

RESEARCH ARTICLE

Gorham-Stout Disease of the Shoulder: Clinical, Pathologic and Therapeutic Considerations

Mohamad Y. Fares, BSc^{1,2,3}; Jawad Fares, MD⁴; Youssef Fares, MD⁵; Joseph A. Abboud, MD¹

Research performed at the Rothman Institute, Philadelphia, USA

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Abstract

Background: Gorham-Stout disease (GSD) is a rare skeletal disorder characterized by massive osteolysis of a bony area in the body. When it hits the shoulder, the patient is faced with a debilitating limitation in terms of motion, stability and quality of life. GSD etiology and pathology are unknown and, as a result, therapeutic modalities remain unclear. The aim of this paper is to explore and offer medical insight into the possible etiologies, pathologies and therapeutic modalities of GSD in the shoulder.

Methods: We explored PubMed/Medline for GSD cases in the shoulder. The search involved all articles published from database inception until February 1, 2019. Only articles published in English were included. Demographics and clinical information extrapolated from the reported cases were analyzed to deduce patterns and infer conclusions.

Results: Only 32 studies met our criteria, with a total of 37 cases (n=37). Males predominated in 21 cases (57%). Twelve cases (32%) were younger than 18 years, and 18 cases (49%) were aged between 18 and 65 years. Shoulder pain was the predominant reporting symptom. The humerus was the most common shoulder site affected (54%), followed by the scapula (35%) and the clavicle (30%). Almost half of the cases affected the right shoulder (51%), the left shoulder was affected in 16 cases (43%). Conservative treatment was opted in 17 cases (46%), while surgery was performed in 13 cases (35%). Good outcomes were reported in 28 cases (76%), while death occurred twice (5%).

Conclusion: Understanding the demographics and clinical characteristics of GSD in the shoulder region will help in formulating better therapeutic interventions and preventive health policies.

Level of evidence: I

Keywords: Bone loss, Gorham-stout disease, Osteolysis, Shoulder

Introduction

Gorham-Stout disease (GSD), also known as primary bone lymphangioma, hemangiomatosis with massive osteolysis, or vanishing bone disease, is a rare skeletal disorder that is characterized by massive osteolysis of a bone or a contiguous group

of bones in the body (1). Bone loss occurs due to the replacement of normal intramedullary fat tissue and bone marrow with proliferating lymphatic vessels (2-6). Gradually, non-neoplastic fibrovascular tissues enclose the affected bone and lead to bone resorption

Corresponding Author: Jawad Fares, Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, USA
Email: jawad.fares@northwestern.edu



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(6). GSD is often included in a group of massively osteolytic diseases like Winchester syndrome and hereditary and non-hereditary multicentric osteolysis. There has been no consensus regarding the etiology or pathology of GSD. As such, therapeutic modalities remain under question (7).

GSD affects bony areas in the body that form via intramembranous ossification like the spine, the ribs, the shoulders, the pelvis and the skull (8-12). GSD in the shoulder joint is especially incapacitating, knowing that the shoulder is the joint with the most motion in the human body. As a result, the spontaneous onset of GSD in the shoulder joint presents a huge limitation to the patient in terms of movement, general stability and quality of life (13).

Given the rarity of this disease, few cases of GSD in the shoulder area exist in the medical literature. This work aims to explore the demographics and clinical characteristics of patients with GSD, describe the possible pathologies of GSD in the shoulder region and extrapolate effective therapeutic modalities based on a systematic review of the literature.

Materials and Methods

Search Strategy and Selection Criteria

To explore the different cases of GSD in the shoulder reported in the literature, sources were identified by searching MEDLINE and PubMed for English language articles published from database inception until February 1, 2019. We used the following search terms: "Gorham Stout" and "shoulder", and the boolean operator "AND" was utilized to combine both search terms. Additional studies were identified from the reference lists of retrieved articles. Only observational studies, interventional trials and case reports were included [Figure 1].

Data Collection

The articles were reviewed critically by authors and included as appropriate to provide readers with a current overview on the etiologies, pathologies, and presentations of GSD in the shoulder. Information was acquired from the final data set on GSD presentation, diagnosis and treatment. In addition, demographics and clinical characteristics including age, sex, site of disease and medical history were also collected.

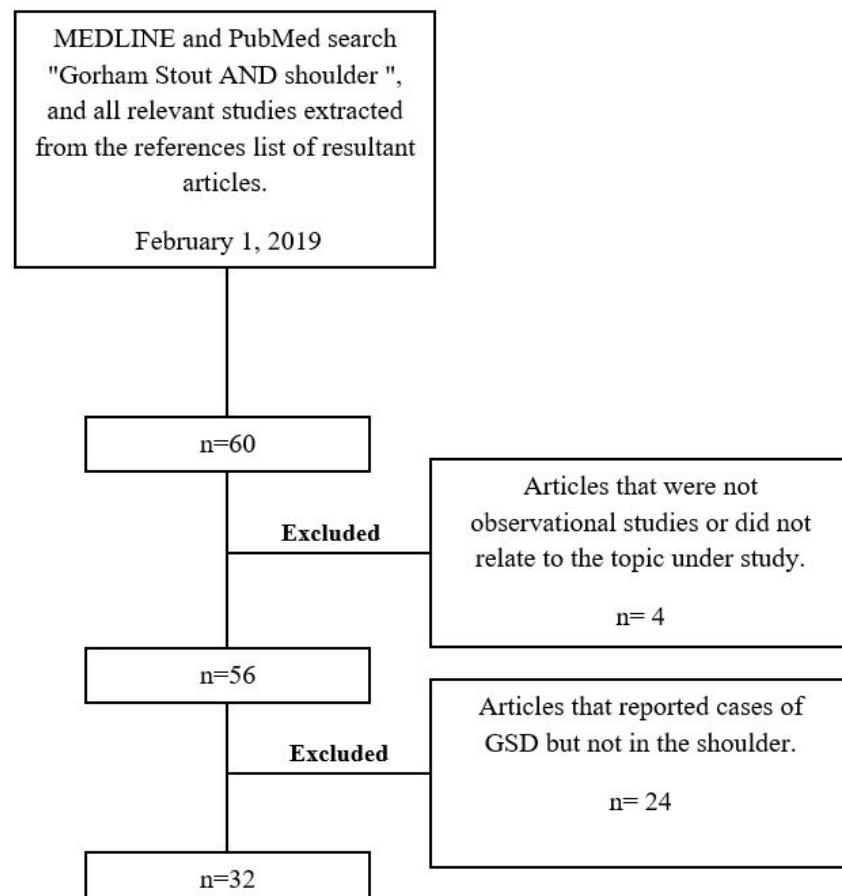


Figure 1. Article selection process.

Results

Only 32 studies met our criteria [Table 1] (5, 12, 14-43). These studies reported a total of 37 cases of GSD in the shoulder region (n=37). The demographics and clinical characteristics of the cases reported were assessed and analyzed [Table 2]. Out of the 37 cases reported in the literature, 21 cases (57%) affected males, while 16 cases affected females (43%). Twelve cases (32%) were younger than 18 years, 18 cases (49%) were aged between 18 and 65 years, and seven cases were older than 65 years (19%).

All cases reported pain or discomfort in the shoulder

area. The anatomical location most prone to GSD in the shoulder seemed to be the humerus, since it was affected in 20 of the cases reported (54%). The scapula and the clavicle followed as they were affected in 13 cases (35%) and 11 (30%) cases, respectively. In addition, 16 cases (43%) affected the left side, 19 cases (51%) affected the right side and two cases (6%) were bilateral.

Moreover, 14 cases (38%) reported no history of trauma prior to GSD, 13 cases (35%) reported a traumatic incident that led to GSD, and nine cases (27%) did not report whether the onset of GSD was traumatic or not.

Therapeutic options were surgical or non-surgical.

Table 1. Documented cases of Gorham-Stout Disease of the shoulder in the medical literature. n/a - non-available

Author	Year	Case Description	Clinical Findings	Prognosis
Gorham et al. (14)	1954	16-year-old male presented with pain and deformation of his right clavicle. The affected clavicle was fractured six months prior.	X-ray revealed total absence of the clavicle and osteolysis of the acromion and the scapula. Radiological and histological findings revealed massive osteolysis.	The patient suffered severe complications, and treatment options failed. The patient died 2 years and 5 months after fracturing his clavicle.
		44-year-old male presented with right shoulder pain of six months duration and no history of trauma.	Radiographic and histological examination revealed osteolysis of the clavicle, yet no diagnosis could be determined.	Due to the lack of a definite diagnosis, no surgical treatment was taken. The patient acquired an abscess on his triceps that was drained and had an uneventful recovery afterwards.
Jacobs (15)	1964	31-year-old male presents with an injured right shoulder due to a car accident.	There was a subluxation of the right acromioclavicular joint. He was unable to resume heavy work and felt weakness for months. Radiographic imaging revealed tapering of the bone.	n/a
		28-year-old male presents with an injured shoulder after playing Rugby. He complained of severe shoulder pain for months.	Radiographic Imaging revealed bone loss in the shoulder area of the patient.	
Feigl et al. (16)	1981	26-year-old female presented with shortness of breath. She had previously fell and contused her right shoulder.	A roentgenogram revealed a lytic process of the distal third of the lateral right clavicle. Further imaging reveals bilateral pleural effusion. Surgical exploration of the right clavicle revealed complete osteolysis. An ill-defined highly vascularized mass replaced the missing bone.	The vascularized mass was removed and repeated thoracocentesis was done to eliminate the excess fluid. Talcum was instilled into each pleural cavity twice before the accumulation of fluid ceased. Follow-up after 2 years showed normal chest roentgenogram and no signs of additional bone resorption.
Hugo and Schmidt (17)	1989	Onset of massive Osteolysis in the shoulder due to Gorham Stout disease	n/a	n/a
Damron et al. (18)	1993	36-year-old male presented with limited motion in the shoulder region	Osteolysis of normal scapular landmarks in the absence of any palpable soft tissue mass. Magnetic Resonance Imaging (MRI) helped assess the extent of the disease.	Open biopsy was performed of the remaining acromion. After the wound healed, the patient underwent physical therapy to increase shoulder strength control and motion and was kept under close monitoring.

Table 1. Continued

Canil et al. (19)	1994	12-year-old male, previously healthy, presents with a 2 week history of dyspnea, left shoulder pain, and chest swelling.	Chest X-ray showed moth-eaten lytic lesions in the ribs, scapula, and clavicle. Computed Tomography (CT) scan showed massive pleural effusion. Histological examination revealed lymphangiomatosis.	A left thoracotomy was performed, and the pleural cavity was evacuated from fluid. The patient was ventilated postoperatively to keep the lungs expanded. At 8 month follow-up, the patient was in a stable condition.
Sato et al. (20)	1995	15-year-old boy presents to the hospital with concerns regarding delay of union of humeral fracture. He had previously suffered immense pain around the left shoulder while playing sports, and without any traumatic incident.	Surgery was done and the humerus was fixed with plate and screws. Three months later, no signs of healing were evident under radiological imaging. The shoulder was atrophied and immobilized. Further radiological imaging failed to detect any abnormality. A temporary diagnosis of GSD was made, later confirmed using histological sections.	After attempts at stopping the osteolysis failed, surgical treatment was chosen. The physicians resected the left humeral head and the proximal quarter of the humerus, performed thorough curettage in the distal humerus, and fixed an intramedullary artificial humeral head. The symptoms later subsided, and the patient's condition became stable.
Pans et al. (21)	1999	72-year-old male presenting with increasing pain in right shoulder along with loss of function.	Radiographs suggested massive osteolysis of proximal humerus and destruction of glenoid fossa.	After radiotherapy failed to solve the problem, arthroscopic debridement was carried out. This limited further osteolysis in the region
Moller et al. (22)	1999	83-year-old female presented with massive osteolysis of the right proximal humerus, with no history of trauma or other events. 56-year-old female presented with increasing pain in her right shoulder of eight weeks duration.	Histological examination revealed bone fragments resorbed by osteoclasts and vascular fibrous tissue. Radiographs showed destruction of the head of the right humerus. Biopsy revealed vascular fibrous tissue, active osteoclasts, and destruction of the spongiosa.	n/a A shoulder arthroplasty was done and the patient made an uneventful recovery. Follow-up 2 months later show no complications.
Hofbauer et al. (12)	1999	8-year-old male present with weakness in his right dominant arm.	Affected shoulder was significantly lower than the healthy one. Scapula and clavicle were absent upon palpation. There was decreased radiodensity of humerus. MRI confirmed bone destruction.	Bone biopsy was not performed due to concerns of reactive osteolysis. After 6-12 months of gradual bone resorption, stability incurred, and no further damage took place.
Mochizuki et al. (23)	2000	14-year-old male presented with a of pain in the right shoulder that started 5 months ago while throwing. Physical examination showed that the contour of the right scapula was smaller than that of the left. The right shoulder also witnessed some limitation in movement.	Radiographic imaging revealed a lytic lesion in the lower part of the right scapula. CT scan revealed a bone defect without a periosteal reaction. Histology revealed hemangiomatosis associated with a few osteoclasts and endothelial-like cells. Massive osteolysis, also known as Gorham Stout disease, was diagnosed.	Radiation therapy failed to stop the osteolysis. Additional therapy was needed to stabilize the scapula and interrupt the osteolysis. The patient reported improvements in mobility and performing daily activities.
Rao et al. (24)	2001	40-year-old male manual laborer presented with a 5 month history of shoulder swelling and 5 week history of not being able to lift heavy objects.	Roentgenographic examinations showed rapid destruction of the humeral head. MRI confirmed the osteolysis. Due to the lack of any clinical evidence supporting neurological cause, Gorham Stout disease was the strongest possibility.	Given the fact that the patient presented late, and that the osteolysis had already ceased, the patient did not undergo any treatment.

Table 1. Continued

Bode-Lesniewska et al. (5)	2002	65-year-old female with a history of pain in the left shoulder and cervico-thoracic regions. She attributed the case to a traumatic dislocation of her humerus 2 years prior to presentation.	Left arm mobility was impaired, and profound tenderness was found at the cervico-thoracic region. Radiographs and MRI showed bone resorption in multiple areas of the shoulder and the affected vertebra.	Conservative therapy failed to stop progression. Massive osteolysis hindered further medical procedures, and consequently, the patient became bedridden. Post-radiation esophagitis and severe depression developed, and the patient died 15 months after clinical investigation.
Vrettos et al. (25)	2004	17-year-old male presented with a history of sudden onset of severe right shoulder pain after lifting himself out of a swimming pool.	Radiographic imaging revealed a pathologic fracture involving the shoulder girdle region. The muscles in that region were significantly atrophied when compared to the contralateral side. Biopsy of the blade and scapula confirmed Gorham-Stout disease.	A total scapular replacement was performed. The patient then made an uneventful recovery. On 6-year follow-up, the patient reported improvements in pain and strength.
Underwood et al. (26)	2006	47-year-old male with a previously fractured right clavicle, presents to the hospital with extreme dyspnea.	After conventional therapy failed to heal the clavicular fracture, autodigestion led to the disappearance of the patient's right clavicle. This led to chylothorax and the patient's respiratory symptoms. After further examination, Gorham-Stout disease was diagnosed.	The patient underwent surgery to drain the chyle from the right pleural cavity. The right thoracic duct was excised and the patient was given neostigmine and glycopyrrolate. After the surgical procedure, the patient became stable and no further complications were reported.
Jangid et al. (27)	2006	8-year-old female presented with a one and a half year pain and swelling in the left arm. There was a history of a fracture at the level of the humerus three years prior. There was a massive swelling in the area, and shoulder and elbow motion was markedly lost.	Radiologic examination revealed massive osteolysis in the humeral shaft and the proximal end of the humerus. An open biopsy of the lesion established a diagnosis of Gorham Stout disease.	A left sided forequarter amputation was performed.
Sestan and Miletic (28)	2006	58-year-old male presented with swelling and weakness of the right shoulder of six months duration. No history of trauma was recorded.	Radiological imaging revealed osteolysis of humeral head and lateral clavicle. Gorham Stout disease was diagnosed.	No intervention was done since the osteolysis had already stopped and the disease had already stabilized.
Malik et al. (29)	2008	8-year-old female presents with a complaint of swelling extending from the tip of the left arm near the shoulder to just above elbow. The swelling was hard and painful upon deep palpation.	X-ray findings showed multicystic expansile lytic areas with loss of cortical definition, and suggested Gorham Stout disease. Histological evidence of cystic angiomas confirmed the diagnosis.	n/a
Buerfeind et al. (30)	2010	46-year-old business economist suffered an inadequate trauma to the humerus and subsequently developed self-limited idiopathic osteolysis of the left humeral head.	Histopathological findings confirmed Gorham Stout syndrome of the shoulder.	Treatment was indicated operatively by means of inverted shoulder joint endoprosthesis.
De Smet et al. (31)	2010	8-year-old male patient presented with dyspnea and tachypnea of recent onset.	CT Scans and chest radiographs revealed massive chylothorax with mediastinal shift. Later imaging with 3D rendering revealed massive bone loss of rib, clavicle, and shoulder regions.	A biopsy of the left scapula confirmed Gorham Stout syndrome associated with chylothorax. The patient was treated with interferon alfa-2b and intravenous bisphosphonate with calcium supplements. Months later, chyle production diminished and eventually stopped.

Table 1. Continued

Garbers et al. (32)	2011	77-year-old female patient with rest pain in both shoulders after suffering minor trauma 8 weeks prior to presentation.	X-rays of both shoulders revealed osteolysis of both humeral heads, glenoids, and lateral clavicles.	Bisphosphonate treatment, calcium, and calcitonin administration was able to stop osteolysis in the left shoulder. However, and after recurrence of osteolysis in the right shoulder, reconstruction using prosthesis on that side was executed.
Busilacchi et al. (33)	2012	36-year-old male dockworker presented with a dislocated shoulder after being hit by a heavy piece of equipment during work. The dislocation was immediately reduced. The shoulder was immobilized in a splint for 4 weeks.	The patient presented for a follow-up after 2 months. He complained of a painful clunk during flexion and adduction. Physical examination showed positive apprehension, posterior stress, and posterior shift and load tests. The symptoms were clearly due to capsulolabral deficiency. However, Radiographs showed small osteolytic areas.	An Arthroscopic posterior capsulorrhaphy was executed as a treatment. However, the patient was readmitted after a month with his shoulder swollen and painful. After multiple tests failed to show the cause of the osteolysis, a shoulder replacement procedure was performed. 12 months later, osteolysis stopped. Histopathological findings later revealed Gorham Stout syndrome.
Zheng et al. (34)	2012	5-year-old female patient presented with back pain of 3 month history. Diagnosis was that of tuberculous pleuritis. However, anti-tuberculous therapy was not successful. 50 days afterwards, a soft mass appeared at her upper leg.	X-rays revealed massive osteolysis of the bilateral clavicle, bilateral scapula, multiple ribs, multiple vertebra, and other bony structures of her body. Histopathological, clinical, and radiographic findings later confirmed Gorham Stout disease.	The patient was given oral anti-osteoclastic medication containing bisphosphonates. No evidence of osteolysis was found 3 years later.
El-Kouba et al. (35)	2015	8-year-old male patient presented with a history of 3 traumatic fractures of his left clavicle in a span of 2 years. Weeks after the third traumatic incident, radiographs showed that part of the bone was missing.	ACT, MRI, and biopsy were requested. The MRI showed no impairment of soft tissue, and the biopsy suggested bone angioma. Due to the patient's history and examination, Gorham Stout disease was the reached diagnosis.	After 3 years of medical follow-up, osteolysis stabilized. Treatment constituted of physical therapy and hydrotherapy to strengthen the muscles. Bisphosphonate and calcitonin were administered to prevent reabsorption.
Liu et al. (36)	2016	37-year-old female presented with bone pain that affected the right scapula and clavicle.	Examination revealed GSD of the right shoulder	The patient was started on Pamidronate and remained stable afterwards.
Brunner et al. (37)	2016	84-year-old female presented with pain, swelling, and hematoma of the left upper arm with no history of trauma.	Clinical, radiological, and histopathological findings revealed Gorham Stout syndrome of the shoulder.	Clinical and radiological follow-up examinations were conducted every year for four years following initial presentation.
Brance et al. (38)	2017	92-year-old female presented with minor left shoulder pain due to a contusion.	Clinical examination revealed an unstable shoulder. MRI revealed destruction of the humeral head. Biopsy of the joint capsule confirmed Gorham Stout disease.	Clinical and radiological follow-up were conducted every three months for four years following initial presentation.
		77-year-old female presented with pain in the right shoulder with no history of trauma.	Radiographic and histological examination revealed Gorham Stout disease.	Patient underwent a reverse shoulder arthroplasty, and recovered without complications.
Papadakis et al. (39)	2017	70-year-old man presented with a history of pain and limited motion in the left shoulder with normal X-ray. A pathological fracture of the humerus occurred 6 months later.	MRI showed severe osteolysis and disorganization in the affected area. After ruling out other diagnoses, and executing further tests, Gorham Stout disease was diagnosed.	The patient was treated using intravenous zoledronic acid. A good response was reported after the first infusion.
		44-year-old male presents with pain and movement limitation in right shoulder.	X-ray revealed absence of largest portion of the scapula. Further examination revealed Gorham Stout disease.	n/a

Table 1. Continued

Stevens et al. (40)	2018	44-year-old female, previously healthy, presented with a history of increasing pain and reduced range of motion in right shoulder.	MRI revealed an infiltrative lesion in the proximal humerus, with cortical thinning and soft tissue involvement. Subsequent radiological findings revealed intramedullary and subcortical radiolucent foci. Gorham Stout disease was diagnosed.	n/a
Suranigi et al. (41)	2018	37-year-old female with presented with a 3-month history of discomfort in her left shoulder and difficulty in using her left arm.	Radiological imaging revealed significant osteolysis and the absence of the humeral head. Gorham Stout disease was suspected. Nevertheless, and due to the fact that the patient only had minimal disability, she was not willing to biopsy or undergo surgical treatment.	The patient underwent physical therapy to strengthen the muscles of the area and to increase range of motion. After 2 years, the patient stated that the disability did not worsen and hence refused further hospital visits.
Li et al. (42)	2018	26-year-old male presented with pain in left shoulder after colliding with other players while playing basketball.	Radiographs revealed osteolysis of the left scapula and the 7 th -9 th left ribs. Further pathological examinations revealed Gorham Stout disease.	In an aim to preserve shoulder function, the patient was treated conservatively. Radiotherapy and bisphosphonate treatment was administered for 6 months, and the patient showed marked improvement.
Wang and Li (43)	2018	3-year-old female presents with dyspnea of one week duration and a firm, violaceous and depressed lesion on her right chest, shoulder, and upper arm.	Chest radiograph revealed major osteolysis of the right humerus, scapula, and most of the clavicle. This was complicated by a right-sided pleural effusion. These findings suggested Gorham Stout disease.	The patient was started on sirolimus therapy, and within 13 months, her status showed marked improvement.

Table 2. Demographic and clinical characteristics of the cases under study

		N	Percent (%)
Sex	Male	21	57
	Female	16	43
	>18	12	32
Age	18-65	18	49
	65<	7	19
	Right	19	51
Side	Left	16	43
	Bilateral	2	6
	Traumatic	13	35
History	Non-traumatic	14	38
	n/a	10	27
	Surgical	13	35
Treatment	Non-surgical	17	46
	n/a	7	19
	Other	5	15
Location (more than one anatomical location in the shoulder can be involved in one case)	Humerus	20	54
	Scapula	13	35
	Clavicle	11	30
	Other	5	15

Conservative treatment was opted in 17 cases (46%), while surgery was performed in 13 (35%). Seven cases (19%) did not report the therapeutic modality used for treatment. Outcomes were reported stable and positive in 28 cases (76%). Death occurred in two cases (5%), whereas seven cases (19%) did not report any outcome.

Discussion

GSD is an idiopathic, rare and debilitating condition of bone lysis that can affect the shoulder. Our study shows that males and females are almost equally affected, and that the condition is common among young adults. Pain is the predominating presenting symptom and the humerus is the most common site of disease. Understanding the demographics and clinical characteristics of GSD in the shoulder region will help in formulating better therapeutic interventions and public health policies.

Shoulder Joint

The shoulder provides the largest extent of motion in the body using a complex of static and dynamic elements (44-47). The bony elements that are prone to GSD in the shoulder girdle region are the humerus, the glenoid, the scapula, the acromion, the clavicle, and the coracoid. The large mobility of the shoulder joint is sacrificed with decreased stability. This stability is maintained using functional muscular groups, the

glenoid labrum, articular cartilage, glenohumeral ligaments and the shoulder joint capsule (45). Together, the stabilizers and the bony components provide a balanced network that is involved in many of our daily movements and functions (46). Hence, any disability in this area would cause a significant impairment in a patient's life. Osteolysis in the shoulder region compromises both its stability and its mobility, and thus, renders the patient incapacitated. Moreover, the severe damage in the affected region causes weakness and progressively loss of function, along with significant pain (21). Patients often suffer from a decreased quality of life due to the inactivity, and may even develop depression due to chronic pain (5, 47-50).

Presentation and Diagnosis

Upon the first visit, patients usually present with a history of trauma or dislocation to the shoulder area (15, 33). Pain persists for long durations and is often accompanied with loss of function and swelling (29). While histology may confirm the presence of lymphatic infiltration and angiomas, it is radiographic examination that confirms the massive osteolysis involved in the shoulder area.

The initial radiologic sign that may suggest GSD can appear on Magnetic Resonance Imaging (MRI) or computed tomography (CT), and constitute lucent changes in the foci of intramedullary and subcortical regions, similar to osteoporosis (51, 52). Concentric reduction of the bone leads to tapering, which often results in bone that resembles a "stick of candy." Complete disappearance and resorption of the affected bone follows, suggesting the term 'Vanishing Bone Disease' [Figure 2] (51).

GSD can occur in both sexes, in any age group, and can affect either sides of the body (54). The scapula and proximal end of the humerus are the most frequent sites for massive osteolysis. GSD in the shoulder area, as well as in other areas like the ribs or the thoracic vertebrae,

can cause further complications that include chylothorax and nerve root compression, leading to a poorer prognosis (55). Chylothorax is usually fatal since it is associated with malnutrition and immunosuppression involving lymphocytopenia (55). Moreover, subsequent respiratory failures due to incapacitation can lead to death (55). Several differential diagnoses exist for GSD. These include osteomyelitis, hereditary multicentric osteolysis, rheumatoid arthritis, osteolysis due to intraosseous malignancies, neuroarthropathic shoulder, hyperparathyroidism and eosinophilic granuloma (24, 56, 57).

Due to the controversy behind its etiology, GSD is often diagnosed late and by elimination. Several criteria should be met for a definitive diagnosis of GSD in the shoulder, and these involve several examinations [Figure 3] (58). The first criterion depends on the histological findings of the patient; presence of angiomatic tissue in the affected shoulder area must be noted. Absence of cellular atypia that may predict malignancy must be noted as well (58). There should also be evidence of progressive bone resorption in the shoulder area and an osteolytic radiographic pattern which is typically visualized using a MRI, X-ray or CT scan (59, 60). Absence of dystrophic calcification and visceral involvement should be noted as well, and the observed lesion should be non-ulcerative and non-expansive (58). Finally, metabolic, hereditary, neoplastic, infectious, or immunologic factors should be eliminated. Once all these criteria are met, a diagnosis of GSD in the shoulder can be confirmed.

Etiology

Even though active osteolysis signifies GSD, its etiology remains under question. Several modalities have been proposed to help describe how the disease progresses. In 1955, Gorham and Stout concluded that GSD is associated with angiomatosis of the blood and the lymph, and is pathologically distinct from hemangiomas of the bones (61). Usually, GSD occurs in

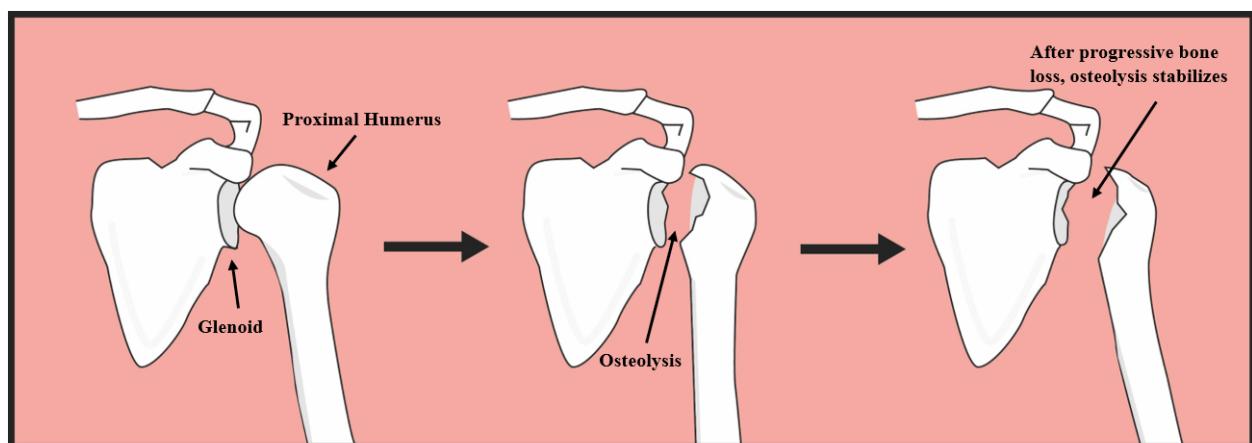


Figure 2. An example of progressive bone loss in Gorham-Stout Disease affecting the proximal humerus and glenoid region. Osteolytic patterns are unpredictable, and progress erratically before reaching a stable state and subsiding.

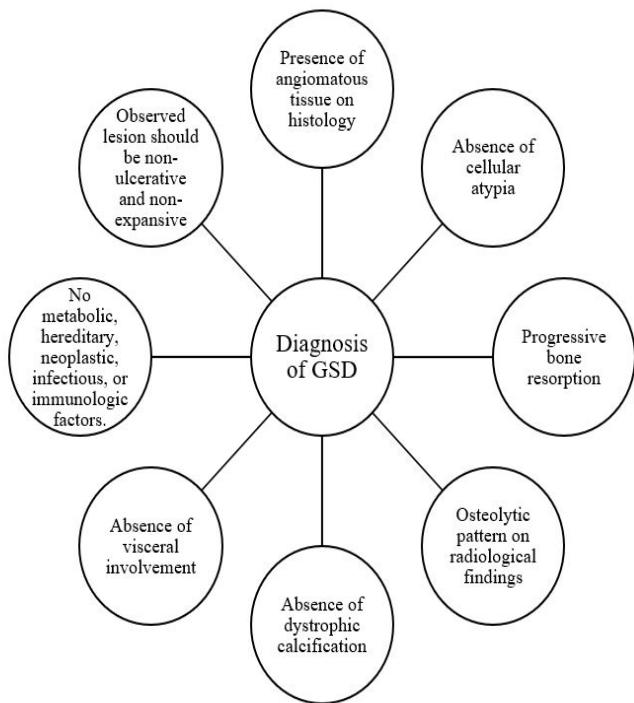


Figure 3. The different criteria needed to diagnose Gorham-Stout disease. These include the presence of angiomatous tissue, evidence of progressive bone resorption and an osteolytic radiographic pattern. Moreover, absence of cellular atypia, dystrophic calcification, and visceral involvement should be noted as well, and the observed lesion should be non-ulcerative and non-expansive. Finally, to confirm the diagnosis, one must eliminate any metabolic, hereditary, neoplastic, infectious, or immunologic factors.

a specific area, but it can be generalized and associated with multiple cutaneous hemangiomas (62). Several other conditions have been associated with GSD, and these include growth of unrestricted granulation tissue, posttraumatic hyperemia, hemangiomatosis, and lymphangiomatosis (55).

In GSD patients, angiogenesis is often present in the affected bones or the adjacent soft tissue, and consequently, osteolysis of the affected area is often associated with angiogenesis of the lymphatic tissues and the blood (55). Multiple approaches have been debated with regards to the etiology of GSD. One approach suggests that this angiogenesis changes the environment of the affected area causing increased hypoxia and acidosis which may induce chelation of calcium ions and activation of hydrolytic enzymes. This, in turn, can cause osteolysis and resorption of the bone in the affected region, suggesting that GSD is mainly due to irregular lymphangiogenesis and angiogenesis. Another approach describes an error in the cellular and humoral machineries of osteoclast formation (63-65). Osteoclasts are activated by Interleukin-6 (IL-6) and this leads to bone resorption. Monocyte cultures show

increased IL-6 concentrations in the serum of GSD patients (37, 63). This increase in IL-6 causes a rise in osteoclast sensitivity to humoral elements which leads to massive bone resorption, leading to a state of osteolysis (65, 66).

The etiology of the disease has also been attributed to the unrestricted growth of granulation tissue in the affected area, which can exert pressure and lead to bone resorption, similar to what happens in enlarged aneurysms (67).

The possibility of agenesis of thyroid C cells which secrete calcitonin has also been suggested as a possible contributor to GSD (68). Calcitonin serves as an inhibitor of bone resorption, and therefore, the lack of development of thyroid C cells would greatly diminish the amount of calcitonin in the body. This in fact can cause, or at least contribute to, the massive osteolysis found in GSD (68).

Therapeutic Modalities

Even though GSD is generally a benign condition with spontaneous remission, the extent of damage and limitation it inflicts on the life of a patient highlights the need for proper therapeutic modalities. Given the mysterious nature of this disease, its unclear pathology and unpredictable prognosis, treatment options remain a challenge and are often catered specifically to the individual case (35, 57). Differences in general health conditions, comorbidities, and extent of loss of functions entail different therapeutic approaches (35).

GSD in the shoulder treatment usually consists of three parts: conservative therapy and medication, radiotherapy, and surgery (69). Conservative therapy often includes physical therapy to strengthen the muscles of the shoulder and provide support to the affected area, in an aim to restore some of its function and stability (34). As for medication, bisphosphonates have shown promising results, and are the first-line treatment for GSD; their anti-osteolytic activity limits bone resorption. Other possible medications include vitamin D, calcium, adrenal extracts, androgens and interferon alpha-2b (70-74).

In cases of severe symptomatology, radiotherapy and surgical intervention are considered (75). Radiotherapy have proven to be adequate in moderate doses but has been shown to cause some serious long-term complications in high doses (76). These include secondary malignancies, and growth restrictions in children and adolescents (75). Surgical intervention includes surgical resection of the affected area in the shoulder, and often involves a replacement of the shoulder joint via arthroplasty (37).

GSD is a rare disease of unknown etiology and unpredictable prognosis that causes spontaneous massive osteolysis in the body. The shoulder girdle is the most common site for GSD. Therapeutic regimens have not been fully established and validated. Given the substantial involvement of the shoulder in our daily lives, it is of pivotal importance to raise awareness on this condition in an aim to provide a correct diagnosis and

delegate proper therapeutic modalities.

Limitations

We focused on studies and reports that explored patients with GSD in the shoulder, exclusively. We took ample precautions to avoid any bias or improper analyses by having two authors (M.Y.F. and J.F.) revise all studies identified and the selection steps. Some information might be missing and/or without follow-up. Nevertheless, this analysis is distinctive and imperative as it provides a wholistic perspective on the current state of GSD in the shoulder and offers researchers and clinicians the opportunity to reflect upon future prospective and observational studies on GSD.

Mohamad Y. Fares BSc^{1,2,3}

Jawad Fares MD⁴

Youssef Fares MD⁵

Joseph A. Abboud MD¹

1 The Rothman Institute, Department of Orthopaedic Surgery, Thomas Jefferson University Hospital, Philadelphia, PA, USA

2 Faculty of Medicine, American University of Beirut, Beirut, Lebanon

3 College of Medical, Veterinary, and Life Sciences, University of Glasgow, Glasgow, Scotland, UK

4 Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, USA

5 Neuroscience Research Center, Faculty of Medicine, Lebanese University, Beirut, Lebanon

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