2* were the driver genes for the disease, but further studies are necessary to confirm this finding.

Despite the fact that Heffez et al.'s criteria ⁶ establish an angiomatous lesion, it has long been observed that some lesions develop into more fibrous lesions ². Thus, fibrous-looking lesions were not excluded since this is found in some cases. After the autopsy from several sites of a patient suspected to have committed suicide because of the consequences of the advancement of the disease, Kawasaki et al. ⁹ pointed out that progressive absorption of bone in GSD is not always accompanied by pathologically significant vascular proliferation.

The natural history of the process is unpredictable. Some cases are self-limiting with stability of the affected part ³³. The reports in the literature show a great variety of treatments performed, and radiotherapy seems to have better results in comparison to other types of treatment. However, due to the limited number of cases, it would have more sense to say that none of them has clearly shown to be effective or associated with a better prognosis in comparison to the others. In some cases, the patient's first consultation took place after the osseous resorption was already inactive, i.e. the disease process had already spontaneously arrested ³⁴, or when the affected bone had already completely disappeared ³⁵. In many other reports there is no long follow-up after the last therapeutic procedure performed. It is, therefore, not entirely easy to state that the prognosis for patients with GSD is good.

We could not find any reasonable explanation for the fact that lesions that crossed the midline could have an influence in the persistence of resorption after the first treatment. This could be related to the fact that the continuous process of resorption would lead these lesions to become large enough to reach the contralateral side of the head and neck region. And larger lesions in a

more advanced phase of resorption would be more difficult to deal with. However, this is a mere assumption.

Due to the low incidence of GSD, the current literature is confined to case reports and case series. There is no standard treatment so far and the therapy depends on patients' conditions. Therapy might include surgery, radiotherapy, and drugs, with varying degrees of success³².

CONCLUSIONS

Half of the cases were found to persist after some treatment modality and five patients died. Among the different clinic-radiological and histopathological variables investigated, only the fact of crossing the midline showed association with the persistence of the lesion. There is still a lot to understand about GSD, a rare condition with no clear consensus on the etiopathogenesis, unpredictable clinical course, and no standard treatment.

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There are no conflicts of interest to declare.

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REFERENCES

1. Halliday DR, Dahlin DC, Pugh DG, Young HH. MASSIVE OSTEOLYSIS AND ANGIOMATOSIS. *Radiology* 1964;**82**:637-44.
2. Johnson PM, McClure JG. Observations on massive osteolysis; a review of the literature and report of a case. *Radiology* 1958;**71**:28-42.
3. Jackson JBS. A boneless arm. *Boston Med Surg J* 1838;**18**:368-9.
4. Römer O. Die Pathologie der Zähne. *Handbuch der Speziellen Pathologischen Anatomie und Histologie*. Vol 4. Berlin: Springer Verlag; 1924:135-499.
5. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009;**151**:264-9, W64.
6. 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**:331-43.
7. Ellis DJ, Adams TO. Massive osteolysis: report of case. *J Oral Surg* 1971;**29**:659-63.
8. 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**:1340-3.
9. Kawasaki K, Ito T, Tsuchiya T, Takahashi H. Is angiomatosis an intrinsic pathohistological feature of massive osteolysis? Report of an autopsy case and a review of the literature. *Virchows Arch* 2003;**442**:400-6.
10. Hampton J, Arthur JF. Massive osteolysis affecting the mandible. *Br Dent J* 1966;**120**:538-41.
11. Kim MK, Hong JR, Kim SG, Lee SK. Fatal Progression of Gorham Disease: A Case Report and Review of the Literature. *J Oral Maxillofac Surg* 2015;**73**:2352-60.
12. Chrcanovic BR, Gomez RS. Squamous odontogenic tumor and squamous odontogenic tumor-like proliferations in odontogenic cysts: An updated analysis of 170 cases reported in the literature. *J Craniomaxillofac Surg* 2018;**46**:504-10.

13. Chrcanovic BR, Gomez RS. Ameloblastic Fibrodentinoma and Ameloblastic Fibro-Odontoma: An Updated Systematic Review of Cases Reported in the Literature. *J Oral Maxillofac Surg* 2017;**75**:1425-37.
14. Chrcanovic BR, Gomez RS. Calcifying epithelial odontogenic tumor: An updated analysis of 339 cases reported in the literature. *J Craniomaxillofac Surg* 2017;**45**:1117-23.
15. Chrcanovic BR, Gomez RS. Cementoblastoma: An updated analysis of 258 cases reported in the literature. *J Craniomaxillofac Surg* 2017;**45**:1759-66.
16. Chrcanovic BR, Gomez RS. Melanotic neuroectodermal tumour of infancy of the jaws: an analysis of diagnostic features and treatment. *Int J Oral Maxillofac Surg* 2019;**48**:1-8.
17. Patel DV. Gorham's disease or massive osteolysis. *Clin Med Res* 2005;**3**:65-74.
18. Saify FY, Gosavi SR. Gorham's disease: A diagnostic challenge. *J Oral Maxillofac Pathol* 2014;**18**:411-4.
19. Evrenos MK, Ozkaya M, Yaman M, Proff LY. Case Report: Gorham-Stoute Syndrome with Involvement of Majority of Mandible, and Partial Maxillary, Temporal and Zygomatic Bones. *J Maxillofac Oral Surg* 2016;**15**:335-8.
20. Kotecha R, Mascarenhas L, Jackson HA, Venkatramani R. Radiological features of Gorham's disease. *Clin Radiol* 2012;**67**:782-8.
21. 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-a**:985-1004.
22. Heyden G, Kindblom LG, Nielsen JM. Disappearing bone disease. A clinical and histological study. *J Bone Joint Surg Am* 1977;**59**:57-61.
23. Young JW, Galbraith M, Cunningham J, et al. Progressive vertebral collapse in diffuse angiomatosis. *Metab Bone Dis Relat Res* 1983;**5**:53-60.
24. Wang W, Wang H, Zhou X, et al. Lymphatic Endothelial Cells Produce M-CSF, Causing Massive Bone Loss in Mice. *J Bone Miner Res* 2017;**32**:939-50.

25. Devlin RD, Bone HG, 3rd, Roodman GD. Interleukin-6: a potential mediator of the massive osteolysis in patients with Gorham-Stout disease. *J Clin Endocrinol Metab* 1996;**81**:1893-7.
26. 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. *J Pathol* 2001;**195**:624-30.
27. Möller G, Priemel M, Amling M, Werner M, Kuhlmeier 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**:501-6.
28. Korsic M, Jelasic D, Potocki K, Giljevic Z, Aganovic I. Massive osteolysis in a girl with agenesis of thyroid C cells. *Skeletal Radiol* 1998;**27**:525-8.
29. Hagendoorn J, Padera TP, Yock TI, et al. Platelet-derived growth factor receptor-beta in Gorham's disease. *Nat Clin Pract Oncol* 2006;**3**:693-7.
30. Hammer F, Kenn W, Wesselmann U, et al. Gorham-Stout disease--stabilization during bisphosphonate treatment. *J Bone Miner Res* 2005;**20**:350-3.
31. Hopman SM, Van Rijn RR, Eng C, et al. PTEN hamartoma tumor syndrome and Gorham-Stout phenomenon. *Am J Med Genet A* 2012;**158a**:1719-23.
32. Li MH, Zhang HQ, Lu YJ, et al. Successful Management of Gorham-Stout Disease in Scapula and Ribs: A Case Report and Literature Review. *Orthop Surg* 2018;**10**:276-80.
33. Thompson JS, Schurman DJ. Massive osteolysis. Case report and review of literature. *Clin Orthop Relat Res* 1974:206-11.
34. Lata J, Sharma R, Parmar M. Massive osteolysis of hemimandible: a case report. *J Maxillofac Oral Surg* 2009;**8**:381-3.
35. Franco-Barrera MJ, Zavala-Cerna MG, Aguilar-Portillo G, et al. Gorham-Stout Disease: a Clinical Case Report and Immunological Mechanisms in Bone Erosion. *Clin Rev Allergy Immunol* 2017;**52**:125-32.

Table 1. Demographic and clinical features of cases of Gorham-Stout disease involving the jaws described in the literature.

Variables	
n	89
Age (years), mean±SD (min-max)	31.7±18.4 (0-76; n=88)
Men	32.4±18.1 (5-76; n=54)
Women	31.2±18.8 (6-72; n=32)
<i>p</i> value ^a	0.792
Gender, n (%)	
Men	55 (63.2)
Women	32 (36.8)
Unknown	2
Involvement, n (%)	
Monostotic	56 (62.9)
Polyostotic	33 (37.1)
Unknown	0
Jaw, n (%)	
Maxilla	6 (6.7)
Monostotic	2 (2.2)
Polyostotic (but not affecting the mandible)	4 (4.5)
Mandible	64 (71.9)
Monostotic	54 (60.7)
Polyostotic (but not affecting the maxilla)	10 (11.2)
Maxilla + Mandible	19 (21.4)
Unknown	0
Other bones involved, n (%)	
Zygomatic	15 (16.9) ^b
Pterygoid	5 (5.6) ^b
Sphenoid	8 (9.0) ^b
Frontal	4 (4.5) ^b
Orbit	9 (10.1) ^b
Temporal	15 (16.9) ^b
Occipital	6 (6.7) ^b
Parietal	4 (4.5) ^b
Hyoid	2 (2.2) ^b
Cervical vertebrae	7 (7.9) ^b
Skull base	14 (15.7) ^b
Lesion crossed the midline, n (%)	
Yes	45 (50.6)
No	44 (49.4)
Unknown	0
Cortical bone perforation, n (%)	
Yes	85 (97.7)
No	2 (2.3)
Unknown	2
Swelling, n (%)	
Yes	30 (34.1)
No	58 (65.9)
Unknown	1
Symptomatic, n (%)	
Yes	45 (51.1)

No	43 (48.9)
Unknown	1
Alkaline phosphatase levels, n (%)	
High	9 (24.3)
Normal	28 (75.7)
Unknown	52
Pathological fracture (jaws), n (%)	
Yes	28 (31.8)
No	60 (68.2)
Unknown	1
Histology of last surgery, n (%)	
Fibrous	19 (25.0)
Vascular	55 (72.4)
Fibrous/vascular	2 (2.6)
Unknown	13
History of previous trauma, n (%)	
Yes	9 (32.1)
No	19 (67.9)
Unknown	61
First treatment, n (%)	
None	20 (22.7)
Debulking	1 (1.1)
Curettage	3 (3.5)
Enucleation	1 (1.1)
Marginal resection	5 (5.7)
Segmental resection ^c	5 (5.7)
Segmental resection ^c + radiotherapy	1 (1.1)
Segmental resection ^c + drugs	1 (1.1)
Segmental resection ^c + reconstruction plate	3 (3.5)
Segmental resection ^c + autogenous graft + reconstruction plate	6 (6.8)
Radiotherapy	13 (14.8)
Autogenous graft	7 (8.0)
Alloplastic graft + reconstruction plate	1 (1.1)
Reconstruction plate + drugs	1 (1.1)
Reconstruction plate	1 (1.1)
Drugs	18 (20.5)
'Surgery'	1 (1.1)
Unknown	1
Persistence of resorption after first treatment, n (%)	
Yes	37 (51.4)
No	35 (48.6)
Unknown	17
Death, n (%)	
Yes	5 (5.6)
No	84 (94.4)
Unknown	0
Duration of symptoms until first consultation (months), mean±SD (min-max)	41.9±47.3 (1-204; n=57)
Time between biopsy and first treatment (months), mean±SD (min-max)	10.0±22.5 (0-144; n=47)
Follow-up time after first treatment (months), mean±SD (min-max)	39.4±48.8 (0-300; n=73)
Total follow-up time (months), mean±SD (min-max)	47.1±49.7 (1-300; n=73)

^a Comparison of the mean age between men and women (Mann-Whitney test)

^b Percentage in relation to the total number of cases (n=89)

^c Resection with continuity defect

Table 2. Persistence of resorption – for the lesions with available information about treatment and persistence of resorption.

Treatment	
Persistence of resorption/total (% persistence)	
None	7/11 (63.6)
Debulking	0/1 (0)
Curettage	3/3 (100)
Enucleation	0/1 (0)
Marginal resection	2/4 (50)
Segmental resection ^a	2/5 (40)
Segmental resection ^a + reconstruction plate	2/3 (66.6)
Segmental resection ^a + autogenous graft + reconstruction plate	1/6 (16.7)
Autogenous graft	5/6 (83.3)
Alloplastic graft + reconstruction plate	1/1 (100)
Reconstruction plate	0/1 (0)
'Surgery'	1/1 (100)
Surgical	17/32 (53.1)
Reconstruction plate + drugs	0/1 (0)
Segmental resection ^a + drugs	1/1 (100)
Surgical + drugs	1/2 (50)
Drugs	10/15 (66.7)
Radiotherapy	2/12 (16.7)
TOTAL	37/72 (51.4)

^a Resection with continuity defect

Table 3. Persistence of resorption for the cases of Gorham-Stout disease involving the jaws according to different factors – for the lesions with available information about both persistence of resorption and the factors here included.

Factor	Persistence of resorption/total (% persistence)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
<i>Involvement</i>				
Monostotic	24/45 (53.3)	0.786 ^a	1	0.787
Polyostotic	13/26 (50.0)		0.875 (0.333, 2.300)	
<i>Jaw</i>				
Maxilla (a)	2/4 (50.0)	0.595 ^b (a-b)	1.304 (0.171, 9.970)	0.798
Mandible (b)	30/53 (56.6)	0.515 ^b (a-c)	0.556 (0.059, 5.241)	0.608
Maxilla + Mandible (c)	5/14 (35.7)	0.138 ^a (b-c)	0.426 (0.126, 1.444)	0.171
<i>Lesion crossed the midline</i>				
No	14/36 (38.9)	0.024 ^a	1	0.026
Yes	23/35 (65.7)		3.012 (1.145, 7.926)	
<i>Cortical bone perforation</i>				
No	0/2 (0)	0.211 ^b	^c	
Yes	37/67 (55.2)			
<i>Swelling</i>				
No	23/46 (50.0)	0.507 ^a	1	0.508
Yes	14/24 (58.3)		1.400 (0.517, 3.791)	
<i>Symptomatic</i>				
No	20/36 (55.6)	0.642 ^a	1	0.642
Yes	17/34 (50.0)		0.800 (0.312, 2.049)	
<i>Alkaline phosphatase levels</i>				
Normal	8/19 (42.1)	0.516 ^b	1	0.707
High	4/8 (50.0)		1.375 (0.262, 7.220)	
<i>Histology of last surgery</i>				
Fibrous	6/14 (42.9)	0.306 ^a	1	0.310
Vascular	28/48 (58.3)		1.867 (0.560, 6.223)	
<i>Pathological fracture (jaws)</i>				
No	23/49 (46.9)	0.130 ^a	1	0.134
Yes	14/21 (66.7)		2.261 (0.778, 6.570)	

CI - confidence interval

^a Pearson chi-squared test

^b Fisher's exact test

^c On at least one case, the value of the weight variable was zero. Such cases are invisible to statistical procedures and graphs which need positively weighted cases

FIGURE LEGENDS

Figure 1. Study screening process.

Gorham-Stout Disease with involvement of the jaws: a systematic review

Table S1. Differential diagnosis of Gorham-Stout disease in the jaws.

Condition	Main clinical features	Radiological features	Histopathological features
Gorham-Stout disease	Progressive osteolysis of one or more bones. Maxillofacial region is one of the regions frequently affected. It can present with skeletal pain and pathologic fractures	Cortical resorption and progressive, often extensive, osteolysis (Lala et al., 2013)	Extensive loss of bony matrix replaced by a proliferation of thin-walled capillary-sized vascular channels, and at a later stage by fibrous connective tissue (Johnson and McClure, 1958)
Osteomyelitis	Depending on the course of the infection, it is characterized by the presence of pain, pus, fistula and/or sequestration (Eyrich et al., 2003)	It can present bone sclerosis, bone hypertrophy, periosteal reaction, and/or osteolysis (Julien Saint Amand et al., 2017)	It can present bone fibrosis, pseudarthrosis, bone resorption, with or without inflammatory signs, depending on the course of the infection (Julien Saint Amand et al., 2017)
Langerhans Cell Histiocytosis	Lesions most commonly present in vertebral bodies, long bones, and mandibles (children), or in cranium and ribs (adults). Lesions may or may not be painful. Papulosquamous granulomatous lesions of the skin, pituitary lesions resulting in endocrinopathies, and cystic lung involvement (DiCaprio and Roberts, 2014)	Isolated lesions of bone are the most common presentation, and can display varying degrees of medullary and cortical bone destruction (DiCaprio and Roberts, 2014)	Proliferations of dendritic cells with Langerhans cell feature
Ewing sarcoma	The most common clinical signs related to the tumor mass are swelling in all cases and pain in most of them (Rattana-Arpha et al., 2017)	Various osteolytic patterns and extensive bone destruction. The form of “sun-ray” spicules is more common in the head and neck, especially in the mandible (Rattana-Arpha et al., 2017)	It consists of sheets or lobules of uniform small round cells showing scant pale cytoplasm, fine-appearing dusty chromatin with a distinct nuclear membrane and inconspicuous or pin-point nucleoli (WHO, 2017)
Angiosarcoma	The intraoral angiosarcoma appears as round or ovoid bluish nodular painless mass. The overlying surface may be ulcerated or intact, with tendency of spontaneous bleeding. Pain is commonly reported (Triantafillidou et al., 2002)	Nonspecific	Multiple vascular anastomoses, with solid necrotic or hemorrhagic areas. The neoplastic vessels present atypical endothelium with prominent hyper chromatic nuclei (Fukushima et al., 2006)
Osteolytic hyperparathyroidism	Vary from asymptomatic to painful cases with swollen masses showing secondary traumatic ulcers, bleeding, tooth mobility, facial deformity, and functional alterations such as masticatory dysfunction, nasal obstruction, epiphora, and	Lesions appear either as small unilocular or extensive multilocular radiolucent areas (Dos Santos et al., 2018)	The same histological features as central giant cell lesion, which include cellular fibrovascular tissue with hemorrhage and hemosiderin deposits, multinucleated giant cell proliferation, osteoblasts and osteoclasts, and in some cases

	diplopia; pathological fracture can also occur. It can present with skeletal pain and pathologic fractures (Dos Santos et al., 2018)		reactive bone neoformation (Dos Santos et al., 2018)
Hajdu-Cheney syndrome	Short stature, severe osteoporosis, acro-osteolysis, dysmorphic facial features (synophrys, prominent epicanthal folds, bathrocephaly - a posterior skull deformity, mild hypertelorism with telecanthus, downslanted eyes, low-set ears, long philtrum, and short neck), dental abnormalities (highly arched palate, cleft palate, impaired tooth eruption, and premature loss of teeth), wormian bones, neurological symptoms, cardiovascular defects and polycystic kidneys (Antoniades et al., 2003; Penton et al., 2012; Canalis & Zanotti, 2014)	Connected to bone anomalies described in the ' <i>Main clinical features</i> ' (on the left)	Nonspecific
Generalized lymphatic anomaly	Multisystem disorder that also commonly affects bone. It can present with skeletal pain and pathologic fractures (Lala et al., 2013)	Multiple lytic areas confined to the medullary cavity; although these lesions can increase in number and in size over time, there is no cortical destruction (Boyle, 1972)	Abnormally dilated lymphatic channels lined by endothelial cells, specifically of a lymphatic phenotype (Wassef et al., 2015)
Paget disease	Focal disorder of bone remodeling that progresses slowly and leads to changes in the shape and size of affected bones and to skeletal, articular and vascular complications. Any bone of the skeleton may be affected. The disease progresses slowly within an affected bone but does not generally appear in other bones. The majority of patients are asymptomatic. Elevation of serum alkaline phosphatase (Appelman-Dijkstra and Papapoulos, 2018)	Increased bone resorption may be detected. Older lesions usually have a mixed sclerotic and lytic appearance and in the last stage of the disease sclerotic lesions predominate. The involved parts of the skeleton are enlarged and deformed and the cortex can be thickened and dense (Appelman-Dijkstra and Papapoulos, 2018)	Numerous hyperactive osteoclasts in the resorptive phase. The marrow is replaced by a highly vascular fibrous connective tissue. In the osteoblastic phase the bone lacks the organized lamellar pattern and the osteoblasts form osteoid rims around its trabeculae. Basophilic reversed lines result the characteristic "mosaic" appearance (Neville et al., 2016)

REFERENCES

- Antoniades K, Kaklamanos E, Kavadia S, Hatzistilianou M, Antoniades V. Hajdu-Cheney syndrome (acro-osteolysis): a case report of dental interest. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003 Jun;95(6):725-31.
- Appelman-Dijkstra NM, Papapoulos SE. Paget's disease of bone. *Best Pract Res Clin Endocrinol Metab*. 2018 Oct;32(5):657-668.
- Canalis E, Zanolotti S. Hajdu-Cheney syndrome: a review. *Orphanet J Rare Dis*. 2014 Dec 10;9:200.
- DiCaprio MR, Roberts TT. Diagnosis and management of langerhans cell histiocytosis. *J Am Acad Orthop Surg*. 2014 Oct;22(10):643-52.
- Dos Santos B, Koth VS, Figueiredo MA, Salum FG, Cherubini K. Brown tumor of the jaws as a manifestation of tertiary hyperparathyroidism: A literature review and case report. *Spec Care Dentist*. 2018 May;38(3):163-171.
- Eyrich GK, Baltensperger MM, Bruder E, Graetz KW. Primary chronic osteomyelitis in childhood and adolescence: a retrospective analysis of 11 cases and review of the literature. *J Oral Maxillofac Surg*. 2003 May;61(5):561-73.
- Fukushima K, Dejima K, Koike S, Tei G, Asano J, Ueda M, Hyuga M, Oshima W. A case of angiosarcoma of the nasal cavity successfully treated with recombinant interleukin-2. *Otolaryngol Head Neck Surg*. 2006 May;134(5):886-7.
- Johnson PM, McClure JG. Observations on massive osteolysis; a review of the literature and report of a case. *Radiology*. 1958;71:28-42.
- Julien Saint Amand M, Sigaux N, Gleizal A, Bouletreau P, Breton P. Chronic osteomyelitis of the mandible: A comparative study of 10 cases with primary chronic osteomyelitis and 12 cases with secondary chronic osteomyelitis. *J Stomatol Oral Maxillofac Surg*. 2017 Dec;118(6):342-348.
- Lala S, Mulliken JB, Alomari AI, Fishman SJ, Kozakewich HP, Chaudry G. Gorham-Stout disease and generalized lymphatic anomaly—clinical, radiologic, and histologic differentiation. *Skeletal Radiol*. 2013 Jul;42(7):917-24.
- Neville BW, Damm DD, Allen CM, Bouquot JE. *Oral and Maxillofacial Pathology*. 4th edition. Saunders/Elsevier: St. Louis. 2016; 928 pp.
- Penton AL, Leonard LD, Spinner NB. Notch signaling in human development and disease. *Semin Cell Dev Biol*. 2012 Jun;23(4):450-7.
- Rattana-Arpha P, Dhanuthai K, Sutthiprapaporn P, Dhanesuan K. Ewing's Sarcoma of the maxillofacial region: A case report. *J Stomatol Oral Maxillofac Surg*. 2017 Oct;118(5):316-319.
- Wassef M, Blei F, Adams D, Alomari A, Baselga E, Berenstein A, Burrows P, Frieden IJ, Garzon MC, Lopez-Gutierrez JC, Lord DJ, Mitchel S, Powell J, Prendiville J, Vikkula M. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. *Pediatrics*. 2015 Jul;136(1):e203-14.
- WHO.El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ (eds). *World Health Organization Classification of Head and Neck Tumours*. IARC Press: Lyon, 2017; 348 pp.

Table S2. Possible etiopathogenesis of Gorham-Stout disease (GSD).

Year	Study	Hypothesis, or new evidence
1955	Gorham and Stout	The progressive osteolysis is always associated with an angiomatosis of blood and sometimes of lymphatic vessels, which seemingly are responsible for it. The authors raised the question of whether the osteolysis occurs as the direct result of active hyperaemia, of mechanical causes, of slight changes in pH, or from other causes.
1963	Knoch	Silent hamartoma may become active after minor trauma and start to resorb the bone.
1968	Tilling and Skobowytsh	Osteolysis through increased osteoclastic activity
1970	Fornasier	Massive osteolysis is the result of a congenital vascular defect, and the direct effect of the vascular proliferation is loss of bone tissue.
1974	Thompson and Schurman	Primary aberration of vascular tissue in bone probably related to unchecked granulation-like tissue and not increased osteoclastic activity. Trauma is suspect as a triggering agent.
1977	Heyden et al.	The slow circulation may cause local hypoxia and lowering of the pH, which may, in turn, favor the activities of hydrolytic enzymes involved in bone resorption.
1983	Young et al.	A basic underlying endothelial dysplasia of either the lymphatic system or the vascular system, or both. The possibility of abnormality of the immune system is also considered.
1986	Cannon et al.	Massive osteolysis may represent a local derangement of osteoclastic activity, perhaps under the influence of a local stimulus.
1987	Dickson et al.	The combined action of mononuclear phagocytes, multinuclear osteoclasts and the vascular endothelium promote bone resorption and some abnormal osteoblasts may contribute to the imbalance between bone formation and resorption.
1996	Devlin et al.	Bone resorption is due to enhanced osteoclast activity, and that interleukin-6 (IL-6) may play a role in the increased bone resorption.
1998	Koršić et al.	Lack of thyroid C cells and calcitonin may play a role in the pathogenesis.
1999	Möller et al.	Increased number of paracrine- or autocrine-stimulated hyperactive osteoclasts.
2001	Hirayama et al.	Increase in the sensitivity of the circulating osteoclast precursors to humoral factors which promote osteoclast formation and bone resorption (RANKL and M-CSF).
2005	Hammer et al.	IL-6 was elevated in a patient with GSD and returned to a normal level following bisphosphonate treatment. Proliferation of lymphatic vessels in GSD leads to activation of osteoclasts.
2006	Hagendoorn et al.	Proliferating vascular tissues that mainly derived from lymphatic endothelium with elevated level of circulating platelet-derived growth factor BB (PDGF-BB).
2007	Bruch-Gerharz et al.	Vascular malformation rather than angiomatous lesions can cause progressive osteolysis.
2010	Dupond et al.	Increased VEGF-A, VEGF-C, and IL-6 in serum of GSD patients have been reported, all of which have the ability to increase osteoclast function <i>in vitro</i> in the presence of RANKL and M-CSF.
2012	Hopman et al.	Reported a proven germline mutation in PTEN in a patient with PTEN hamartoma tumor syndrome and GSD. Hypothesis that

		the PTEN mutation was the first of two or more steps in the progression of GSD.
2017	Wang et al.	Lymphatic endothelial cells promote osteoclast formation and bone resorption by producing high levels of M-CSF <i>in vivo</i> in a mouse model.
2018	Li et al.	After the investigation of the whole genome signature of the lesions and healthy tissues, mutations of the genes <i>TNFRSF11A</i> and <i>TREM2</i> were suggested to be the driver event of the disease.

REFERENCES

- Bruch-Gerharz D, Gerharz CD, Stege H, Krutmann J, Pohl M, Koester R, Ruzicka T. Cutaneous lymphatic malformations in disappearing bone(Gorham-Stout) disease: a novel clue to the pathogenesis of a rare syndrome. *J Am Acad Dermatol*. 2007 Feb;56(2 Suppl):S21-5.
- Cannon SR. Massive osteolysis. A review of seven cases. *J Bone Joint Surg Br*. 1986 Jan;68(1):24-8.
- Devlin RD, Bone HG 3rd, Roodman GD. Interleukin-6: a potential mediator of the massive osteolysis in patients with Gorham-Stout disease. *J Clin Endocrinol Metab*. 1996 May;81(5):1893-7.
- Dickson GR, Mollan RA, Carr KE. Cytochemical localization of alkaline and acid phosphatase in human vanishing bone disease. *Histochemistry*. 1987;87(6):569-72.
- Dupond JL, Bermont L, Runge M, de Billy M. Plasma VEGF determination in disseminated lymphangiomatosis-Gorham-Stout syndrome: a marker of activity? A case report with a 5-year follow-up. *Bone*. 2010 Mar;46(3):873-6.
- Fornasier VL. Haemangionatosis with massive osteolysis. *J Bone Joint Surg Br*. 1970 Aug;52(3):444-51.
- 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 Oct;37-A(5):985-1004.
- Hagendoorn J, Padera TP, Yock TI, Nielsen GP, di Tomaso E, Duda DG, Delaney TF, Gaissert HA, Pearce J, Rosenberg AE, Jain RK, Ebb DH. Platelet-derived growth factor receptor-beta in Gorham's disease. *Nat Clin Pract Oncol*. 2006 Dec;3(12):693-7.
- Hammer F, Kenn W, Wesselmann U, Hofbauer LC, Delling G, Allolio B, Arlt W. Gorham-Stout disease--stabilization during bisphosphonate treatment. *J Bone Miner Res*. 2005 Feb;20(2):350-3.
- Heyden G, Kindblom LG, Nielsen JM. Disappearing bone disease. A clinical and histological study. *J Bone Joint Surg Am*. 1977 Jan;59(1):57-61.
- 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. *J Pathol*. 2001 Dec;195(5):624-30.
- Hopman SM, Van Rijn RR, Eng C, Bras J, Alders M, van der Horst CM, Hennekam RC, Merks JH. PTEN hamartoma tumor syndrome and Gorham-Stout phenomenon. *Am J Med Genet A*. 2012 Jul;158A(7):1719-23.
- Knoch HG. Die Gorhamsche Krankheit aus klinischer Sicht. *Zentralbl Chir* 1963;18:674-83.
- Koršić M, Jelasić D, Potocki K, Giljević Z, Aganović I. Massive osteolysis in a girl with agenesis of thyroid C cells. *Skeletal Radiol*. 1998 Sep;27(9):525-8.

- Li MH, Zhang HQ, Lu YJ, Gao P, Huang H, Hu YC, Wang Z. Successful Management of Gorham-Stout Disease in Scapula and Ribs: A Case Report and Literature Review. *Orthop Surg*. 2018 Aug;10(3):276-280.
- Möller G, Priemel M, Amling M, Werner M, Kuhlmeier AS, Dellinger G. The Gorham-Stout syndrome (Gorham's massive osteolysis). A report of six cases with histopathological findings. *J Bone Joint Surg Br*. 1999 May;81(3):501-6.
- Thompson JS, Schurman DJ. Massive osteolysis. Case report and review of literature. *Clin Orthop Relat Res*. 1974;(103):206-11.
- Tilling G, Skobowytsh B. Disappearing bone disease, morbus Gorham. Report of a case. *Acta Orthop Scand*. 1968;39(3):398-406.
- Wang W, Wang H, Zhou X, Li X, Sun W, Dellinger M, Boyce BF, Xing L. Lymphatic Endothelial Cells Produce M-CSF, Causing Massive Bone Loss in Mice. *J Bone Miner Res*. 2017 May;32(5):939-950.
- Young JW, Galbraith M, Cunningham J, Roof BS, Vujic I, Gobien RP, Liebscher L, Butler WM, Fudenberg HH. Progressive vertebral collapse in diffuse angiomatosis. *Metab Bone Dis Relat Res*. 1983-1984;5(2):53-60.