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Teaching Case

A Case of Gorham-Stout Disease of the Skull Base Treated With Intensity Modulated Radiation Therapy



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Introduction

Gorham-Stout disease (GSD) is a rare, locally destructive musculoskeletal disorder of unknown etiology. GSD affecting the skull base is a particularly challenging disease entity. Skull-base GSD has a high propensity for causing life-threatening complications such as cerebrospinal fluid (CSF) leaks, meningitis, and osteomyelitis. Additionally, skull-base GSD is often surgically unresectable. Although the primary treatment modality for GSD is surgery, prior series demonstrate that GSD is radiosensitive, and radiation therapy (RT) is indicated for refractory or symptomatic cases not amenable to surgery. Older case series have described the management of skull-base GSD with 2-dimensional or 3-dimensional RT techniques. Recent technological advances, such as intensity modulated RT (IMRT) and image guided RT, have allowed for the delivery of highly conformal RT, potentially improving disease outcomes and minimizing toxicity for head and neck

cancer. Here we describe a case of GSD of the skull base successfully treated with conformal IMRT, and provide a review of the pertinent literature.

Patient Case

Presentation

A 27-year-old previously healthy woman initially presented in May 2017 with several months of progressive tooth loss and a 5-day history of progressive left mandibular swelling, trismus, and decreased oral intake after minor trauma to her face. Maxillofacial computed tomography (CT) without contrast revealed a nondisplaced fracture of the left mandibular angle with hypoplastic appearance of the left mandibular body and ramus with superimposed areas of permeative destruction and erosion (Fig 1A). She then underwent left mandibulectomy, reconstruction of left mandibular defect with left fibular fascio-osseous free-flap, and placement of mandibular plate in June 2017. Final pathology revealed chronic inflammation, marrow fibrosis, and vascular malformation consistent with GSD. Her postoperative course was uncomplicated.

She was seen for routine follow-up in January 2018, at which time she began to have pain in her left jaw region

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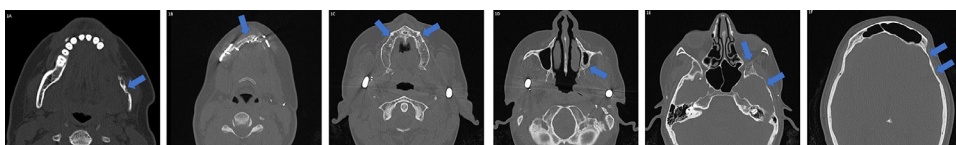


Fig 1 Axial diagnostic computed tomographic images of the maxillofacial bones without contrast reveal osseous changes indicative of Gorham-Stout disease (blue arrows) including osteolysis and bone resorption. May 2017 scan demonstrating changes in left mandible (A). January 2018 scan demonstrating progressive mandibular disease crossing midline to the right (B). February 2020 scan demonstrating further disease progression with new osteolysis within the maxilla (C-D), left sphenoid, lateral orbital wall, zygomatic arch, and squamosal temporal bone (E-F).

and was noted to have progressive, near complete tooth loss in the mandibular region. Maxillofacial CT without contrast medium demonstrated progressive bone resorption of her left mandible extending into her right mandible (Fig 1B). She received 1 dose of intravenous bisphosphonate therapy (zoledronic acid, 5 mg) in April 2018 and was recommended to take calcium 1200 mg daily and vitamin D 50,000 IU per week. She then underwent total mandibulectomy and reconstruction with a total mandibular prosthesis with right radial forearm free-flap in August 2018. Final pathology demonstrated atrophic-appearing bone with focal vascular malformation, consistent with GSD. Her postoperative course was again uncomplicated.

She was seen in routine follow-up in February 2020, at which time she felt a knot in her left cheek region. Maxillofacial CT without contrast demonstrated interval osteolysis involving the left sphenoid, lateral orbit, zygomatic arch, and squamosal temporal bones, consistent with GSD (Fig 1C-F). She was evaluated by a multidisciplinary team including otolaryngology, radiation oncology, and neurosurgery, and the patient elected to proceed with conventionally fractionated IMRT.

Treatment planning and delivery

The patient received a CT simulation without intravenous contrast lying supine with a custom thermoplastic immobilization mask with head neutral and arm on arm. CT images were transferred to the RT planning system.

Diagnostic CT from February 2020 was fused to the primary image data set to assist with target delineation. The treating radiation oncologist contoured a clinical target volume (CTV) with multidisciplinary input from the patient's otolaryngologist and neuroradiologist (Fig 2 A-D), as reported in a previous study.¹ The CTV was designed to encompass all areas of GSD. Planning target volume (PTV) was created using a margin of 3 mm from the CTV. PTV was trimmed from skin to 3 mm to limit skin dose. Organs at risk were delineated including the optic nerves, optic chiasm, brain stem, lacrimal glands, middle ears, corneas, esophagus, eyes, larynx, lens, lips, pharyngeal constrictors, spinal cord, and submandibular glands.

An IMRT treatment plan was developed to deliver 4200 cGy in 21 once daily fractions (Fig 3A-F and Fig 4). The dose was within the recommended range of 3600 to 4500 cGy based on the German Society of Radiation Oncology (DEGRO) guidelines.² Institutional dose constraints were used during planning as follows: spinal cord maximum dose <40 Gy, spinal cord +5 mm maximum dose <45 Gy, optic nerve maximum dose <54 Gy, optic chiasm maximum dose <54 Gy, brain stem maximum dose <54 Gy, lacrimal gland mean dose <26 Gy, middle ear mean dose <35 Gy, eye maximum dose <45 Gy, larynx mean dose <25 Gy, parotid gland mean dose <20 Gy, submandibular gland mean dose <25 Gy, lips mean dose <20 Gy, esophagus mean dose <20 Gy, and pharyngeal constrictors mean dose <50 Gy. Maximum dose within PTV was <120% prescription (Rx) dose, and minimum dose within PTV was $\geq 95\%$ Rx dose. PTV coverage goal was V95% Rx dose $\geq 95\%$.

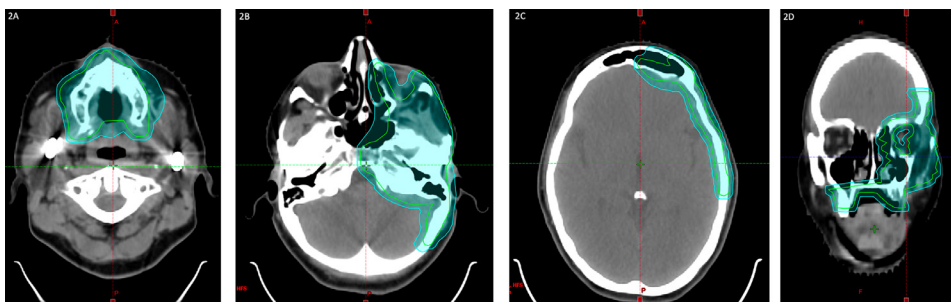


Fig 2 Axial (A-C) and coronal (D) computed tomographic images of the head and skull base from simulation radiation therapy planning study demonstrating clinical target volume in green and planning target volume in cyan.

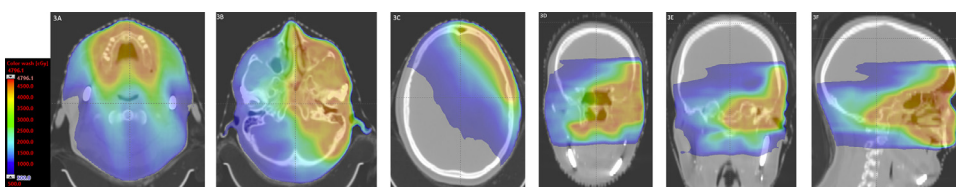


Fig 3 Axial (A-C), coronal (D-E), and sagittal (F) views of the intensity modulated radiation therapy plan for the patient.

All treatments were performed using the Ethos system (Varian Medical Systems Inc). The patient received a daily cone beam CT before RT delivery to assist with set-up. During treatment the patient experienced expected side effects as per Common Terminology Criteria for Adverse Events version 5.0, including grade 2 oral mucositis (managed with oral narcotic pain medications), grade 1 dysphagia, grade 1 xerostomia, grade 1 skin erythema (managed with over-the-counter skin creams), and grade 1 xerophthalmia (managed with over-the-counter eye lubricants). The patient did not require any treatment breaks. After completion of RT, the patient has had an excellent clinical course without evidence of disease progression or significant late morbidity. She does have mild grade 2 lymphedema in the left facial region, attributed to a combination of surgical disruption of facial lymphatics and RT. Maxillofacial CT without contrast performed approximately 3, 9, and 12 months post-RT demonstrated stability of osteolysis (Fig 5A-F).

Discussion and Literature Review

GSD, or “vanishing bone disease,” is a rare, locally destructive musculoskeletal disorder of unknown etiology. The first case was described in 1838.³ In 1955, Gorham and Stout summarized the clinical and histopathologic features in 2 cases.⁴ GSD typically affects younger adults (<40 years old) and does not have any predilection for race, gender, or familial history.^{5,6} GSD can affect any anatomic region but is more commonly found in the

skull, ribs, shoulders, and pelvis.^{4,5,7,8} The symptoms are nonspecific and based on the musculoskeletal site affected. Symptoms can include pain or muscle weakness, and patients often present with pathological fracture.^{5,9,10} GSD is a diagnosis of exclusion, and workup is required to rule out infectious, neoplastic, or osseous disease processes. Although there are a combination of radiologic and histologic features that support the diagnosis of GSD,^{4,11,12} the precise pathophysiological mechanism is not well understood.⁶ Furthermore, the clinical course is unpredictable, as both spontaneous regression and rapid progression have been reported.^{5,9}

There is no standard treatment approach for GSD. The 2 primary forms of treatment are surgery and RT.⁷ Medical therapy with osteoclast inhibiting drugs such as bisphosphonates or interferon (alfa-2b) therapy has also been reported, although these are typically used in conjunction with surgery or RT. Surgical options include resection of effected bone with reconstruction or amputation.⁷ The DEGRO guidelines suggest RT is an effective therapy with local control of ~80% and minimal toxicity.^{2,7,13} The prognosis for GSD is generally good, though patients with GSD affecting areas such as the skull base and spine can have increased morbidity and mortality given the proximity to critical structures.¹⁴

To the best of our knowledge, this is the first case of skull-base GSD treated with conformal IMRT reported in the literature. Skull-base GSD is particularly challenging and can be life-threatening secondary to CSF leaks, resulting in recurrent meningitis, medullary compression, or cervical instability.^{15,16} In addition, skull-base GSD has a

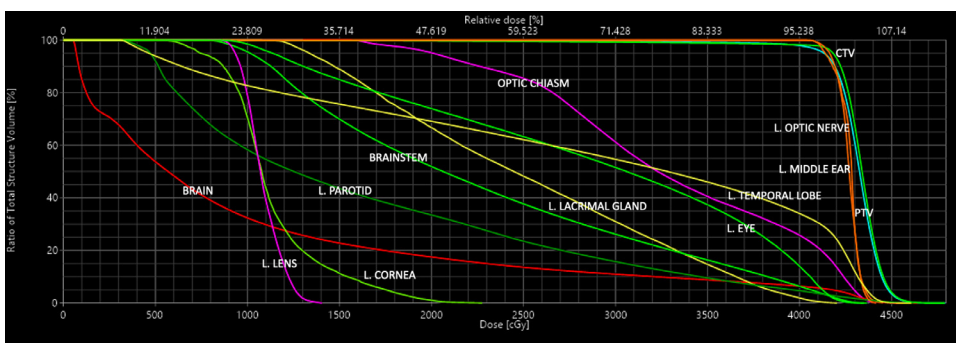


Fig 4 Dose volume histogram of the intensity modulated radiation therapy plan for the patient.

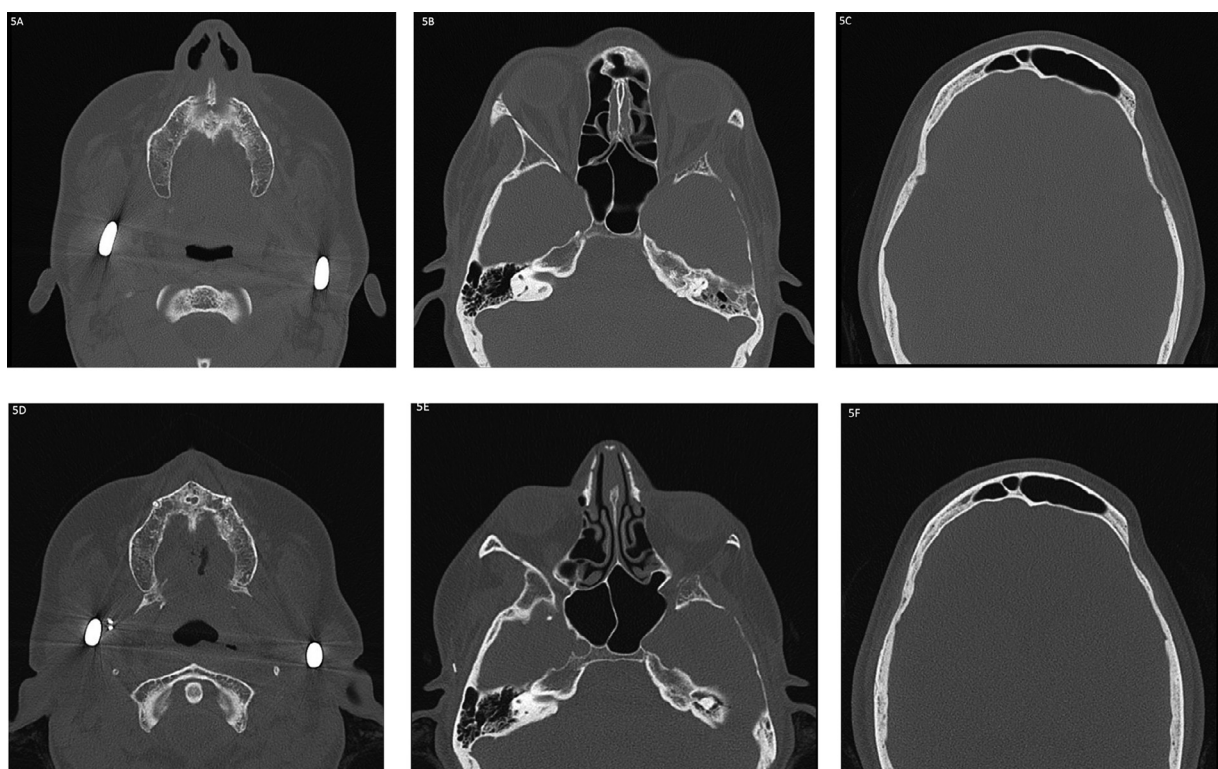


Fig 5 Follow-up axial diagnostic computed tomograms of the maxillofacial bones without contrast at 3 months (A-C) and 9 months (D-F) post completion of radiation therapy demonstrate stabilization of disease without new areas of osteolysis.

high propensity for causing local symptoms, as seen with our case, that significantly affect patient quality of life. Therefore, optimal management of skull-base GSD is crucial. Surgery can be considered for up-front management but can result in significant morbidity, including graft resorption, recurrent CSF leaks, and infections.¹⁵⁻¹⁷ In patients with particularly advanced disease, surgery may be technically challenging due to the lack of bone substance for fixation of autologous or alloplastic materials. Our patient's GSD was refractory to 2 surgical procedures and medical therapy, with RT used as a salvage therapy option.

Descriptions of RT for GSD have historically been for cases of progressive GSD resistant to surgical intervention, as with our patient. RT has also demonstrated efficacy as definitive first-line therapy. RT for skull-base GSD has mostly been reported in single case reports (Table 1) using 2-dimensional or 3-dimensional RT techniques, with a total RT dose ranging from 20 to 45 Gy. A majority of patients (10 of 13) described in the literature demonstrated no local progression after RT. Although data are limited, there is a suggestion of dose-dependency with regard to control of GSD, with in-field progression occurring in 2 cases after total doses of 36 Gy and 35 Gy, and out-of-field progression in 1 case after 36 Gy, whereas no patients who received >36 Gy had disease progression.

These data inform the DEGRO guideline recommendations (36 to 45 Gy).²

Our case highlights the safety and early efficacy of conformal IMRT for the treatment of skull-base GSD refractory to surgery and medical management. Our patient was treated with a total dose of 42 Gy, consistent with the DEGRO guidelines. Our patient tolerated her RT course well with minimal acute toxicity. In-field progression has been reported as late as 46 months post-RT.⁷ Although long-term disease control and late toxicity cannot be fully assessed without longer follow-up, the patient is currently 12 months post-RT without evidence of disease progression or significant late morbidity. IMRT has demonstrated significant benefit in decreasing toxicity from RT for head and neck cancer.¹⁸⁻²⁰ Our patient is young, and further disease progression or development of treatment-related toxicity could have devastating consequences. Furthermore, radiation-induced sarcoma after management of skull-base GSD has been reported, placing importance on reducing the total treatment volume.²¹ Proton therapy has emerged as another modality to deliver RT for skull base tumors while minimizing integral dose to organs at risk.^{22,23} Therefore, we recommend that conformal RT techniques (IMRT or proton therapy) be considered for the treatment of skull-base GSD refractory to surgical and medical management.

Table 1 Summary of published studies of radiation therapy for management of skull base Gorham-Stout disease

Authors	Site(s)	Dose (cGy)	Dose per fraction (cGy)	Follow-up (mo)	Results
Kurczynski and Horwitz (1981) ²²	SB	2000	200	24	No progression, +BR
Heffez et al (1983) ¹²	SB	4500	180	12	No progression, +BR
Dunbar et al (1993) ¹³	SB	4500	180	65	No progression/remodeling
	SB, CS	4400	200	118	No progression/remodeling
Schiel and Prein (1993) ²³	SB	4000	200	77	No progression
Frankel et al (1997) ²⁴	SB	2340	180	12	Stabilization and sclerosis
Khosrovi et al (1997) ²⁵	SB, CS	4000	200	24	No progression, +BR
Mawk et al (1997)	SB, CS	4140	180	3	No progression, +BR
Girn et al (2006)	SB, CS	3500	175	12	In-field progression
Heyd et al (2011) ⁷	SB, CS	3600	200	24	Out-of-field progression
	SB, CS	3600	200	46	In-field progression
	SB, CS	4000	200	54	No progression
	SB, CS	3060	180	111	No progression

Abbreviations: BR = bone remineralization; CS = cervical spine; SB = skull base.

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