A Case of Vanishing Mandible: Diagnosis and Treatment Considerations for Gorham-Stout Disease of the Mandible

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ABSTRACT

Gorham-Stout disease is a rare osteolytic disorder with an unclear pathophysiology. It presents as lesions characterized by the loss of the bony matrix and the proliferation of malformed vasculature. At present, there are no gold-standard diagnostic evaluation protocols and it is diagnosed through a mixture of clinical, histopathologic, and radiographic findings. We report a case of a 19-year-old female with Gorham-Stout disease presenting with an 8-year progressive soft tissue mass in the mandible. Extensive osteolysis of the mandible with clustering of the mandibular dentition is noted on computed tomography (CT) imaging. Her case was discussed in a multidisciplinary conference and her treatment was radiotherapy followed by surgery ± reconstruction. We used a CT-based three-dimensional planning technique to give 40 Gy over 20 treatment sessions to the involved areas. Post treatment, a repeat CT was done at six weeks to reassess for disease progression or stabilization, followed by surgical excision. As of 31 October 2021, no evidence of recurrence is noted 48 months after treatment. Arriving at a definitive diagnosis with Gorham-Stout disease is challenging and a multidisciplinary team approach can help determine the treatment choice with best outcomes.

Keywords: Gorham-Stout disease, vanishing bone disease, disappearing bone disease, progressive osteolysis

INTRODUCTION

Gorham-Stout disease (GSD) is a rare disorder that is characterized by the spontaneous and progressive loss of bony matrix and its replacement initially by proliferating capillary-sized thin-walled vasculature and eventually by fibrous connective tissue.[1,2] It can be extensive with contiguous bone loss and whole or partial bone destruction.[1] Often described in literature as 'massive osteolysis', 'vanishing bone disease', 'phantom bone disease', and 'progressive osteolysis'.[3–5] It can affect any bone but is more frequently seen in the pelvis, humerus, axial skeleton, and mandible.[6] Gorham-Stout disease is common in young adults, with a mean age of 25 years, with no inheritance pattern or race predilection[3], equally affecting both males and females[7].

Presenting clinical symptoms depend on the affected bone and include progressive weakness, pain, deformity, and instability which ultimately lead to fractures and functional deficits.[3,7] In the maxillofacial region, the mandible is the most commonly involved site[4] and presents initially with mobile but viable teeth with gingival hemorrhage. This is then followed by hypoplasia, pain, malocclusion, and resorption of the affected alveola and adjacent bone.[1] With mandibular involvement, form and function are affected,

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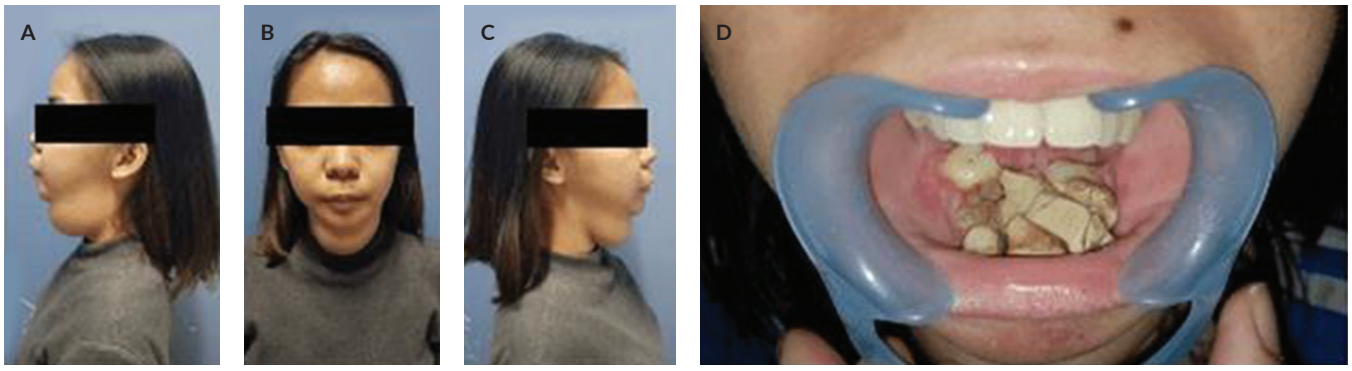

Figure 1. ***Physical exam findings (March 2019).*** Photographs showing the submandibular soft tissue mass on frontal and lateral views **(A-C)**; oral exam showing the loose, grossly deformed and crowded dentition **(D)**.

including mastication, swallowing, speech, breathing, and cosmetic appearance.[1]

GSD is usually a disease of exclusion and its diagnosis can be made through radiographic and histopathologic findings. There are no available guidelines in the management of such cases. Treatment goals are usually directed towards arresting the progression of the osteolytic process with several treatment options available: surgery, radiation therapy, anti-osteoclastic medication (bisphosphonates), and angiogenesis inhibitors. These are prescribed either alone or in combination[1,7] but conservative management can also be done as the disease is often localized and self-limiting[1].

Objectives of this case report are to show the unique challenge faced at arriving at a definite diagnosis of GSD and the possible treatment options to stop disease progression. A multidisciplinary team approach in the diagnosis and treatment is essential to optimize patient outcomes.

CASE REPORT

History and Physical Examination

A 19-year-old female with an unremarkable past medical and family history presented with an eight-year history of a gradually enlarging left submandibular mass. It was first noticed at age 11 (2011) as a barely noticeable 1.0 x 1.0 cm soft, movable, doughy, non-tender, nodular mass with no other symptoms. Initial medical consult in 2013 included an ultrasound which showed a large, well-defined complex cystic mass in the sublingual / submandibular region. Fine needle biopsy showed benign cyst contents. Assessment at the time was hypoplastic mandible with multiple dental caries.

She consulted again in 2017 after being lost to follow-up for almost five years because of the increasing size of the mass. An initial aspiration biopsy of the submandibular mass showed an acute-on-chronic inflammatory pattern and subsequent intraoral biopsy showed vascular channels with lymphoid follicles, consistent with lymphangioma. The plan then was to do a segmental mandibulectomy with fibular and clavicular reconstruction, but this was not done due to poor follow-up.

Physical exam in 2019 showed a 6.0 x 8.0 x 3.0 cm, soft, doughy, non-tender mass at the submandibular area which did not move with deglutition or tongue protrusion (Figures 1A-C). The mandibular teeth were loose, grossly deformed, and crowded (Figure 1D). She already had difficulty eating solid food and preferred soft foods.

Radiography

She underwent multiple radiographic examinations including an ultrasound, panoramic x-rays, CT scans in 2013, 2017, and 2019.

The panoramic x-rays from 2017 and 2019 (Figures 2A-C) demonstrated the progression of the osteolysis. The mandibular bodies were thinned out and tapering toward the midline, with the lesion confined to the mandibular bodies and the symphysis in 2017 (Figure 2A). This progressed to include lysis of the left angle in 2019. Dental malalignment also progressed in that two-year period and notable in the 2019 study was the disappearance of the mandibular symphysis, resulting in a floating teeth appearance (Figures 2B and C).

A November 2017 contrast-enhanced CT scan showed a hypoplastic mandible and a 4.4 x 4.8 x 6.2 cm (CC x W x AP) well-marginated, lobulated, hypodense (HU ~ 30) mass in the submandibular / submental space. The impression then was hypoplastic mandible; the differential diagnoses included hemangioma, lymphangioma, and hemangio-lymphangioma. A subsequent CT scan was done in April 2019 (Figures 3A and B) showing the same large, lobulated, non-enhancing, hypodense mass (HU: 26-31), now measuring approximately 4.9 x 8.6 x 5.3 cm (CC x W x AP). A finding not present in the earlier 2017 scan was the encasement of the left submandibular gland and the distal branches of the left facial artery by the mass, with extensive osteolysis of the mandible notably on the left body (Figures 3C and D). In both scans (2017 and 2019), the mass was delineable from the surrounding muscles.

Bone scintigraphy was also done at this time and showed no tracer uptake in the body and angle of the mandible. The rami of the mandible were also thinned out, the left more than the right.

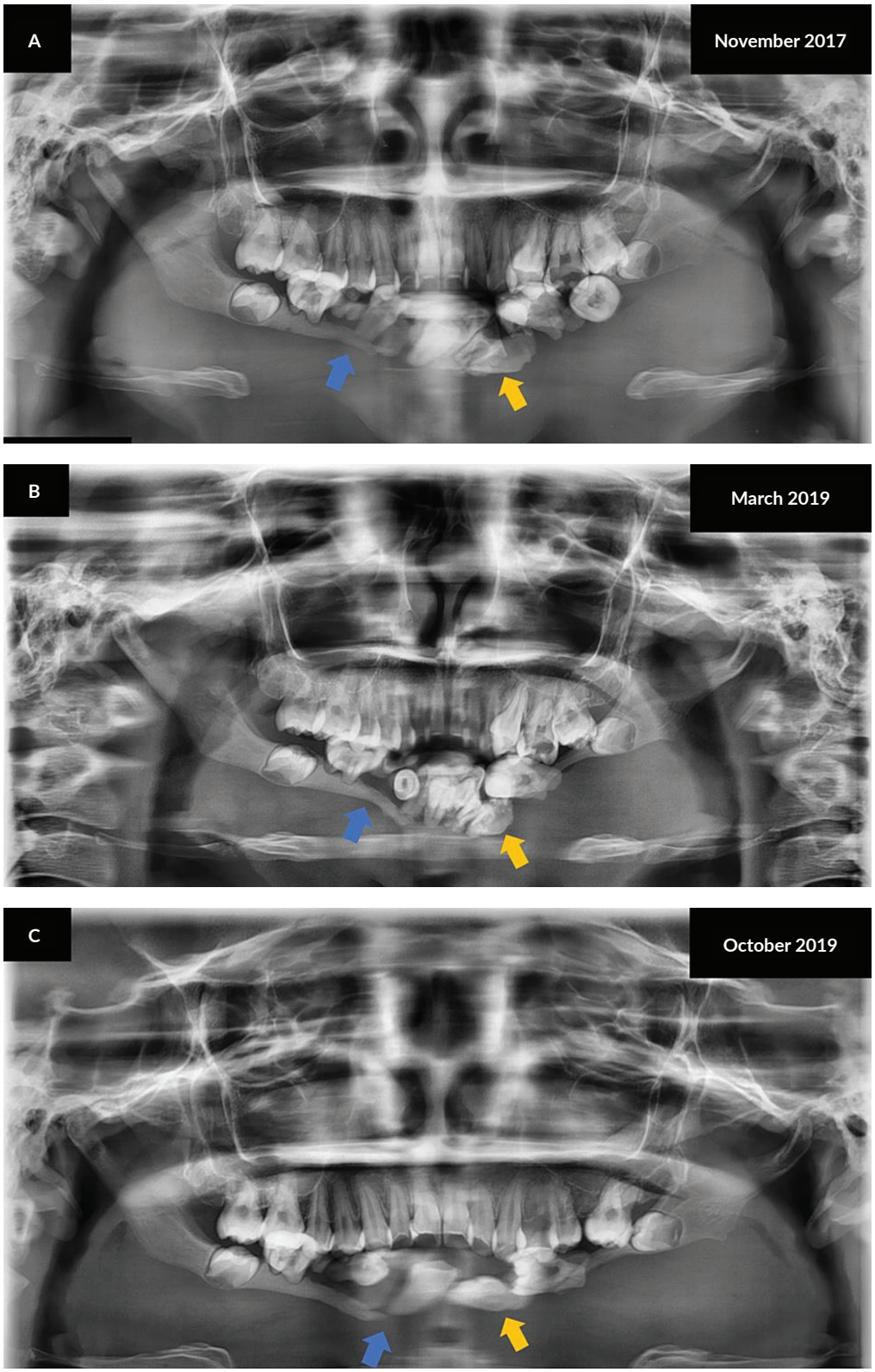

Figure 2. ***Series of panoramic x-rays (November 2017 – October 2019).*** Panoramic x-rays showing the lysed left angle of the mandible and progressive tapering of the right body of the mandible at midline *(blue arrows)* with progression of dental malalignment and loss of the mandibular teeth *(orange arrows)*.

Treatment

At a multi-disciplinary conference, it was agreed that she would be offered radiation therapy (RT) followed by definitive surgery ± reconstruction once osteoclastic activity had halted. The goal of RT was to halt the proliferation of endothelial cells and progression of osteolysis. Definitive surgery ± reconstruction aimed to remove the submandibular mass and provide a functional jaw with good cosmesis.

Her RT treatment involved CT-based, 3-dimensional external beam RT delivered over 20 treatment sessions (Figure 4). The total dose delivered was 40 Gy. During her RT treatment, she experienced mild skin desquamation (CTCAE v5.0 grade 2) on the involved areas and mild dysphagia (CTCAE v5.0 grade 1). Her treatment course was otherwise unremarkable.

Post-RT/pre-surgical imaging was planned for six weeks after completion of RT. CT scan done showed no significant interval change from the pre-treatment scans in the submandibular/submental mass and its associated extensions, mass effects, and mandibular lytic changes. She eventually underwent excision of the submandibular mass, 15 weeks after RT. The operative specimen measured 9.0 x 5.5 x 3.0 cm and was signed out as being consistent with angiolymphangioma.

Outcome and follow-up

Follow-up imaging was planned for the patient, however, COVID-19 lockdowns precluded this. In 2021, two years post-treatment, she has no signs of recurrence or progression and is able to tolerate soft solid foods (Figure 5).

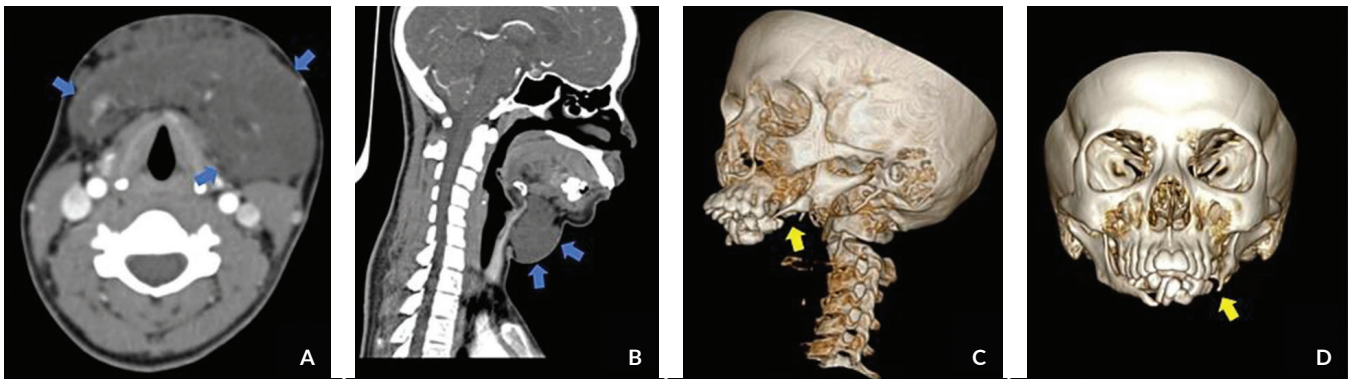

Figure 3. ***Computed tomography scans done in April 2019 with 3D reconstruction.*** Representative CT images showing a large, lobulated, non-enhancing, hypodense mass is seen at the submandibular to submental regions (blue arrows) in the axial plane **(A)** and sagittal plane **(B)**. 3D bone reconstruction showing the extensive osteolysis of the left mandibular body (yellow arrows) as seen in the left anterior oblique view **(C)** and frontal view **(D)**.

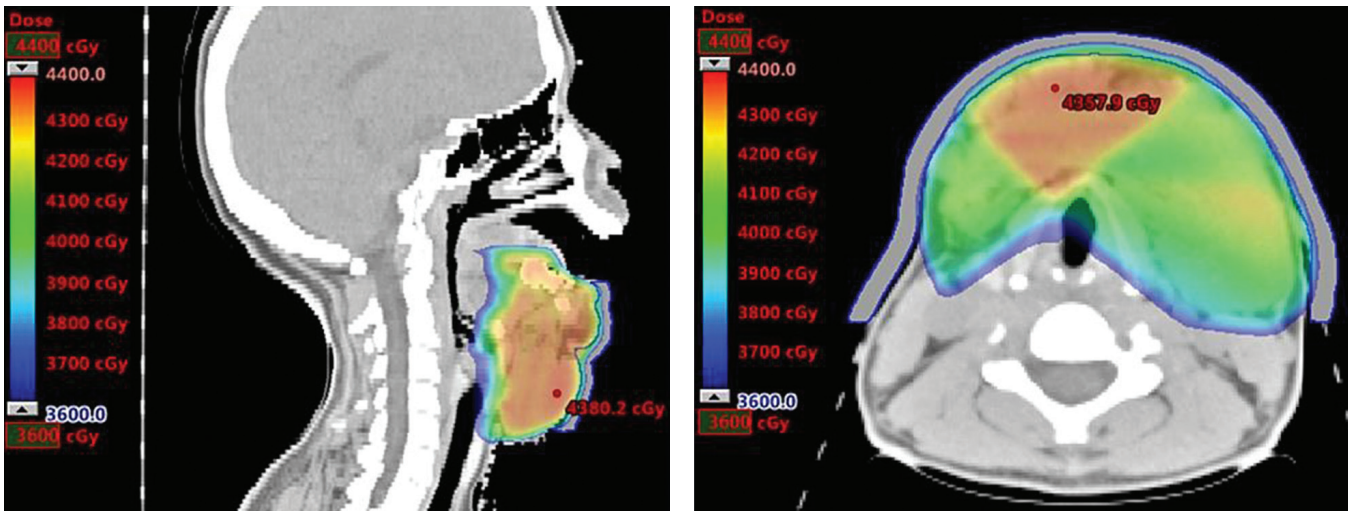

Figure 4. ***Radiation therapy (RT) treatment plan.*** Representative images of the treatment plan showing the doses received by the soft tissue mass in the submandibular area where the prescription was 40 Gy in 20 fractions. Dose color-wash depicts doses ranging from 36-44 Gy.

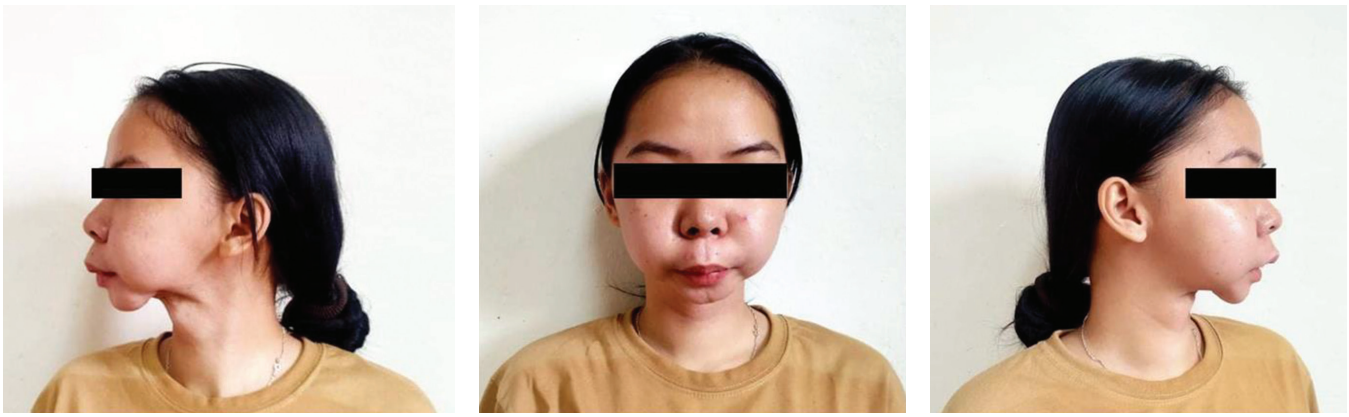

Figure 5. ***Post-treatment photographs.*** Representative images in 2021 showing post-radiotherapy and post-excision appearance of the mandible.

DISCUSSION

Pathophysiology

GSD is characterized grossly by lymphatic vessel proliferation and histologically by angiomatous dysplasia and proliferation.[2,8] It occurs in two stages: hemangiomatosis, where there is vascular proliferation in the connective tissues, and fibrosis, where the absorbed bone is replaced by fibrosis.[1,9] The exact pathophysiology of GSD has not yet been clearly defined but there are several proposed mechanisms which are not mutually exclusive. The bone resorption seen in GSD may be due to the disturbance in osteoblast and osteoclast activity from the local increase in blood flow, favoring bone degradation over formation(10). Another mechanism is the increase in interleukin-6 and humoral factor levels leading to enhanced osteoclast activity and increased osteoclast precursor activity, respectively.[1,2,4,10] Yet another is the local hypoxia/acidosis caused by the increased pressure from the soft tissue mass which in turn increases the hydrolytic activity of enzymes such as leucine aminopeptidase and acid phosphatase.[9,10] Other mechanisms include trauma[1,9], as well as the lack of thyroid C cells and calcitonin[10].

In our patient, the long history of the slow-growing vascular proliferation in the submandibular connective tissues may have led to tipping the balance in favor of bone degradation. The gradual increasing size of the soft tissue mass may have added pressure to the surrounding tissues causing local hypoxia, promoting further degradation of the bony structures. The lack of a history of trauma to the mandible makes it less likely as the mechanism for our patient.

Diagnosis

Due to the chronic and non-specific histologic and radiographic appearance of GSD, it is usually a diagnosis of exclusion. Other osteolytic entities that need to be excluded include infections, inflammatory disorders, primary and metastatic neoplasms, and endocrine disorders.[3,4,7] In literature, there are eight suggested criteria distinguishing GSD from other bone diseases with osteolysis and establishes an angiomatous lesion: (a) a positive biopsy for angiomatous tissue; (b) absence of cellular atypia; (c) minimal or no osteoblastic response, and absence of dystrophic calcification; (d) evidence of local progressive osseous resorption; (e) non-expansile, non-ulcerative lesions; (f) absence of visceral involvement; (g) an osteolytic radiographic pattern; and (h) negative hereditary, metabolic, neoplastic, immunological, or infectious etiology.[1,8,11,12]

Histologically, most biopsies appear non-specific and usually only show evidence of chronic inflammation.[4] A biopsy to exclude a malignant process is challenging as it would also presents with the typical histologic pattern of vascular and lymphatic proliferation, the eventual disappearance of bone, and in the later stages, its replacement by fibrous tissue.[2,10]

Disease progression can be radiographically distinguished in four stages. First, a radiolucent focus resembling patchy osteoporosis is seen. Next, bone deformity is present but not radiographically apparent and can be accompanied by further decrease in bone mass. Third, cortical disruption with endothelial invasion into adjacent soft tissues and/or across joints is noted. Lastly, a "sucked candy" appearance with the reduction of the ends of the affected bones is seen.[13]

For our patient, the clinical course and physical findings were non-specific, making clinical diagnosis of GSD difficult. Our patient underwent various examinations including ultrasound, panoramic x-rays, CT scans, bone scintigraphy, and multiple biopsies in aid of diagnosis. The three biopsies yielded non-conclusive results—benign cyst contents in 2013, acute-on-chronic inflammation in 2017, and lymphangioma thereafter.

With inconclusive biopsy results, the importance of imaging becomes greater. Since there are no standard imaging protocols for GSD, the choice of imaging study would depend on the disease location, presenting symptoms, and available resources. Each imaging modality can contribute different information regarding the disease (Table 1).

Table 1. Imaging Modality

X-ray	Ideal as an initial diagnostic tool, especially when pathologic fractures are being ruled out
CT scan	Provides more information than X-ray on the extent of the disease especially when evaluating bony structures
MRI	Able to better characterize the soft tissue components of the GSD, especially when it is adjacent or involving critical structures
Bone scintigraphy	Able to characterize areas affected with increased activity

For our patient, the panoramic x-rays and the CT scans were adequate for determining the size and extent of the mass, leading to a final diagnosis and assessment of resectability. Since the loss of the mandibular bone was the most pressing concern, a CT scan was done to better delineate the extent of bone lysis. MRI was not done since the soft tissue component was localized to the submandibular area and it offered little added benefit to the treatment plan but would significantly increase the cost of workup.

Treatment options

There is no optimal treatment for GSD due to its rarity and lack of large clinical studies.[1,7,11,14] Treatment is aimed at arresting the proliferation of endothelial cells and the progression of osteolysis, as well as providing mechanical support for the loss of bone structure.[3,4] Treatment modalities currently being utilized include surgery, radiation therapy, interferon therapy, anti-osteoclastic medications, and biologicals.[9,12,14] Among these, surgery and/or RT are the commonly used treatment modalities.[1,4,7,9,15] A multidisciplinary approach enables the different clinical specialties to determine on the best treatment utilization and sequence, depending on the circumstances of the patient.

Our patient initially underwent radiotherapy with the goal of halting the proliferation of endothelial cells and progression of osteolysis. This was followed by definitive surgery to remove the submandibular mass and provide a functional jaw and resulted in good disease control nearly three years after treatment.

Her RT regimen delivered a total of 40 Gy over 20 fractions, the higher end of the recommended dose range of 25 Gy to 40 Gy needed to arrest disease progression.[3,4,10] A German national database and literature review showed that doses of 36 Gy to 45 Gy were 77-80% effective in preventing local disease progression.[7,15]

Despite the increased risk of secondary malignancy[1], treatment with radiation therapy have yielded excellent outcomes with few complications in the long-term.[3,10] RT can be used as part of a definitive treatment strategy rather than as adjuvant treatment post-operatively, especially if the disease is extensive and if the patient is a poor surgical candidate. The recommended RT technique is the use of a CT-based three-dimensional treatment planning to obtain a precise target volume while ensuring the inclusion of the affected bones and adjacent soft tissue mass.[7,10]

Prognosis

There is some unpredictability when it comes to the natural history of Gorham-Stout disease. It is usually progressive with consequent bone destruction and absence of bone repair but there are reports of spontaneous regression.[2] Bone remineralization and regrowth are unusual after treatment with sparse reports by different authors.[1,3,12] GSD is usually compatible with life, especially if the affected area is in the extremity, but it can be fatal if the disease is persistent and if vital structures are involved.[4] Overall, the prognosis is usually favorable, with mortality ranging from 13% to over 30%, depending on the location and rate of disease progression.[7]

There is no recommended follow-up schedule for GSD. Regular long-term follow-up however, is important to monitor for morbidity and disease progression with physical exam and imaging individualized to the patient's circumstances. This is easier said than done as in the case of our patient. Despite the suboptimal follow-up at two years, her prognosis seems favorable with no recurrence and is able to adequately cope with her post-treatment mandibular function.

CONCLUSIONS

In conclusion, GSD is a rare osteolytic disorder which requires a high index of suspicion to be correctly diagnosed. It should be considered as a differential diagnosis in cases where an osteolytic process is presented as there are no characteristic clinical findings. Preliminary diagnostic imaging plays an important role in its diagnosis with the choice of imaging highly dependent on the disease presentation. Early detection and treatment avoids serious morbidity and disability.

This case also highlights the importance of a multidisciplinary approach in coordinating the various diagnostic examinations and treatment modalities individualized to the patient as no definite consensus and guidelines exist.

For GSD of the mandible, RT alone or in combination with other treatment modalities can be effectively given with good outcomes. Combined treatment with a CT-based 3D plan for RT delivering 40 Gy to the involved mandibular area followed by excision of the lesion can be done safely and effectively with good compliance and tolerability. Lastly, proper follow up is important to monitor for disease regression and morbidity.

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Consent for publication

A written consent for publication was obtained from the patient.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declare that they have no conflicts of interest.

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