# Chronic recurrent Gorham-Stout syndrome with cutaneous involvement

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## Abstract

Type IV osteolysis or Gorham-Stout syndrome is a rare condition characterized by recurrent vascular tumors that disrupt normal anatomical architecture. Gorham-Stout syndrome is most commonly associated with the skeletal system with resulting replacement of bone with scar tissue following tumor regression. The loss of entire bones has given Gorham-Stout syndrome the moniker vanishing bone disease. Natural progression of Gorham-Stout syndrome is characterized by spontaneous disease resolution. However, rare variants of recurrent, progressive, and/or systemic disease have been reported. We present a patient with a history of recurrent Gorham-Stout disease refractory to all treatment options considered. In addition to skeletal disease, our patient had soft tissue and cutaneous involvement, thus reflecting the more aggressive disease variant. Previous surgical attempts to control disease had been ineffective and the patient was referred to us for radiation therapy. Treatment with external beam radiation therapy resulted in good local control and symptom palliation, but full disease resolution was never accomplished. In addition to presentation of this patient, a review of the literature on etiological hypotheses and past/future treatment options was conducted and is included.

## Introduction

Type IV osteolysis or Gorham-Stout syndrome is a rare variant of idiopathic osteolytic disease.[1] In 1838 Jackson first described the disease in an 18-year-old man with a gradually vanishing humerus.[2] Later, in 1955 Gorham and Stout identified and reported 16 patients with similar disease.[3] Gorham-Stout syndrome is characterized by progressive angiomatosis of venous, capillary, or lymphatic origin.[4-6] The pathology of Gorham-Stout syndrome is associated with angiomatosis coupled with active osteolysis resulting in vascular tumor replacement of bone. The osteolysis can be monostotic or polyostotic and has the potential to result in the physical loss of entire bones – hence the term "vanishing bone disease." Involution and resolution, whether spontaneous or treatment induced, will result in replacement of the lesion with connective tissue; thus changing the underlying anatomy and physiology of the region. Often, presentation of Gorham-Stout syndrome is a consequence of the compromised skeletal framework.[1,7] Anatomical malformations and pathological fractures are often seen as common symptoms of presentation. Other presenting signs or symptoms are associated with underlying inflammation, such as fatigue and generalized pain.[7] Diagnosis is a combination of clinical suspicion with supportive imaging, but is confirmed by histopathological analysis of the lesions. Biopsy always shows extensive nonmalignant hyperproliferation of small vessels.[1,5,7]

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## Gorham-Stout Syndrome Review

Gorham-Stout syndrome has been described in all anatomical locations and tissue types, but is seen most commonly in the anatomical girdles (pelvic or shoulder) or in the long bones of the extremities. Rarely, soft tissue or skin lesions are seen and their presence reflects an increased severity of disease. One review noted that only five of the 220 (2.27%) reported cases of Gorham-Stout syndrome had cutaneous involvement in their disease.[5] When present, soft tissue lesions are reflective of involved bone distribution.[5]

Patient age ranges have been reported from one month to 75 years,[1] with children and young adults being most commonly afflicted. To date, there has not been an epidemiologic correlation with race, gender, or geography.[7-10]

Originally, Gorham and Stout postulated the tumors to be secondary to progressive hemangiomatosis.[3,10] The etiology is largely unknown but is thought to be multifactorial. Review of current literature yielded many possible etiological factors. In summary, Gorham-Stout syndrome is thought to result from a complex interaction between growth factors, angiogenic factors, and inflammatory mediators. A previous study identified histological markers on the characteristic cells of Gorham-Stout syndrome that indicate a monocyte lineage.[11] These so-called Gorham cells (GCs) have been shown to respond to known osteoclastic and angiogenic factors resulting in disease specific pathology. In particular, vascular endothelial growth factor (VEGF) subtypes, platelet-derived growth factor subtypes (PDGF), and inflammatory cytokines (TGF, IL-6, and IL-1) lead to increased activity of the GCs.[11,12] In 2006 Bruch-Graher and colleagues argued a lymphatic origin of the angiomatosis leading to lesion formation.[5,10] A publication written by Hagendoorn *et al.* emphasized the evidence supporting lymphatic vasculature as the tissue of origin for Gorham-Stout syndrome tumors. Hagendoorn *et al.* found that the majority of endothelial cells in the lesions expressed a surface protein indicative of lymphatics, lymphatic vascular endothelial hyaluronan receptor-1 (LYVE-1).[4,13] In concordance with previously reported findings, Hagendoorn *et al.* identified high circulating levels of VEGF and PDGF subtypes.[11,13]

The majority of cases reported show spontaneous resolution of disease for unknown reasons.[4,14,15] However, rare cases of chronic recurrent angiomatosis have been reported, many ultimately resulting in death. Chylothorax and spinal cord compression are two of the more severe examples of complications resulting from chronic disease. Chylothorax results from occlusion of the large lymphatic vessels in the thorax and in turn leads to fluid collection.[5,10,11] Osseous degeneration of the vertebrae leads to skeletal framework compromisation and spinal cord compression. Prompt therapeutic intervention is recommended with evidence of lymphatic or vertebral invasion.[1,7,10,16,17]

There is no known cure for Gorham-Stout syndrome and as such treatment depends on patient specific variables. Historically, local control was the primary therapeutic goal for recurrent disease. Classically, local disease was managed with a combination of surgical resection or radiation therapy.[10,18-21] Investigation of the literature indicates radiotherapy to be the best option to halt disease progression, with reported results showing foci of bone regrowth.[7,10,18-21] Investigation into the pathophysiology behind Gorham-Stout syndrome has resulted in an evolution in treatment options targeting proposed pathophysiological pathways. For example, bisphosphonate therapy has been shown to decrease osteolytic activity,[22] and as such may play a role in limiting the osteolytic breakdown of bone in Gorham-Stout syndrome. In addition, mono-

clonal antibodies targeting specific vascular growth factors currently are being investigated to target the receptors promoting angiogenesis.[4,23] In theory, these newer therapeutic options show promise, but for the most part are unproven and need further investigation. Past pharmaceutical treatment of Gorham-Stout syndrome often utilized a combination of multiple medications. No evidence-based pharmaceutical treatment protocols were discovered during the literature review, but in general an approach utilizing different agents was encountered. Examples of medications used are: vitamin D, calcium, adrenal extracts, parathyroid hormone, bisphosphonates, $\alpha$-2b interferon, and androgens.[4,5,24]

The side effects of radiotherapy in treating Gorham-Stout syndrome are similar to the side effects seen with any radiation therapy (skin hyperpigmentation and fatigue). However, pneumonitis, fibrosis, and secondary malignancy are complications that need to be considered on a per-patient basis. As with any therapeutic intervention a patient discussion should be conducted to balance risks and potential benefits of therapy. We present a patient with a multi-year history of progressive Gorham-Stout syndrome characterized by recurrent angiomatosis involving the skin, skeletal system, liver, mediastinum, and chest wall. Over her disease course the patient was treated with multiple surgical resections and radiation treatments with the goal of pain palliation. Our patient's disease was progressive and protracted, leading to a life of recurrent tumor formation, chronic pain, pathological fractures, and ultimately death.

## Case Report

The patient initially presented as a 37-year-old African American woman with a history of recurrent "hemangiomas" of the right chest wall, right shoulder, and right arm. Since childhood she had undergone multiple surgical procedures as treatment for the lesions. Biopsies of the lesions were done prior to presentation and were classified as hemangiomas. Initially, the complaint was chronic intermittent pain in her right upper extremity. Laboratory testing conducted at initial presentation did not indicate the presence of a primary metabolic or infectious disease process. Imaging of the right upper extremity showed multiple phleboliths and osteolytic changes of the distal ulna. Thoracic spine X-rays illustrated progressive dextroscoliosis and deformation of the posterior second to fourth right ribs. Physical examination showed multiple papules, nodules, and tumors scattered throughout the right arm, right shoulder, and right chest wall. The masses were described as flesh-blue in coloration and their associated mass effect led to hypertrophy and deformation of the right thorax and upper extremity. Also noted in a distribution similar to the masses were multiple scars reflecting the previous surgical procedures. In conjunction with the pain that made up the chief complaint, our patient described limited motion in all right upper extremity joints. With the exception of the right upper extremity and chest wall, the physical examination was without significant findings. Other history of note, at the age of 34 years our patient experienced a spontaneous fracture of her right arm and was treated with reduction and fixation utilizing a metal plate and screws.

The patient was given the diagnosis of Gorham-Stout syndrome and was referred for radiation treatment. Initial radiation was targeted to the right arm in an effort to treat the pain owing to the mass effect of the hemangiomas. The radiation therapy was shown to be effective at reducing the size of the tumors and relieving her pain. Because of the lack of definitive treatment for Gorham-Stout syndrome, management of the patient's pain guided therapeutic interventions. In addition to the radiotherapy treatments, the pain was managed pharmacologically with a spectrum of pharmacologic agents that ranged from ibuprofen to pethidine.

As the disease progressed tumor formation was shown to occur at other sites throughout our patient's body. For example, one year after initial presentation, thoracic involvement of the tumors resulted in the formation of multiple blebs and severe chest pain. At the age of 39 years magnetic resonance imaging (MRI) of the chest showed soft tissue densities consistent with hemangiomas in the mediastinum, anterior to the descending thoracic aorta. Avascular necrosis of the left femoral medial and lateral condyles was diagnosed after our patient complained of progressive knee pain at the age of 43 years. The onset of severe progressive abdominal pain led to an abdominal MRI that showed hepatic involvement of Gorham-Stout syndrome. Over the course of nearly 20 years our patient underwent approximately 15 separate radiation therapy treatments to alleviate pain secondary to hemangioma formation. Both electron and photon particle radiation therapeutic techniques were utilized as part of her treatment. The choice of dose given or particle subtype was guided by the specific location of the current disease. Unfortunately our patient was unable to avoid further pathological fractures when, at the age of 46 years, a full body X-Ray showed fractures of the seventh to ninth right ribs.

An autopsy was performed on 7/21/2009 but was limited to the right thorax and right arm (the forearm was not included). Relative to the left hemisphere of the patient, external examination indicated atrophic changes in both the right arm and the right thorax. Gross examination of the thorax showed hemi-diaphragmatic elevation and right fibrothorax. Congruent with external findings the musculature and bony framework of the right upper arm and thorax were atrophied. The humerus was thin and triangular-shaped on cross section, with a thin rim of cortical bone. Cystic changes within the trabecular bone were observed in the head of the humerus. Microscopy of the right humerus following formalin fixation and decalcification showed a slight prominence of blood vessels within the cortical bone, consistent with but not diagnostic of Gorham-Stout syndrome.

## Discussion

Gorham-Stout syndrome is an extremely rare disease, with slightly more than 200 cases having been reported since the disease was first described in 1955. The patient presented had a chronic progressive disease course with soft tissue/cutaneous involvement; both factors being rare variants of the already rare disease.[5,15] As discussed earlier, the treatment for Gorham-Stout syndrome mainly targets the patient's symptoms, especially in consideration of the high rate of spontaneous remission.[1,8,15] Treatment options utilized in the past consisted of surgical resection and radiotherapy.[14-16,18-21,25] Our patient presented with a chronic history of recurrent tumors and surgical interventions. A review of the literature indicated radiosensitivity of Gorham-Stout syndrome specific cells, and radiation therapy had been reported with mixed results as a treatment of recurrent Gorham-Stout syndrome.[14,16,18-21,25] Our treatment followed an aggressive yet controlled model similar to that of Dunbar and his colleagues. Dunbar found success in treating patients with moderate doses of EBR (40-45 Gy in 1.8-2 Gy fractions).[26] In a review of 22 cases Dunbar found 64% success (14/22).[26] Another review of 18 cases by Choma had 11 patients achieving local control with five showing signs of reossification.[14] In general, radiotherapy is a valid alternative for patients who have found poor success with surgery, who are not good surgical candidates or simply want to avoid the anesthesia and the protracted recovery time associated with surgical procedures.

Owing to the lack of optimal symptom control with previous treatment modalities the decision was made to proceed with radiation therapy in our patient. She received 20 different prescriptions of radiotherapy over a 15-year time period. Doses ranged from 15 Gy in 10 fractions of 1.5 Gy to 40 Gy in 20 fractions of 2 Gy. Because of the external location of many of her masses (cutaneous, superficial bones in the hand, etc.), electron beam radio-

therapy was also used in our patient. There was no therapeutic difference noted in the effectiveness between the photon or electron beams. Similar to the photon fraction doses, the prescribed electron fractions ranged from 1.5-2.0 Gy per fraction. As expected, the masses targeted by radiotherapy responded well to the treatments and the patient's symptoms were managed adequately. However, she experienced multiple recurrences at both local and distant sites and as such she never found full relief of her symptoms. The case presented illustrates important points associated with rare diseases such as Gorham-Stout syndrome, and which present many obstacles during clinical investigation. For example, there is difficulty accumulating a population sufficiently large enough to conduct clinical trials to investigate treatment options. Lacking that ability to test hypotheses in valid evidence-based trials leads to treatment guided by consensus medicine and pathophysiological "best guesses." Gorham-Stout syndrome is a perfect example; newer options for curative therapy are based on targeting the proposed pathophysiological angiogenic growth factors. These newer techniques offer theoretical promise but are largely unproven. Evidence-based randomized trials need to be conducted to identify the benefit or lack thereof. Another obstacle in the investigation of treatment for Gorham-Stout syndrome is the relatively high spontaneous remission rate. Disease resolution, whether in clinical studies or practice, cannot be definitively quantified as a treatment response because of such spontaneous remission. In addition, there is still much work to be done in elucidating the etiological process and treatment options for Gorham-Stout syndrome.

Our patient presented with a chronic, recurrent, and progressive disease course. She was highly symptomatic (pain) and found little relief from surgery and analgesics. To that end, radiation therapy was utilized to control the tumors locally and to alleviate the associated pain. To the benefit of our patient, the radiation proved to be successful and vastly improved her quality of life. Yet, owing to its solely palliative role, the radiation did not cure her disease. This case illustrates the therapeutic effectiveness of radiotherapy for local control/bone regrowth as well as the need for further investigation into curative treatment options for Gorham-Stout syndrome.

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