Case report

OPEN ACCESS

Gorham-Stout disease and multiple cervical lymphangiomas: case report

María Alejandra Amezquita[1], Luz Fernanda Sua[2,3], Carlos Alejandro Garcia[4,3], Liliana Fernandez-Trujillo[5,3]

[1]Clinical Research Center, Fundación Valle del Lili, Cali, Colombia; [2]Department of Pathology and Laboratory Medicine, Fundación Valle del Lili, Cali, Colombia; [3]Faculty of Health Sciences, Universidad Icesi, Cali, Colombia; [4]Department of Diagnostic Imaging, Fundación Valle del Lili, Cali, Colombia; [5]Department of Internal Medicine, Pulmonology Service, Interventional Pulmonology, Fundación Valle del Lili, Cali, Colombia.

ABSTRACT

Introduction: Gorham-Stout disease is a rare condition characterized by extensive bone loss due to the proliferation of new vascular and lymphatic structures. It can occur in any bone and cause pathologic fractures with poor bone healing. Complications such as effusions and lymphangiomas can also develop. Gorham-Stout disease pathogenesis is still being studied, and treatment options are limited, but sirolimus has shown promise in stabilizing or reducing symptoms.

Case presentation: We present a case of a 19-year-old male with Gorham-Stout disease, multiple cervical lymphangiomas, and several thoracic complications successfully treated with sirolimus.

Conclusions: Rare lymphatic diseases should be considered as a potential cause in adult patients with bone involvement and multiple cystic lesions in the neck, axillary, or abdominal regions after excluding more common causes. The complexity of diagnosing Gorham-Stout disease should be emphasized.

Key words: Lymphangioma; Gorham-Stout Disease; Pleural Effusion; Sirolimus

Correspondence: Liliana Fernández-Trujillo, M.D. Department of Internal Medicine, Pulmonology Service, Interventional Pulmonology. Fundacion Valle del Lilil. Av. Simón Bolívar. Carrera 98 # 18-49. Torre 6, 4th Floor. Cali, Colombia. Zip code 760032. Phone: +(57) 3155006300 - E-mail: liliana.fernandez@fvl.org.co, lilianafernandeztrujillo@gmail.com - ORCID 0000-0003-0789-9154.

Authors' contributions: All authors have read and approved the manuscript, and significantly contributed to this paper. MAA: Literature review, manuscript writing and correction, final approval of manuscript. LFS: Conception and design, literature review, manuscript writing and correction, final approval of manuscript. CAG: Literature review, manuscript writing and correction, final approval of manuscript. LFT: Conception and design, literature review, manuscript writing and correction, final approval of manuscript.

Ethics approval and consent to participate: This report was prepared in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration. We have approval letter of Ethics Committee in biomedical research IRB/EC No. 121-2023 of the Fundación Valle del Lili to publish this manuscript.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Data availability statement: Datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest: The authors declare that they have no competing interests. This manuscript has not been published and is not under consideration for publication elsewhere. Additionally, all the authors have approved the contents of this paper and have agreed to the journal´s submission policies.

Funding: The authors declare that they did not receive financial support for the publication of this manuscript.

Acknowledgement: Not applicable

Introduction

Gorham-Stout disease (GSD), or Vanishing Bone Disease, is a rare benign condition of unknown origin that causes extensive bone loss due to the non-cancerous proliferation of new vascular and lymphatic structures. The disease can affect the whole body, but it generally affects the ribs, scapula, humerus, pelvis, and femur, leading to pathologic fractures and a lack of bone healing. Complications such as pleural and pericardial effusion and chylothorax can also occur, and some patients may develop lymphangiomas in different parts of the body.

While most lymphangiomas are congenital and typically occur in childhood [1,2], some may be associated with rare diseases like GSD. New lymphangiomas rarely develop in adults. Therefore, investigating complex lymphatic diseases is crucial [3,4]. Diagnosing GSD is primarily based on clinical information and radiographic findings, with confirmation made by irregularly dilated lymphoid tissue lined by endothelium on bone biopsy [5]. It is essential to exclude other possible causes of osteolysis and lymphangiomas that are more common, such as osteomyelitis, cancer, rheumatoid arthritis, renal disorders, and hyperparathyroidism [4]. A mammalian target of rapamycin (mTOR) inhibitor, such as sirolimus [6], has been described as a promising treatment option [7].

The development of lymphangiomas secondary to GSD has been previously described, primarily in the abdominal region [8]. Approximately 200 cases of GSD have been reported worldwide, with no cases reported in Colombia. We present a case of a patient with GSD and multiple cervical lymphangiomas. This case highlights the importance of considering rare diseases in the differential diagnosis of adult patients with multiple osteolysis and unexplained development of lymphangiomas after a thorough clinical evaluation.

Case presentation

This case report describes a 19-year-old African American male nursing student with a complex medical history. The patient had a left cervical lymphangioma, confirmed by biopsy and surgically treated during childhood. Additionally, he experienced pathologic fractures of the humerus and femur, which were treated with osteosynthesis. At the age of 14, the patient had an episode of bilateral chylothorax that required bilateral pleurodesis. Later, he developed recurrent left chylothorax, leading to multiple hospitalizations, pleurodeses, and ultimately thoracic duct ligation. The patient denied past exposure to cigarettes, allergies, and prescriptions. However, his family history revealed that his mother had hypertension and systemic lupus erythematosus. No other diseases were reported among the family members.

The patient presented to the emergency department with a two-day history of fever, greenish expectoration, dry cough, and dyspnea at rest, accompanied by pain during inspiration in the left cervical and thoracic region. Upon admission, the patient exhibited fever (38.3°C), hypotension (112/63 mmHg), tachycardia (125 beats/minute), and tachypnea (22 breaths/minute), with an oxygen saturation of 96%. Physical examination revealed dyspnea at rest using accessory muscles, pale conjunctivae, and a non-pulsatile soft mass in the left supraclavicular area without inflammatory changes. This mass was interpreted as a recurrence of the previously surgically treated lymphangioma from childhood. The heart exhibited rhythmic tachycardia, while diminished respiratory sounds were noted in the left hemithorax. Abdominal examination revealed no masses, and the extremities had regular pulses. The neurological examination was unremarkable. Laboratory test results are provided in (Table 1).

An initial chest X-ray (CXR) (Figure 1) depicted a left pleural effusion and diffuse thickening of the left pleural space with complete atelectasis of the lower lobe and mixed opacities with predominant alveolar involvement affecting the left upper lobe. Also, multiple lytic lesions with sclerotic and well-defined edges were observed in bone structures. A chest CT scan was performed (Figure 2), confirming the left pleural thickening and pleural effusion, as well as revealing a cystic lesion occupying the supraclavicular fossa and extending to the left axillary region. The thoracic wall showed multiple lytic lesions and sclerotic margins involving vertebral bodies, bilateral costal arches, and the scapulae. Blunting on the left costophrenic angle and pleural thickening suggested a superinfected pleural

Table 1. Laboratory results.

Test	Reference values	At admission, ED	At admission, ICU	Before discharge, ICU
Hemogram				
WBC (×103/μL)	4.23 – 9.07	21.58	10.45	11.61
Neutrophils (×103/μL)	1.78 – 5.38	20.25	9.93	6.58
Hemoglobin (g/dL)	13.7 – 17.5	9	13.7	12.3
Hematocrit (%)	40.1 – 51	43	40.9	37.7
Platelet count (×103/μL)	163 – 337	308	276	529
C-reactive protein (mg/dl)	0 – 0.5	23.35	-	2.86
Lactic acid (mmol/L)	0.5 – 2.2	-	3.79	-
Renal function				
Serum creatinine (mg/dl)	0.67 – 1.17	0.98	1.45	-
BUN (mg/dl)	6 – 20	9.80	20.40	-
Arterial blood gases (ABG)				
pH	7.35 – 7.45	-	7.33	7.43
$PaCO_2$ (mmHg)	35 – 48	-	29.1	43.9
PaO_2 (mmHg)	83 – 108	-	126.9	94.8
SO_2 (%)	94 – 98	-	98.7	97.9
HCO_3 (mmol/L)	21 – 28	-	15.1	28.8

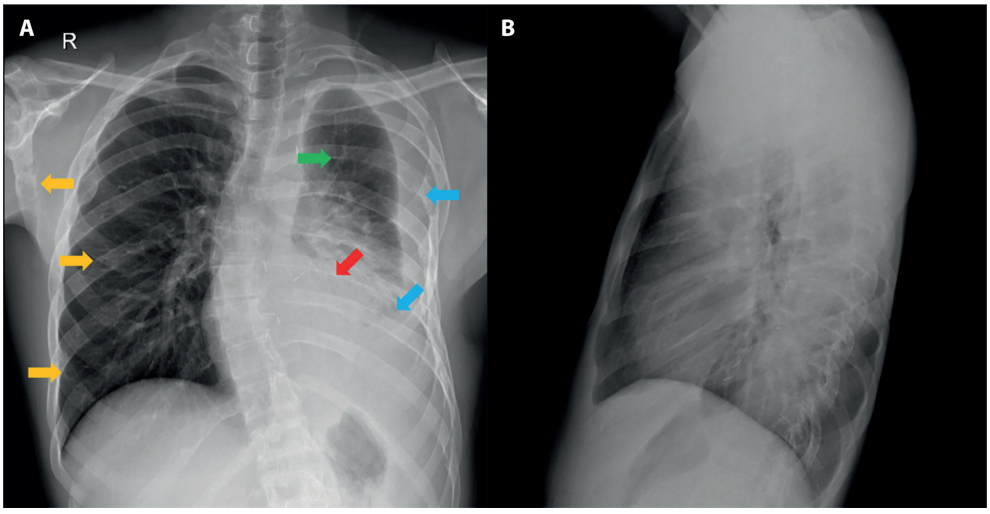

Figure 1. Chest X-ray. A. Posteroanterior projection (R= right side). Right thoracic scoliosis. Central trachea with patent source bronchi. The right lung hilum has a normal configuration, the left lung hilum cannot be assessed. Pleural effusion on the left side is evident. The cardiac silhouette is appreciated with limited evaluation due to haziness of the left lung field (red arrow). Diffuse thickening of the left pleural space with complete atelectasis of the lower lobe is observed (blue arrow). There are mixed opacities with predominant alveolar involvement affecting the left upper lobe (green arrow). Multiple lytic lesions with sclerotic and well-defined edges are seen in bone structures (yellow arrows). B. Lateral projection.

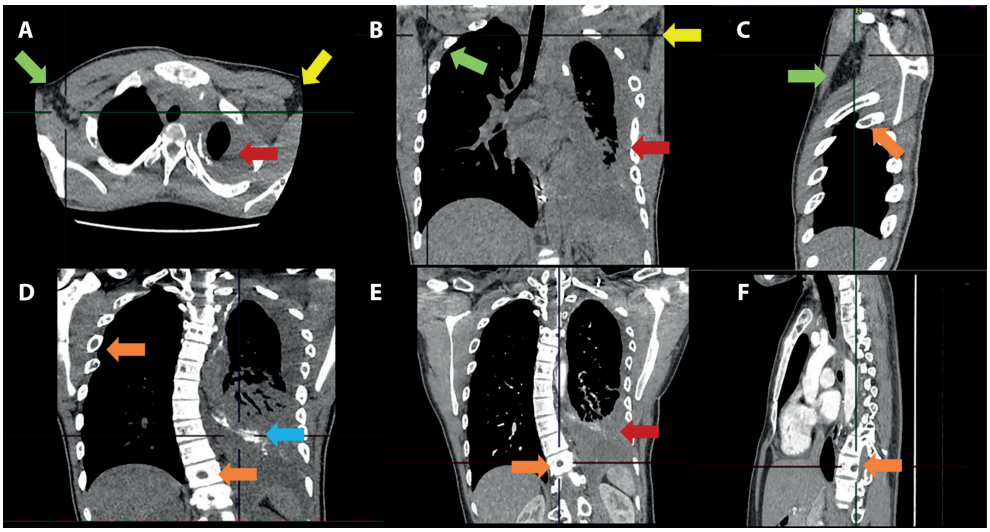

Figure 2. Chest CT scan, mediastinal window. A, B, C, D, E, F. Diffuse pleural thickening and pleural effusion with an average density of 18 Hounsfield units (HU) are observed on the left side (red arrows), calcifications of the visceral pleura in the left lower lobe (blue arrow). Cystic lesions with poorly defined borders extending into the axillary area are seen in the supraclavicular fossae, identified with green arrows on the left side and yellow arrows on the right side. Additionally, there is scoliosis with convexity to the right and multiple lytic lesions in the ribs and vertebral bodies (orange arrows).

effusion. Broad-spectrum antibiotic therapy was initiated with intravenous (IV) vancomycin 1 gram twice daily, in addition to IV cefepime 1 gram three times daily.

The patient's clinical status deteriorated a few hours later, as evidenced by a decrease in blood pressure to 77/48 mmHg and the laboratory results presented in Table 1. A subsequent CXR (Figure 3) revealed worsening of the left pleural effusion. This was further confirmed by posterior chest computed tomography (CT) (Figure 4). The patient was transferred to the intensive care unit (ICU) and diagnosed with septic shock from pulmonary origin. Ultrasound-guided thoracentesis was performed to drain and examine the pleural fluid, revealing characteristics consistent with empyema (Table 2). Hemocultures reported sensitive *Streptococcus pyogenes*, prompting the initiation of IV ceftriaxone 2 gram daily. Over the following days, the patient gradually improved, and was subsequently transferred to the hospitalization floor.

While hospitalized, the patient developed a new slow-growing lesion in the right cervical region, which was warm and painful to the touch. A multicystic lesion measuring 5.8 x 2.8 cm, along with two smaller lateral cysts, was observed behind the right sternocleidomastoid muscle during a soft tissue ultrasound. Additionally, a cystic lesion of 2.8 x 1 cm was detected in the suprasternal region (Figure 5). Due to the previous history of lymphangiomas and the characteristics of the new lesion, the possibility of it being a lymphangioma was high. However, an underlying infectious process was suspected due to inflammatory changes. Therefore, the current antibiotic therapy was extended to 21 days.

The diagnosis of GSD was suspected based on multiple osteolytic lesions in the thoracic cage, along with the previous pathologic fractures of the humerus and femur, and the recurrent chylothorax and superinfected pleural effusion. An extra-institutional bone biopsy was reviewed by a pathologist, who identified findings consistent with osteolysis, fibrosis, and reactive vascular proliferation, confirming the diagnosis and highlighting the complex diagnostic process required for GSD.

After the patient recovered from the infection, sirolimus was initiated at a dose of 2 mg/day and gradually increased until blood levels reached 5 ng/ml for a week. Once the target blood level was

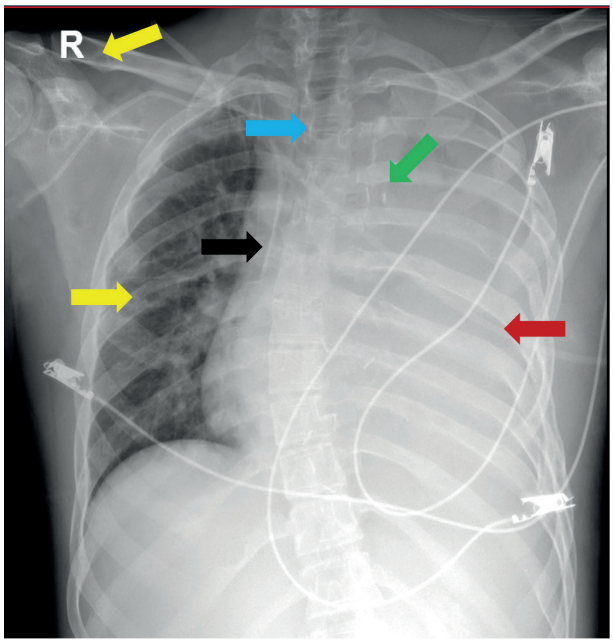

Figure 3. Chest X-ray, anteroposterior projection (R= right side). The trachea deviates to the right (blue arrow), with a non-evaluable cardiac silhouette. Compared to the previous X-ray, there is a marked increase in opacification of the left hemithorax due to pleural effusion, with underlying lung alterations unable to be ruled out (red arrow). Multiple metallic clips from a previous operation are projected onto the midline and mediastinum (green arrow). Right subclavian catheter with its tip projected into the superior vena cava (black arrow). No signs of pneumothorax are present. Multiple hypodense lesions with a lytic appearance are observed in the clavicle, scapulae, and rib cage (yellow arrow).

achieved, the dose was adjusted to 4 mg/day, and the patient was discharged. During the follow up appointment a month later, the patient reported experiencing acne as a side effect of the medication, and sirolimus blood levels were at 5 ng/ml. Consequently, the dose was reduced to 2 mg/day, improving the skin lesions. The patient was monitored over the following year, during which GSD symptoms were well-controlled with the current therapy. A CXR showed improvement in the pleural effusion as well as the lytic lesions (Figure 6).

Discussion

GSD is a bone disease characterized by abnormal vascular and lymphatic vessel proliferation throughout the body, resulting in massive osteolysis. It mainly affects children and young adults with no sex or ethnic predilection [3,9]. The development of lymphangiomas has been described before in these patients, mainly in the pelvic and abdominal regions [8].

Lymphangiomas are typically benign, congenital lesions derived from lymphatic malformations, frequently diagnosed before the age of two [1]. They are commonly found as unilateral head and neck lesions, unlike GSD, which may present with multiple lymphangiomas throughout the body at any age [8]. In this

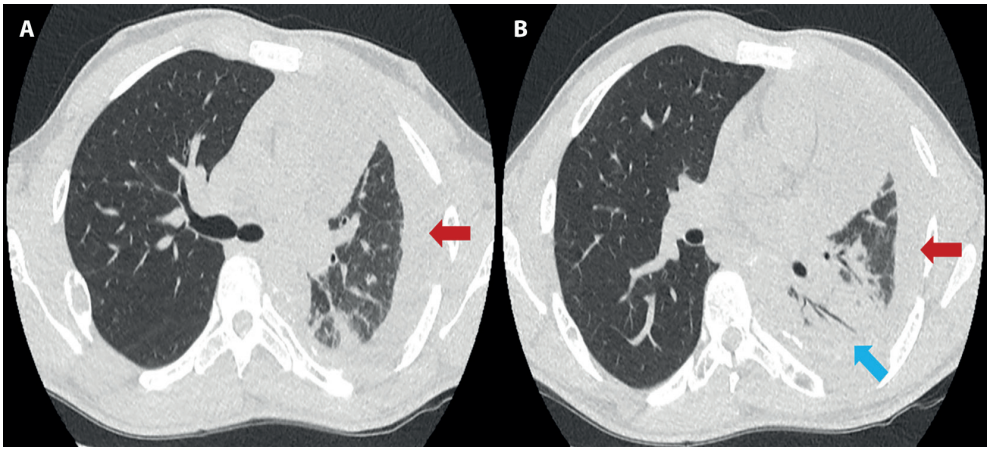

Figure 4. Chest CT scan, lung window. A, B. There is a loss of volume in the left hemithorax, left pleural effusion (red arrows), and infiltrates of alveolar occupation with consolidation of the apical segment of the left lower lobe (blue arrow).

case, the patient presented with multiple cystic lesions in the neck, which is uncommon as lymphangiomas are usually unilateral and rarely develop in adults [3,4].

Lymphangiomas in the neck are usually slow-growing and asymptomatic [10]. Pain may indicate infection, hemorrhage, or compression of the lesion. Imaging studies are necessary for assessment, and ultrasound is commonly used [11]. Sclerotherapy and surgical resection are the main treatment options [10]. However, some lesions tend to recur [8]. In this case, the patient had surgical treatment for a left cervical lymphangioma during childhood, which later recurred. The treatment for lymphangiomas secondary to lymphatic complex anomalies is to treat the primary disease.

Table 2. Pleural fluid.

	Results	Reference values
Pleural fluid		
Glucose (mg/dl)	55	-
LDH (µ/l)	440	-
Proteins (g/dl)	2.9	-
Serum		
LDH (µ/l)	177	135 - 225
Total proteins (µ/l)	5	6.4 - 8.3

LDH, Lactate dehydrogenase.

The diagnosis of GSD is complex and requires a high level of clinical suspicion. It is essential to exclude other causes of osteolysis, such as osteomyelitis, cancer, rheumatoid arthritis, hyperparathyroidism, among others, before suspecting GSD [12]. Diagnosis is based on clinical information and histopathologic and radiographic findings [5]. In the early stages, GSD may be asymptomatic, and routine laboratory tests are usually normal, except for slightly elevated serum alkaline phosphatase levels [9]. Radiographs, magnetic resonance imaging (MRI), and CT scans may show

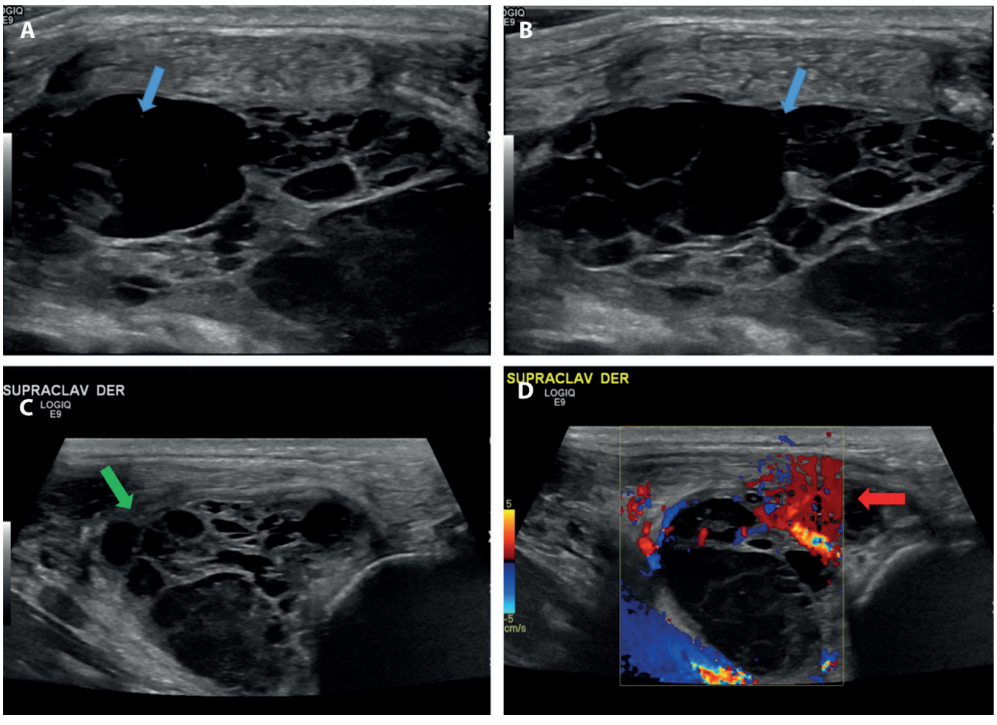

Figure 5. Soft-tissue ultrasound of the right supraclavicular region. A, B, C, D. (Blue arrow) Behind the right sternocleidomastoid muscle is a 5.8 x 2.8 cm multi-cystic lesion with multiple septations, filled with anechoic and heteroechoic content and (Red arrow) some vascular structures crossing it. Two other lateral smaller cysts, less than 9 mm in size, accompany the lesion. (Green arrow**)** There is another cystic lesion in the suprasternal region of 2.8 x 1cm.

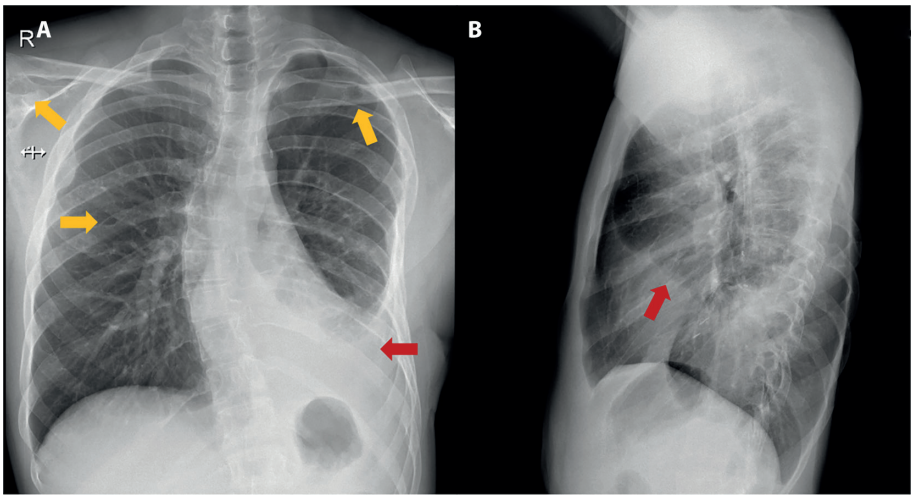

Figure 6. Chest X-ray. A. Posteroanterior projection. B. Lateral projection. Image corresponding to the latest medical check-up showing moderate residual free pleural effusion in the left lung field (red arrow), with fewer lytic lesions observed compared to the onset of the disease (yellow arrow).

osteolytic bone changes [8,13], and osteoporotic findings are common due to increased bone resorption [4]. A bone biopsy with replacement of normal bone with fibrous tissue and non-neoplastic proliferation of capillary or cavernous blood vessels usually confirms the diagnosis.

The natural history of the disease is unpredictable and can be progressive, leading to serious complications, such as pericardial effusion, pleural effusion, and chylothorax when the thoracic bones are involved [14], although there have been rare cases of spontaneous resolution [15]. The patient in this case had recurrent chylothorax due to thoracic bone involvement and persistent pleural effusion, which are further manifestations of GSD. This underscores the importance of heightened awareness of this rare disease entity, particularly when encountering patients with unexplained bone lesions and lymphatic complications after exhausting other diagnostic options.

There is no standard therapy available for the disease, and different therapeutic options have been proposed, including medications, radiation, and surgery, either alone or in combination [16]. Reported therapeutic options include interferon, bisphosphonates, bevacizumab, and mTOR inhibitors, such as sirolimus, which has been described as a promising treatment option for GSD and other complex lymphatic anomalies. A clinical trial using oral sirolimus showed improved disease in 83% of cases, with symptomatic or functional improvement in most patients [6]. Adverse effects related to sirolimus are less than 21%, with oral mucositis having the highest incidence [17,18].

Conclusion

GSD should be considered in young adults with new lymphangiomas in the neck or other areas and associated focal or multifocal osteolysis who are negative for inflammatory, infectious, metabolic, and neoplastic conditions. The complexity of diagnosing Gorham-Stout disease should be emphasized. Currently, sirolimus has been shown to stabilize or reduce signs and symptoms of GSD and other complex lymphatic anomalies.

Abbreviations

GSD: Gorham-Stout disease
mTOR: Mammalian target of rapamycin
CXR: Chest X-ray
IV: Intravenous
CT: Computed tomography
ICU: Intensive care unit
MRI: Magnetic resonance imaging

References

1. Lu D, Wang Y, Zeng W, Peng B. Giant fetal lymphangioma at chest wall and prognosis: case report and literature review. Taiwan J Obstet Gynecol 2015;54(1):62-5.
2. Miceli A, Stewart KM. Lymphangioma. En: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [citado 6 de diciembre de 2022]. Disponible en: http://www.ncbi.nlm.nih.gov/books/NBK470333/
3. Boyle MJ, Alison P, Taylor G, Lightbourne BA. A case of Gorham's disease complicated by bilateral chylothorax. Heart Lung Circ 2008;17(1):64-6.
4. Dellinger MT, Garg N, Olsen BR. Viewpoints on vessels and vanishing bones in Gorham-Stout disease. Bone 2014;63:47-52.
5. Tateda S, Aizawa T, Hashimoto K, Kanno H, Ohtsu S, Itoi E, et al. Successful Management of Gorham-Stout Disease in the Cervical Spine by Combined Conservative and Surgical Treatments: A Case Report. Tohoku J Exp Med 2017;241(4):249-54.
6. Ricci KW, Hammill AM, Mobberley-Schuman P, Nelson SC, Blatt J, Bender JLG, et al. Efficacy of systemic sirolimus in the treatment of generalized lymphatic anomaly and Gorham-Stout disease. Pediatr Blood Cancer 2019;66(5):e27614.
7. Watanabe T, Yazama H, Kunimoto Y, Koyama S, Fujiwara K. A case of gorham-stout disease treated with fistula closure by transmeatal approach. Yonago Acta Med 2021;64(3):318-23.
8. Hou G, Jiang Y, Jing H, Xu W, Xu KF, Chen L, et al. Usefulness of 99mTc-ASC lymphoscintigraphy and SPECT/CT in the evaluation of rare lymphatic disorders: Gorham-Stout disease, lymphangioma, and lymphangioleiomyomatosis. Medicine (Baltimore) 2020;99(39):e22414.
9. Patel DV. Gorham's disease or massive osteolysis. Clin Med Res 2005;3(2):65-74.
10. Wang J, Yang Y, Guo J, Yao Y, Dong L, Mou Y, et al. Cervical lymphangioma in adults: A report of seven cases and review of the literature. Laryngoscope Investig Otolaryngol 2022;7(3):751-6.
11. Ranzenberger LR, Pai RB. Lymphoscintigraphy. En: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [citado 19 de diciembre de 2022]. Disponible en: http://www.ncbi.nlm.nih.gov/books/NBK563213/
12. Bosco F, Giustra F, Faccenda C, Boffano M, Ratto N, Piana R. Gorham-Stout disease: A rare bone disorder. J Orthop Rep 2022;1.
13. Nikolaou VS, Chytas D, Korres D, Efstathopoulos N. Vanishing bone disease (Gorham-Stout syndrome): A review of a rare entity. World J Orthop 2014;5(5):694-8.
14. Lala S, Mulliken JB, Alomari AI, Fishman SJ, Kozakewich HP, Chaudry G. Gorham-Stout disease and generalized lymphatic anomaly--clinical, radiologic, and histologic differentiation. Skeletal Radiol 2013;42(7):917-24.
15. Liu M, Liu W, Qiao C, Han B. Mandibular Gorham–Stout disease: A case report and literature review. Medicine (Baltimore) 2017;96(42):e8184.
16. Gorham-Stout syndrome in mainland China: a case series of 67 patients and review of the literature | SpringerLink [Internet]. [citado 31 de enero de 2023]. Disponible en: https://link.springer.com/article/10.1631/jzus.B1200308
17. Wiegand S, Dietz A, Wichmann G. Efficacy of sirolimus in children with lymphatic malformations of the head and neck. Eur Arch Otorhinolaryngol. 2022;279(8):3801-10.
18. Zhang Z, Li Y, Zhang G, Yang K, Qiu T, Zhou J, et al. Safety Evaluation of Oral Sirolimus in the Treatment of Childhood Diseases: A Systematic Review. Child Basel Switz 2022;9(9):1295.

Received for publication: 29 January 2024 - Accepted for publication: 2 May 2024

Licensee Mattioli 1885, Italy
Multidisciplinary Respiratory Medicine 2024; 19: 957
doi: 10.5826/mrm.2024.957