Gorham-Stout Disease. Case report and narrative literature review

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Abstract

Gorham's disease, also known as vanishing bone disease, is a rare condition of unknown etiology characterized by progressive destruction and bone resorption. The disease can affect any part of the skeleton, but it is more frequently found in the head and neck, upper extremities, pelvis, humerus, and the axial skeleton. The mechanism of bone resorption is unclear; however, osteolytic lesions exhibit localized endothelial proliferation of lymphatic vessels. The diagnosis is based on clinical, radiological, and histological features after excluding other infectious, inflammatory, endocrinologic, and neoplastic etiologies.
The medical treatment for Gorham's disease includes anti-osteoclastic medications (bisphosphonates), alpha-2b interferon, sirolimus, and propranolol. Radiation therapy acts by inducing sclerosis of proliferating vascular tissue within the bone. The surgical treatment options include resection of the lesion and reconstruction using bone grafts and/or prostheses.
In this paper, we present a case of Gorham's disease affecting the right maxilla, alveolar process, zygoma, and floor of the orbit in a 67-year-old female.
At the onset of the disease, the clinical manifestation was mobility of the upper right molars, mimicking a periodontal disease, followed, after some weeks, by increased diplopia already present.
The patient received medical treatment with Zoledronic acid, vitamin D, and calcium carbonate, which proved effective in controlling the disease's progression for 12 months.

Keywords: Gorham-Stout Disease, varnish bone disease, phantom bone, hemangiomatosis, osteolytic lesion, tumor-like lesion

Introduction

Gorham-Stout Disease (GSD), first described by Jackson in 1838 [1] and mentioned in the literature in 1955 by LW Gorham and AP Stout [2], is a rare disorder characterized by spontaneous and progressive osteolysis of one or more skeletal bones, which can lead to spontaneous fractures.
Multicentric forms are rarely described [3, 4, 5]. The disease does not exhibit a gender predilection or an inheritance pattern; it may begin at any age, characterized by an abnormal proliferation of lymphatic vessels that replace the reabsorbed bone. The only epidemiological feature worthy of note is the predilection for childhood. GSD can occur at any age, but statistically affects patients younger than 40 years of age with an average age at diagnosis of 25 years [6-13].

How to Cite

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Various definitions have been proposed to describe the disease, including phantom bone, massive osteolysis, disappearing or vanishing bone disease, acute spontaneous absorption of bone, hemangiomatosis, and lymphangiomatosis [3,4,5].
Gorham's disease has been classified by Hardegger et al. together with four other types of idiopathic osteolysis based on the reports of Torg et al. and Macpherson et al. (Table 1) [14].
In GSD, bone resorption is not due to endocrine or metabolic alterations, and the mechanism of osteolysis, as well as its etiological factors, are unknown [15]. Increased osteoclast activity, accompanied by the proliferation of blood and lymphatic vessels, has been considered a possible pathogenetic mechanism, resulting in progressive bone resorption [16,17,18]. The disease can involve the periosteum and, in some cases, even the proximal soft tissues. Surgical treatment, radiotherapy, or chemotherapy have been proposed as possible therapeutic options, often with equivocal results, so that the treatment of GSD is still controversial. The prognosis of GSD is variable and unpredictable, from minimal disability to death [19].
Even though different theories have been hypothesized to explain the pathogenic mechanism of GDS [15-18], the etiology remains undetermined (Table 2) [20]. Hence, the prognosis of the disease can vary depending on the location.
Trauma has been suspected to play a role in the development of the disease, but in about half of the cases of Gorham's disease, any traumatic origin can be excluded [21].
Neurovascular changes, primary aberration of vascular tissue in bone, endothelial dysplasia of blood and

Table 1. Classification with five types of idiopathic osteolysis proposed by Hardegger et al.

Types	Clinical features
1.Hereditary multicentric osteolysis with dominant transmission	Between the ages of 2 and 7 years, spontaneous pain and swelling begin in the hands and feet. Carp tarsal osteolysis occurs over the period of a few years. Progression ceases normally in adolescence.
2.Hereditary multicentric osteolysis with recessive transmission	Similar to type 1 but it may be associated with severe generalized osteoporosis
3.Nonhereditary multicentric osteolysis with nephropathy	Appears in childhood. There is a gradual disappearance of the carpus with the tarsal bones involved, but to a lesser degree, and an association with proteinuria.
4.Gorham's massive osteolysis (Gorham-Stout syndrome)	Monocentric occurrence in any part of the skeleton may start at any age. Normally "hemangiomatous tissue" is found in the osteolytic region. It has neither a hereditary pattern nor an associated nephropathy. The disease is benign and the osteolysis usually stops after a few years.
5. Winchester syndrome	Autosomal recessive transmission. Rare childhood carp tarsal osteolysis in association with contractures, shortness of stature, skin lesions, corneal clouding, and osteoporosis without nephropathy.

Table 2. Possible etiopathology of Gorham-Stout syndrome

Gorham and Stout 1955	Abnormal proliferation of blood vessels and sometimes lymphatics with no role of osteoclasts
Knoch 1963	Silent hamartoma may become active after minor trauma and start to resorb the bone
Thompson and Schurman 1974	Primary aberration of vascular tissue in bone, related to hyperemic granulation tissue
Heyden et al. 1977	Angiomatosis could leads to local hypoxia and change of pH with increased activity of local hydrolytic enzymes
Young et al. 1983	Endothelial dysplasia of lymphatics and blood vessels or both
Cannon et al. 1986	Good evidence of active osteoclastic resorption in 3 out of 7 cases with massive osteolysis
Dickson et al. 1986	Mononuclear phagocytes, multinuclear osteoclasts, and the vascular endothelium are involved in bone resorption
Hirayama et al. 2001	Increase in the sensitivity of the circulating osteoclast precursors to humoral factors that promote osteoclast formation and bone resorption
Hagendoorn et al. 2003	Proliferating vascular tissues that mainly derived from lymphatic endothelium with elevated level of circulating platelet-derived growth factor BB
Bruch-Gerharz et al. 2007	Many types of vascular malformations, including capillary, venous, and lymphatic

lymphatic vessels have been suggested as possible alternatives in the pathogenesis, since the osteolytic phenomenon in GSD seems to be related to proliferation of vascular elements, inflammation, variations of PH or other local conditions, rather than the result of an alteration of osteoclastic activity [22,23].
Immunohistochemical analysis with markers for lymphatic endothelial cells suggests that in GSD-affected soft tissues, as well as cortical and medullary bone, lymphatic vessels are infiltrating areas that usually are not present in bone tissue [22,23].
Altered lymphatic vessels do not exhibit neoplastic features, suggesting that in GSD, a non-tumoral proliferation of lymphatic vessels, rather than blood vessels, is involved in the bone resorptive process. Bone resorption could also be a consequence of the proliferative activity of fluid-filled lymphatic vessels or result from the altered activity of osteoclasts and/or osteoblasts, mediated by factors secreted by endothelial cells. It has been reported that patients affected by GSD exhibit a loss of osteoblastic repair response, which appears to be localized only to the affected bones, while bone homeostasis remains relatively normal in the unaffected areas [24,25,26,27,28,29].
Since GSD is a diagnosis of exclusion, it must be based on clinical, radiological, and histological investigations. Other conditions, such as infectious, inflammatory, endocrinologic, and neoplastic diseases, must be excluded [30] (Table 3).
Biochemical and hematological tests are usually regular, and the disease is not associated with endocrine or metabolic alterations.
X-rays are the gold standard of the diagnostic process, showing the total or partial absence of bone due to resorption phenomena, which can eventually extend to contiguous areas without a marginal sclerotic reaction. Early radiologic findings correspond to a loss of bone density, mimicking an osteoporotic condition. In advanced disease, progressive and continued resorption of bone leads to partial or total disappearance of contiguous bones, tapering of bony remnants, or pathologic fractures.
CT is beneficial for the diagnosis and evaluation of disease progression [31].
MR is also beneficial because it can demonstrate hypo-intensity to iso-intensity signal on T1-weighted images and hyper-intensity on T2-weighted images [32,33].
Biopsy for histologic evaluation is required to confirm the diagnosis [34].
Histologic features of the disease are described as an early phase, characterized by vascularized tissue substitution of the reabsorbing bone tissue, and a subsequent phase of sclerosis, in which the dominant pattern is dominated by fibrous tissue.
Blood tests are usually negative and not useful for diagnosis [13].
The symptomatology depends on the localization of the disease, but generally, localized pain and functional problems associated with deformity are reported.
One-third of cases of maxillofacial localization of the disease present with malocclusion, deformity, and pain. Tooth mobility and gum bleeding indicate alveolar bone involvement, while other localizations of the disease can be responsible for different symptomatology. Silent onset of the disease is not unusual [35].
Complications can be potentially fatal and death or cause severe disability, can occur when the cervical spine, thorax, pelvis, or skull are involved [36].
It has been reported that chylothorax can occur in approximately 25% of patients, eventually evolving into respiratory distress or failure. And vertebral involvement can be complicated by neurological defects, paralysis, and death [36-45].

Case report

A 67-year-old female was referred to the Department of Oral and Maxillofacial Surgery of San Giovanni Battista Hospital of Foligno (Italy) by the Ophthalmology unit of the same hospital, due to a diplopia associated with a correct zygomatic asymmetry and localized pain.
The patient visited a general dentist 6 months prior, complaining of dental mobility in the upper right alveolar process, which was diagnosed as periodontal disease and treated according to the guidelines.

Table 3. Diagnostic Workup for GDS.

CLINICAL EVALUATION	RADIOLOGIC INVESTIGATION	LABORATORY INVESTIGATION	HISTOPATHOLOGY	DIFFERENTIAL DIAGNOSIS
Extraoral clinical examination	Orthopantomography	Hemogram, blood glucose level, serum calcium, serum alkaline phosphatase serum acid phosphatase, thyroid and parathyroid hormone, erythrocyte sedimentation rate, tumor markers (CA 15-3, CA 125, CEA, a-FP)	Biopsy	Massive osteolysis
Intraoral clinical examination	Computed Tomography Cone Beam			Idiopathic multicentric osteolysis
	Computed Tomography Total Body			Multicentric osteolysis
	Magnetic Resonance Imaging			Hereditary multicentric osteolysis
	Limbs Radiography			Neurogenic osteolysis

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The dentist also performed the extraction of 1.7 dental elements, but the mobility of the other teeth was worsening despite the therapies. Afterwards, she noted the onset of facial asymmetry, characterized by right cheek flattening, increased diplopia, and pain in the right maxilla. For these reasons, the patient underwent an ophthalmology examination and was referred to the Maxillofacial Unit for further evaluation.

The extra-oral clinical examination revealed right zygomatic and orbital asymmetry, as well as horizontal and vertical diplopia. Besides, there was no history of trauma, numbness in the upper lip, or lymph node swelling (Figure 1). Clinicians also required a Hess screen test to quantify the diplopia. (Figure 2).

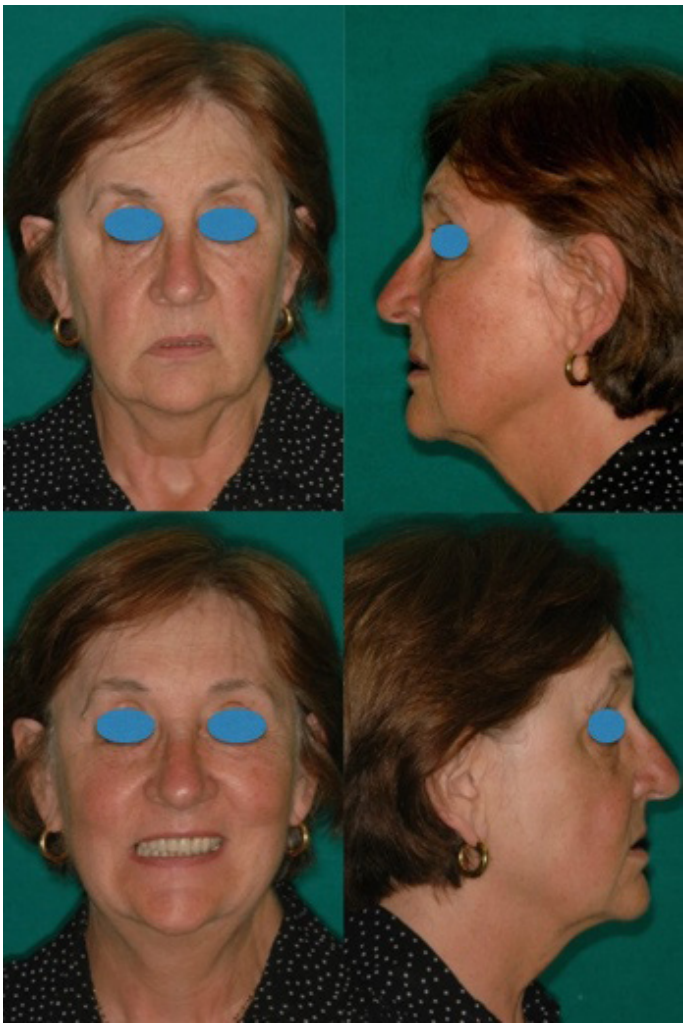

Figure 1. Right zygomatic asymmetry; no neurological lesion was observed.

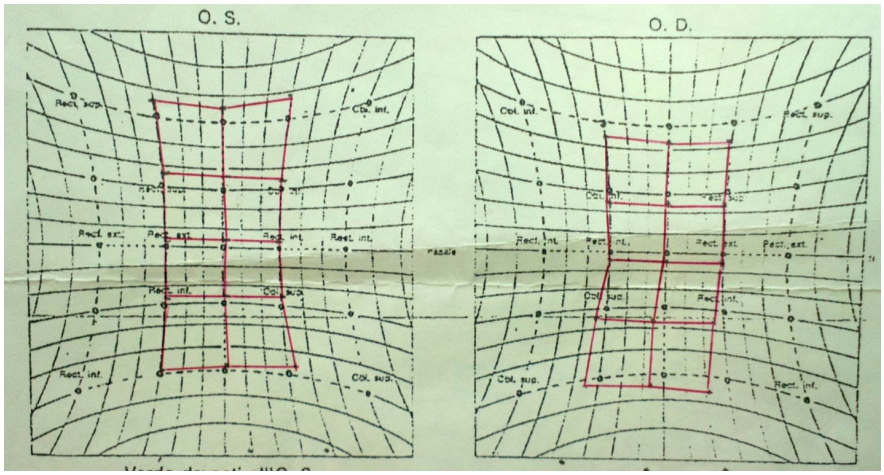

Figure 2. Hess screen test. Diplopia was observed when looking at the top, along with a deficit of the superior rectus muscle, which was already partially present.

Orthopantomography, CT, MR imaging of the head and neck, and a Total Body CT scan have been requested for evaluation of the disease. The orthopantomography (Fig. 3) revealed the presence of an osteolytic area of alveolar bone of the right upper jaw.
CT of the jaws (Fig. 4) confirmed the presence of an osteolytic lesion of the right maxilla associated with collapse of the right sinus, osteolytic alteration, and solid tissue replacement of the lateral part of the right orbit.
The MR (fig. 5) showed an osteolytic-erosive right maxillary lesion involving the maxillary sinus, zygomatic arch, and floor of the orbit; the maxillary sinus was reduced in volume, collapsed, and deformed.
The total body CT (Fig. 6) did not reveal any features suggestive of neoplastic lesions or tumor-like lesions.
Intra-oral clinical examination revealed the absence of gingivitis, adequate oral hygiene, and grade 2 mobility of dental elements, ranging from 1.5 to 1.6. Additionally, the dental crown prosthesis was noted to be from 1.4 to 2.6. Periodontal probing showed loss of attachment and periodontal pockets. Laboratory tests, biopsy of the osteolytic lesion, and histological examination were required (Fig. 7). During biopsy, 1.6-1.5 and 1.4 showed severe loss of stability and were extracted.

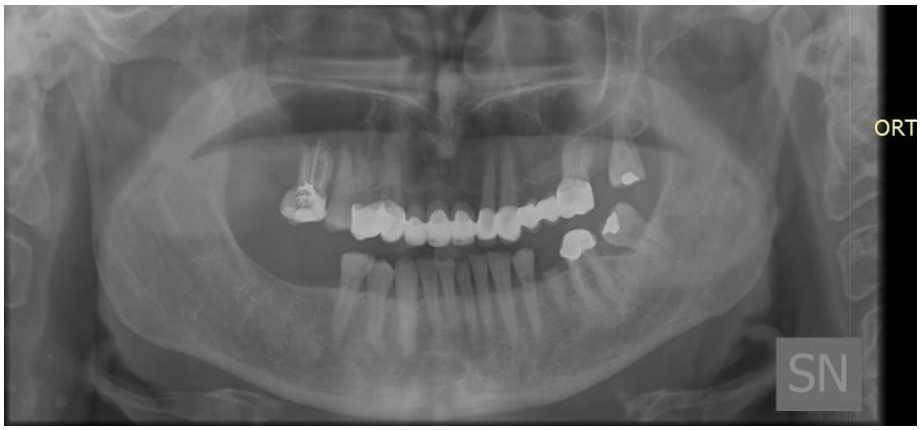

Figure 3. The panoramic radiograph showed an osteolytic area of the alveolar bone of the right jaw.

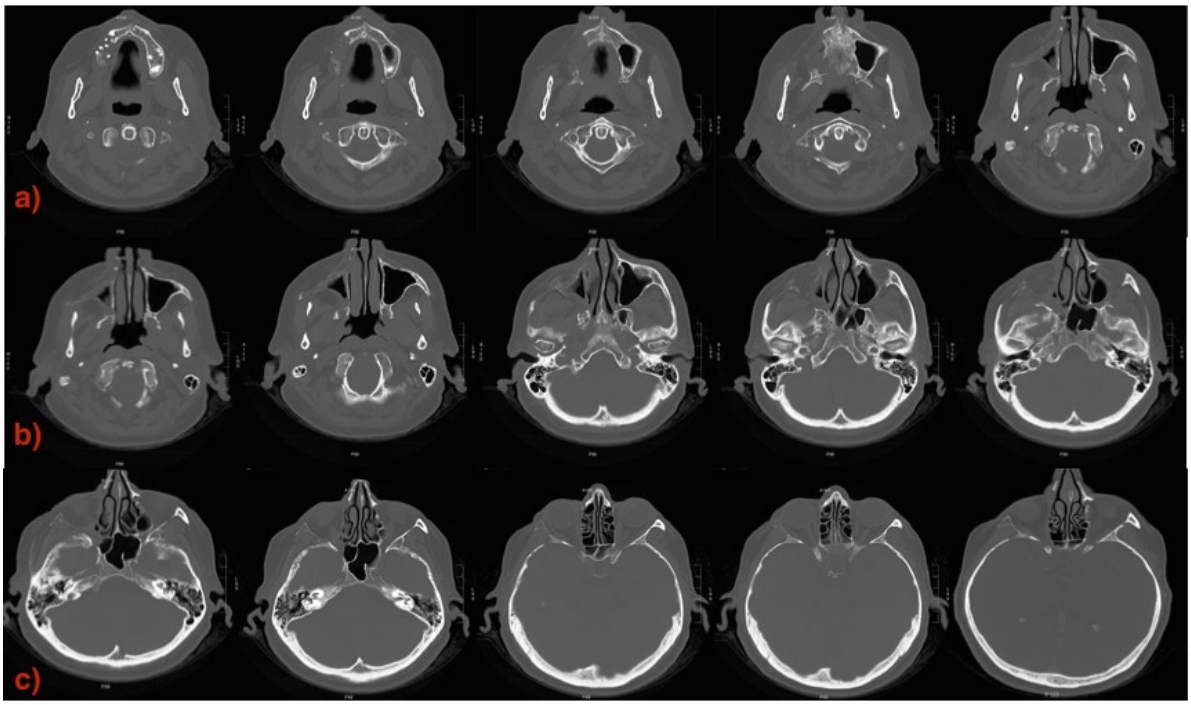

Figure 4. CT. a) Osteolytic alteration in the right maxillary region, characterized by erosion of the alveolar bone and palate. b) Asymmetric expansion of the maxillary sinus for a collapse of the right maxillary sinus. Osteolytic alteration of the zygomatic arch, close to the zygomatic process of the frontal right bone. c) Osteolytic alteration with erosion of the right lateral area of the orbit and sinking of the orbital floor due to the collapse of the maxillary sinus; osteolytic alteration involved the right orbital process of the frontal bone and diploe.

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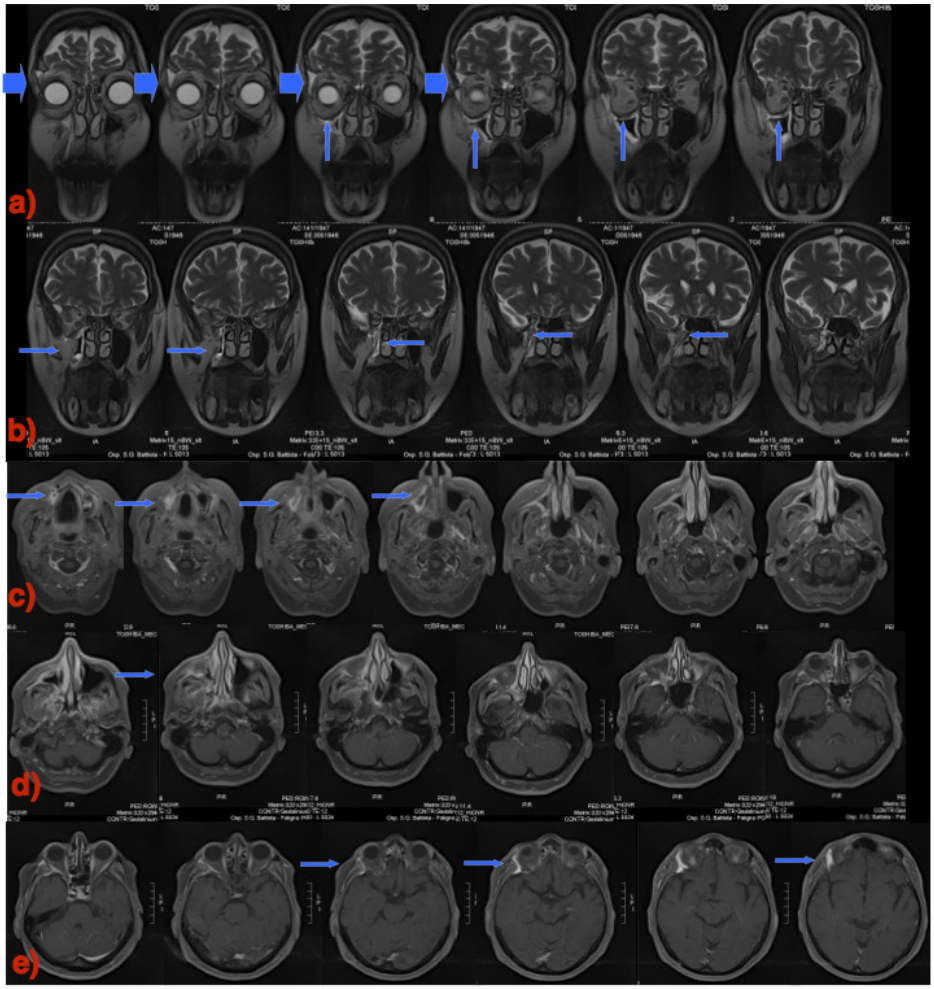

Figure 5. MR. a, b) Toshiba 1,5 T MR COT T2w: Orbits asymmetry; collapse of the right maxillary sinus; signal alteration of the right maxillary bone. c,d,e) Toshiba 1,5 T MR T1w mdc: Signal alterations of the soft parts of the right upper jaw, the right maxillary sinus, and the orbit.

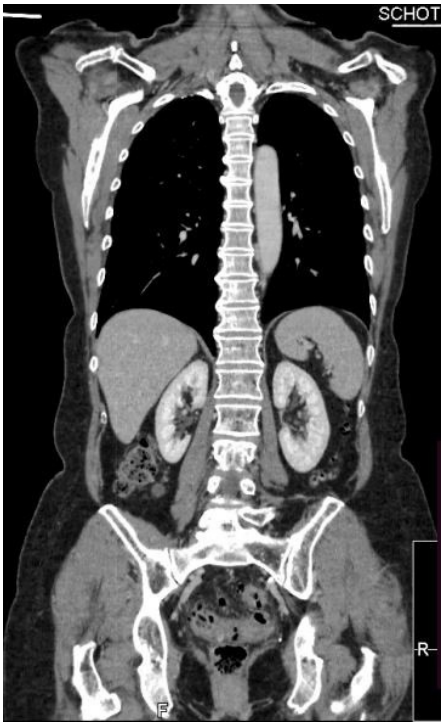

Figure 6. Total Body CT. No neoplastic lesions observed.

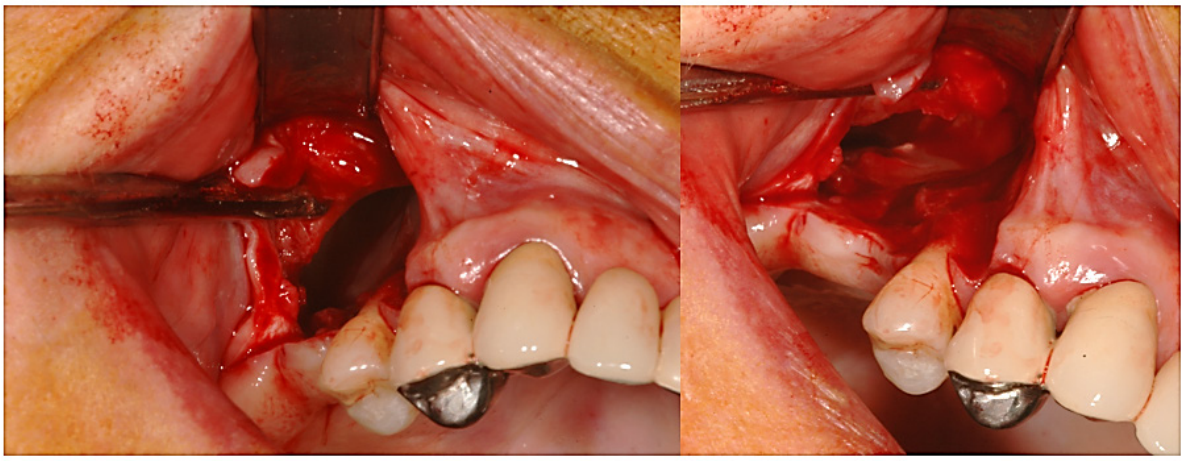

Figure 7. Biopsy, intraoperative view. Osteolytic lesion of the right maxilla with collapse of the sinus.

A fragment of the fibrous tissue replacing the alveolar bone was submitted for histological evaluation (Figure 8). Histology revealed an angiomatous tissue, with no cellular atypia, minimal or no osteoblastic response, and absence of dystrophic calcification.

Laboratory tests (red and white blood cell examination, serum electrolytes, creatinine, alkaline phosphatase, calcitonin, thyroid and parathyroid hormones, urine analysis, CA 15-3, CA 125, CEA, a-FP) were within normal ranges.

Conventional radiographs of the breast, limbs, spine, and claws did not show any pathologic features.

The present case satisfies the diagnostic criteria for Gorham's disease proposed by Heffez et al. (1983), excluding hereditary, metabolic, neoplastic, immunologic, or infectious etiologies.

Clinically, a non-expansile and non-ulcerative lesion with an osteolytic radiographic pattern and local progressive osseous resorption was observed, accompanied by no signs of visceral involvement.

Due to the recurrence of the disease, surgery was excluded as initial treatment in this case.

Surgical reconstruction will eventually be performed after stabilization of the disease by non-surgical treatment.

Both radiotherapy and pharmacological therapy are valid treatment options for Gorham's disease. Considering the risk of potentially dangerous side effects of radiotherapy on the orbital area, the patient refused it, and pharmacological therapy was considered the best treatment modality in this case.

Consequently, the patient was scheduled for drug therapy with intravenous zoledronic acid (4 mg every 28 days) for 6 months. Creatinine and calcium levels were checked monthly.

Results

After six months of pharmacological therapy, the progression of the disease ceased, and there was no further bone resorption. The patient reported the absence of pain and normal tooth stability.

The CT scan confirmed the quiescence of osteolytic phenomena, indicating that the disease progression had stopped and there was no further bone resorption (Fig. 9).

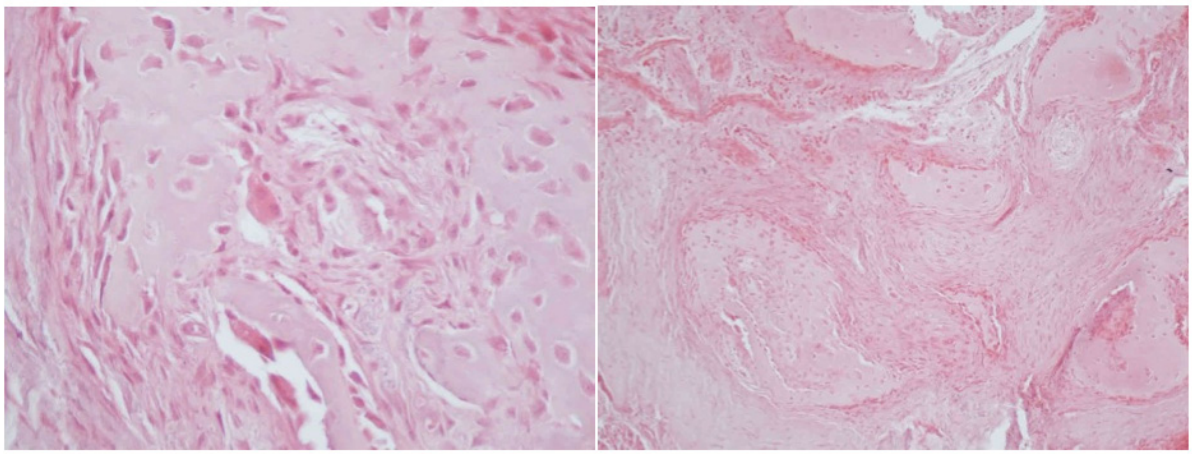

Figure 8**.** Microscopically, fibrous tissue, vascular proliferation, lymphocytes, plasma cells, and bone trabeculae are observed, surrounded by osteoclasts.

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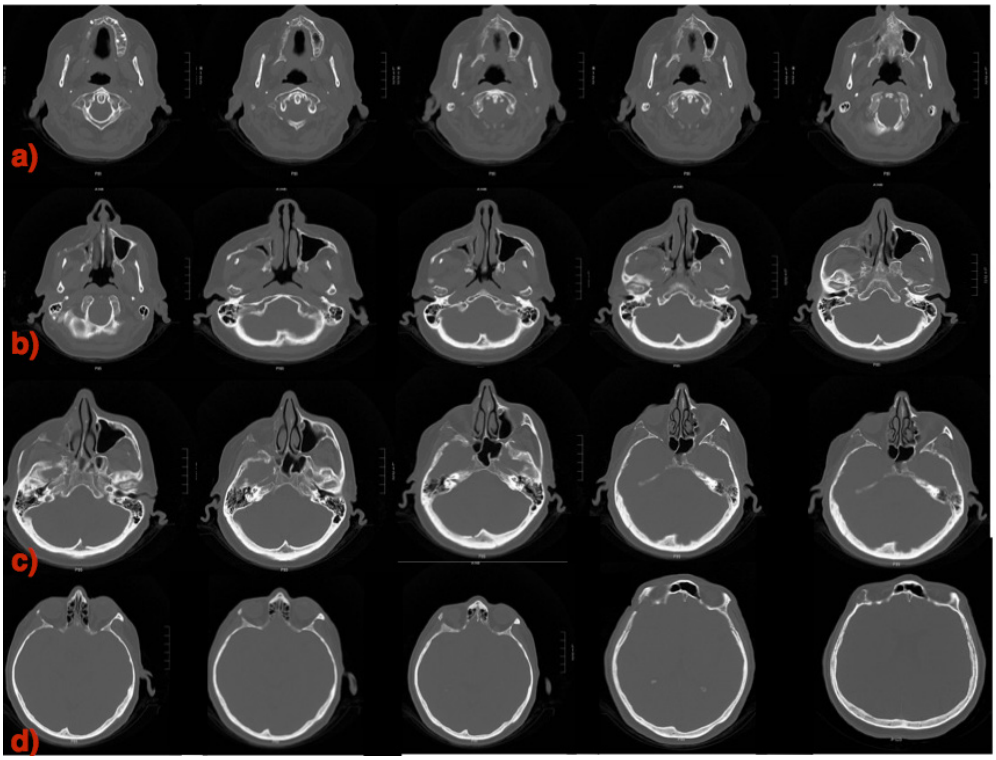

Figure 9. CT after 6 months. a) Reparative sclerosis in the alveolar bone and palate. b) Bone repair with sclerosis of the zygomatic bone and collapse of the right maxillary sinus. c) Bone repair with sclerosis of the lateral wall of the right orbital bone. d) Bone repair with sclerosis of structures initially involved in lytic alteration.

The patient did not show any adverse effects to the drugs; thus, it was decided to continue the therapy for another 6 months.

After one year of therapy, no signs of disease progression were observed, so medical treatment was discontinued.

If the quiescence of the disease is confirmed, after proper follow-up, a reconstruction of the orbital floor, right zygoma, and alveolar process can be scheduled. (Figs. 10-11-12)

Discussion

The first case of vanishing bone disease was described by Jackson in 1838, while Romer was the first author to report a case affecting the jaws of a young child in 1924. Gorham in 1954 and Stout in 1955 presented a case series, defining the condition as a specific pathological process [1,2]. The disease is rare, with approximately 350 cases described in the literature [34]. Head and neck localization is typical and is frequently associated with malocclusion, alveolar bone loss, teeth mobility, gingival bleeding, and facial asymmetry.

Even if it is considered a benign lesion, GSD has an unpredictable prognosis, and there is no standard therapy available. Therefore, its treatment remains the subject of research, although several therapeutic options have been proposed with varying results.

Pharmaceutical treatment is one of the modalities for treating the disease; several medications have been tested with unsatisfactory results. Calcitonin, vitamin D, alpha-2 b interferon, bisphosphonates, propranolol, and sirolimus seem to be effective therapies, especially in association, and, due to the relative absence of adverse effects, can be suggested as a first treatment modality. The mTOR inhibitor rapamycin (Sirolimus) seems to be more effective in children and young patients than adults with several different vascular anomalies involving bone, including GSD. [46-57]

Radiation therapy acts by accelerating the sclerosis of proliferating blood vessels, thanks to the radiosensitivity of endothelial cells, and prevents the regrowth of these vessels. In 2014, Skidmore et al. suggested that 30-45 Gy in 2-Gy fractions appears to result in a good clinical outcome with few long-term complications. However, nowadays, drug therapy represents the first approach, with fewer long-term complications than radiotherapy [58-62].

Surgery can be mandatory to treat complications of GSD, such as chylothorax or loss of stability in case of severely affected bones. Although resection of the affected segment and eventual reconstruction with bone grafts and/or prostheses is considered by some authors to be the therapy of choice, it can be complicated or lead to recurrence of the disease due to the osteolytic nature of GSD, which may cause failure of the bone grafts and/or prostheses.

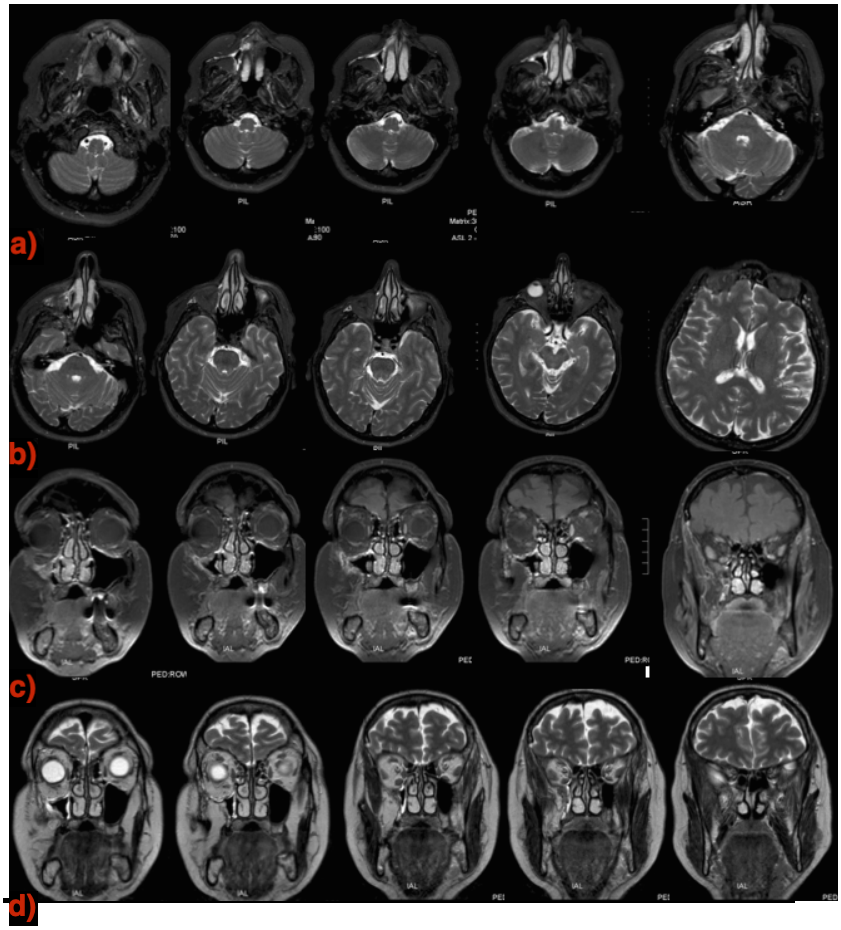

Figure 10. MR. a,b) MR AX FSE T2w: c,d) MR COR T2w.

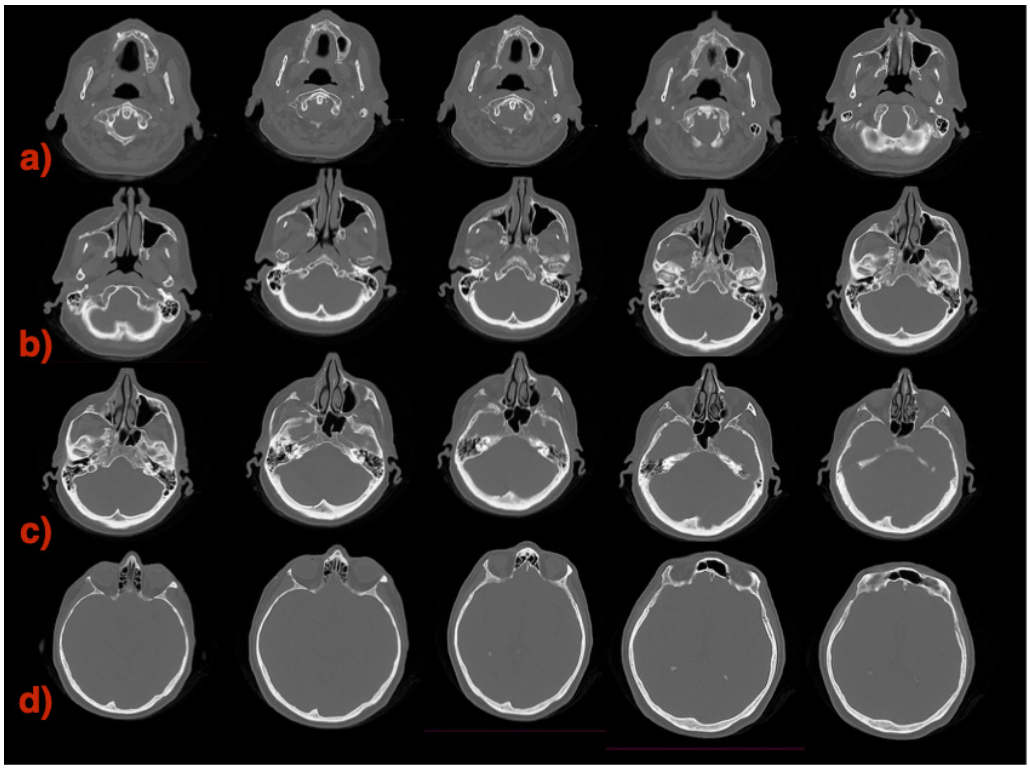

Figure 11.CT after 12 months. Reparative sclerosis in the alveolar bone, palate, zygomatic bone, and orbital bone is initially involved in an osteolytic alteration.

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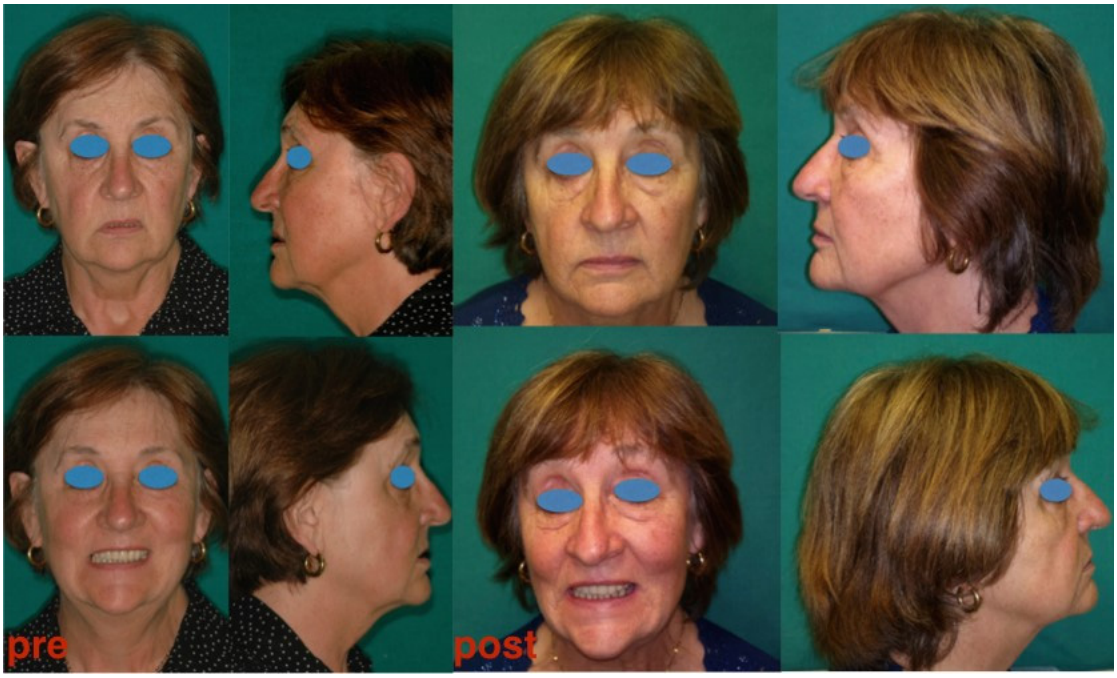

Figure 12. After one year of medical therapy. No significant changes in the right profile were found on the extra-oral examination.

Other studies suggest performing reconstructive surgery during the cold phase of the disease, when bone resorption appears to be stationary. In cases without bone fracture or massive resorption, selective embolization could be recommended or associated with surgery, preferably before [63-74].

To confirm the diagnosis of Gorham-Stout syndrome, Heffez et al. suggested the following 8 criteria [75]:

- positive biopsy for angiomatous tissue
- absence of cellular atypia
- minimal or no osteoblastic response and absence of dystrophic calcification
- Evidence of progressive local bone resorption
- non-expansile, non-ulcerative lesion
- absence of visceral involvement
- osteolytic radiographic pattern
- negative hereditary, metabolic, neoplastic, immunologic, or infectious etiology

Our case falls within the framework mentioned above. We presented a 64-year-old woman with tooth mobility and diplopia due to resorption of the right maxillary bone. No personal history of hereditary, metabolic, neoplastic, immunologic, or infectious disease was mentioned. CT scan revealed no evidence of visceral or local progressive bone involvement. Histology confirmed the angiomatous tissue replacing the bone tissue without cellular atypia.

The peculiarity of this case lies in the rapid response to drug therapy, which is based solely on bisphosphonates, without the use of other medications (such as propranolol, sirolimus, or calcium) or radiotherapy. After one year of treatment, the disease seems to have already stopped. Although GDS affects younger individuals, the first sign of disease was reported in the presented case report at 64 years old.

Alveolar bone loss and tooth mobility have been noted as early signs in most cases of Gorham's disease of the jaws. Hence, an accurate oral examination can be helpful in the early diagnosis of head and neck (H&N) localizations.

Surgical treatment, including resection of the affected bone and reconstruction, can be followed by a recurrence of the disease. It could be recommended to perform surgical reconstruction of the bone after clinical and radiological signs of stabilization of the disease.

Conclusions

Gorham's disease is a rare and little-known disease characterized by a slow and progressive resorption of bone tissue. Nowadays, there are no therapeutic guidelines, and treatment depends on the individual case, tailoring it to the patient's needs and affected area.

Despite its rarity and predilection for young age, signs and symptoms may also appear in adult patients. Consequently, doctors and dentists should consider this disease in differential diagnosis.

Maxillofacial surgeons and dentists play a crucial role in identifying this pathology, as early diagnosis and effective management are essential to prevent further complications and improve quality of life, particularly when the disease affects aesthetic regions, such as the neck and face.

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