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Gorham–Stout disease with life-threatening pleural effusion treated with a pleuro-peritoneal shunt: a case report

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Summary

Gorham–Stout disease (GSD) is a rare bone disease characterized by massive osteolysis and lymphatic proliferation. The origin of the condition is unknown, and no established treatment protocol exists. Massive pleural effusion is a frequent complication of GSD in the thoracic region. We present the case of a 23-year-old male with thoracic GSD, subsequent paraparesis, and life-threatening pleural effusion. The patient was managed by a multidisciplinary team with a good recovery. The pleural effusion was successfully treated with a pleuro-peritoneal shunt. This is the first report of the use of this mini-invasive technique in the management of pleural effusion related to GSD. Further, we present the potential role of interleukin-6 and bone resorption markers in the measurement of the disease activity.

Learning points:

- Multidisciplinary approach is important in the management of rare and severe disorders such as Gorham-Stout disease.
- Pleuro-peritoneal shunting is a valuable option in the treatment of pleural effusion related to GSD.
- Interleukin-6 and bone resorption markers appear useful in measuring the disease activity of GSD.

Background

Gorham–Stout disease (GSD), or Gorham's syndrome, is an extremely rare condition of massive osteolysis with associated lymphatic, vascular, and fibrous hyperproliferation, defined by Gorham and Stout in 1955 (1, 2, 3). The origin of the disease remains undiscovered. The excessive osteolysis seems to be derived from the augmented osteoclast activity mediated by inflammatory cytokines, such as interleukin-6 (IL-6), and tumor necrosis factor-alpha (4). Dysregulation of the lymphangiogenic pathway in the pathogenesis remains under investigation (5).

The active phase of GSD may present with local pain, swelling, and progressive deformity, but a pathologic fracture may be the first manifestation of the disease (3). The diagnosis of GSD is made on the basis of suggestive clinical and histological findings, and by the exclusion of other potential causes (6). The clinical course varies from a spontaneous resolution to severe complications and death. Osteolytic lesions may lead to pathological fractures, and especially in the spine, even to devastating complications, such as paraplegia. Thoracic involvement of GSD is frequently linked to pleural effusion and chylothorax, which have a poor prognosis (7).

The relevant literature consists of merely case reports and small patient series. Hence, established treatment protocols do not exist. Several medications aiming to control the inflammatory cytokines and bone resorption,

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such as bisphosphonates and interferon-α, as well as radiation therapy to cease the disease process, have been reported (4, 5, 6, 8, 9).

Here, we present a case report of a young man with GSD located in the thoracic spine and thoracic wall. This is the first report of pleural effusion associated with GSD that was successfully treated with a pleuro-peritoneal shunt.

Case report

A 23-year-old Caucasian male was presented to our institution with progressive back pain and lower limb weakness. Already 5 years earlier, an abnormality was noticed in the left third and fourth ribs (Fig. 1), but no further investigations were conducted. The back pain had lasted for several months, while a mild walking difficulty developed in 2 months resulting in the loss of walking ability 2 days prior to the admission. He presented with clonal patellar and Achilles reflexes, positive Babinsky sign, and anesthesia below the mamillary level. However, the strength of the lower limbs in the supine position was good. MRI showed abnormal osseous structure in the T4–T5 region with local kyphoscoliosis and medullary compression. CT revealed osteolytic lesions and anomalous vertebral structure in T4–T5 and the posterior absence of ribs 4–5 on the left side (Fig. 2).

The patient underwent an urgent surgery in which transpedicular screws were inserted into T2–T8 vertebrae, and medullary compression was relieved by correcting the local deformity and performing laminectomies T4–T5. A bone graft was harvested from the posterior iliac crest (Fig. 3). In the affected area, the anatomy and structure of the bone were abnormal. The laminar bone resembled cartilaginous tissue, and hypertrophic venous plexus surrounded the medulla.

Postoperative histologic analysis of the bone showed osteolysis with hemorrhage and rich vascular proliferation, with no osteoblasts nor malignancy, suggestive of GSD. Bone scintigraphy revealed increased activity in the sternum, ribs, thoracic spine, and iliac bones. A wide range of malignant and inflammatory diseases was excluded with imaging and laboratory tests. Bone resorption measured with urinary excretion of type I collagen cross-linked aminoterminal telopeptide (NTx) was clearly increased while bone formation markers, such as procollagen type 1 N-terminal propeptide (P1NP) and osteocalcin, were

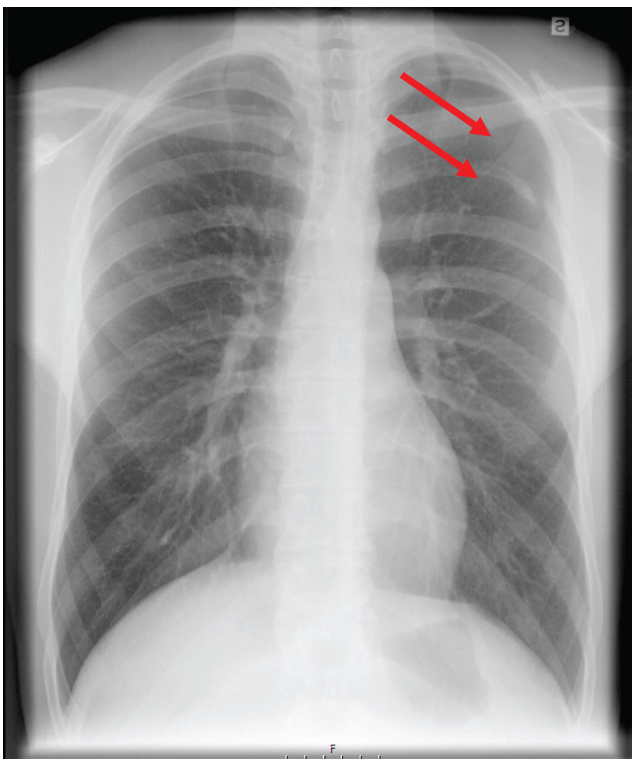

Figure 1
Mild abnormality was noticed in the left third and fourth ribs 5 years prior to the onset of the spinal problem.

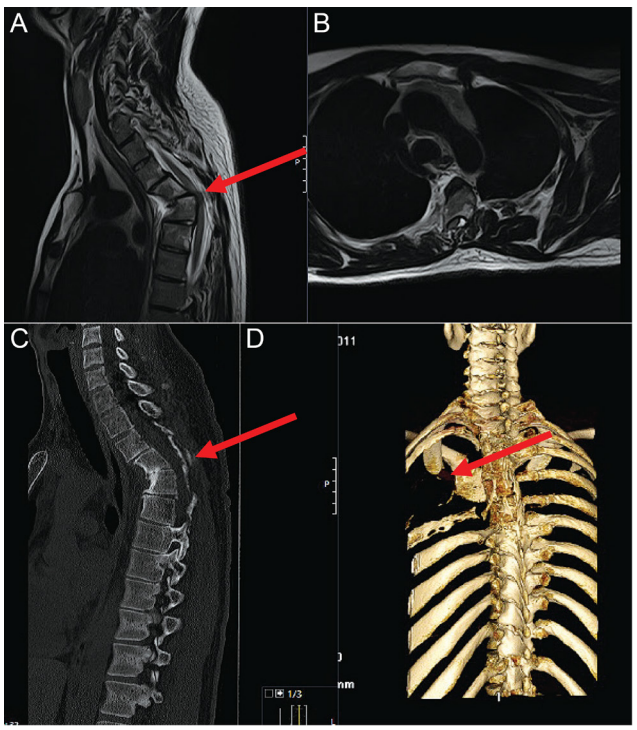

Figure 2
MRI, above, and CT, below, of the thoracic spine before the spine surgery. Local kyphoscoliosis and a subsequent compression of medulla was seen on T4–5 level. Posterior osseous structures were anomalous, and left ribs 3–5 were missing.

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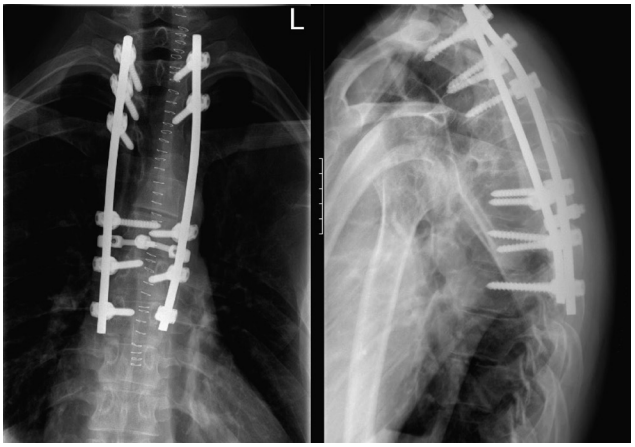

Figure 3
Postoperative thoracic spine radiographs showing the fusion of T2–T8.

normal, as shown in Table 1. Inflammatory cytokine,IL-6 was clearly increased.

Postoperatively, the patient gradually recovered from the paraparesis. However, after 1 month, he developed dyspnea and bilateral pleural effusion, as shown in Fig. 4A. Repetitive pleural aspirations were performed. The effusion was rich in proteins, but it contained no triglyserides – thus, it was not chylous. Zoledronic acid was given intravenously (5 mg per month for seven times) to cease the disease process in bone. Interferon-α 2b (1 µg/kg/week) was given to diminish the pleural lymphangiogenesis and effusion. In addition, the patient was administered calcium and vitamin D supplementations.

Three months after the spine surgery, radiation therapy of 45 Gy in fractions of 1.8 Gy was administered to the affected thoracic wall and spinal region. At the beginning, interferon-α was discontinued because of its possible cytotoxic effect with radiation therapy. That provoked the pleural effusion and weight loss, and administration of interferon-α was continued with a reduced dose (0.6 µg/kg per week).

Despite the gradual neurologic recovery, the overall condition of the patient weakened due to the ongoing pleural effusion and loss of muscle mass and weight. Six months after the spine surgery, the patient was seriously underweighted with a BMI of 16.4 kg/m^2, and parenteral nutrition was started. Pleural emptying and pleurodesis were pursued by drainage. Nevertheless, the drain production remained excessive, over 1000 mL per day (Fig. 4B). After 2 weeks of parenteral nutrition, the patient was scheduled to thoracoscopy. In a mini-invasive procedure, a single valve, 15.5 French pleuro-peritoneal shunt (Denver; Beckton, Dickinson and Company, Franklin Lakes, NJ, USA) was applied to the left side. The shunt was designed to transfer liquid from the pleural space to the peritoneal cavity with ventilation movements and coughing, as well as by manual activation of the pump mechanism located near costal arch. The goal was to retain the proteins by a reabsorption of them from the peritoneal cavity.

After the application of the shunt, the patient started to recover. Gradually, he regained weight and normal muscle mass. No accumulation of ascites was observed on ultrasonography. Zoledronic acid and nutritional supplements were discontinued three months after the thoracic surgery when BMI (17.6 kg/m^2) was still low but increasing, and the IL-6 level was normal (Table 1).

Table 1 Laboratory test results at different time points.

Laboratory test	Reference range	A	B	C	D	E	F
Time (months) from the spine surgery		0	1	2	3	5	8
Hemoglobin	134–167 g/L	**103**	148	157	139	**128**	139
Leukocytes	3.4–8.2 10E9/L	**10.1**	4.5	4.1	**3.0**	**3.0**	3.9
Lymphocytes	1.2–3.5 10E9/L		**0.49**	1.51	**0.12**	**1.08**	1.20
Trombocytes	150–360 10E9/L	166	**365**	**356**	282	220	198
C-reactive protein	0–10 mg/L		5.4	2.5	7.4	1.2	<1
Creatinine	60–100 umol/L	86	84	90	64	**53**	89
P-Albumin	36–48 g/L		36		**33**	**24**	39
Alanine aminotransferase	10–70 U/L		**114**	**93**	**76**	55	33
Alkaline phosphatase	35–105 U/L		**157**	**164**	**312**	**169**	77
fP-Phosphate	0.71–1.53 mmol/L		1.39	1.09	1.20		1.38
S-Calcium ionized	1.20–1.35 mmol/L		1.28	1.23	1.24	1.23	1.31
P-IL-6	0–5.9 ng/L			**11.0**	**98.0**	**9.7**	2.5
S-Osteocalcin	24–70 ng/L		29	26			
S-PINP	20–76 ug/L		79	62	50	36	
U-NT-x	0–63 (ratio)		**110**	18	19	19	23

A, immediately after the spine surgery, B, at the beginning of pleural effusion and medication, C, at 1 month of medication, D, at the beginning of radiotherapy, E, before the thoracic surgery, and F, after recovery. Values outside the reference range are bolded.

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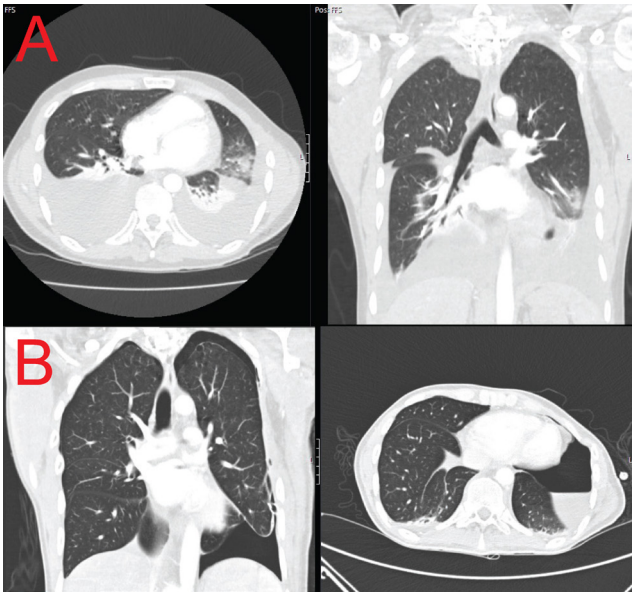

Figure 4
Pleural effusion in the CT of thorax, (A) at 1 month after the spine surgery, and (B) before the thoracic surgery.

At 6 months after the thoracic surgery, BMI was normalized (20.8 kg/m^2) and the disease process was regarded as silent. Interferon-α was discontinued. During the recovery phase, the patient developed primary hypothyroidism due to interferon-α treatment requiring thyroxin substitution. Three years after the spine surgery, the patient underwent a spinal revision surgery for breakage of the rods, from which he also fully recovered.

During the 9-year follow-up after the recovery, the disease has remained in remission. The grip force of the left hand, as well as pectoral and latissimus dorsi muscles on the left side, remained weaker than on the contralateral side. Otherwise, the patient had fully recovered from paraparesis and life-treating thoracic effusion, and he had returned to normal daily activities and working life.

Discussion

As no established treatment protocols for GSD exist, a multidisciplinary approach proved useful in the management of this rare and life-threatening condition. Orthopedic surgeons managed the paraparesis and initially suspected the GSD, an endocrinologist confirmed the diagnosis with a pathologist, and coordinated the multidisciplinary cooperation in the management of the disease with a rheumatologist and an oncologist, and a thoracic surgeon saved the life of the patient by treating the prolonged pleural effusion.

No specific laboratory markers for GSD have been reported, yet. In our patient, only minor abnormalities were seen in common blood tests. C-reactive protein remained in the reference range. IL-6 was elevated during the active disease, showing potential in monitoring the disease activity. We also reported increased bone resorption markers (NTx) without a respective increase in bone formation markers (normal P1NP and osteocalcin) suggesting a dissociation of coupling of bone resorption and formation during the active disease. The slight increase in liver enzymes could be linked to disease activity since we found no liver pathology in CT or ultrasonography. Namely, a case of Gorham-Stout disease with liver angiomatosis has also been described in the literature (10).

Medical treatment commonly reported consists of anti-resorptive drugs (bisphosphonates), chemotherapy, radiation therapy, and drugs targeting hemangiogenesis (8, 9, 11). Spinal complications are managed according to the established principles of spine surgery, as no disease-specific guidelines exist. Spinal instability may require stabilization, and symptomatic neural compression usually requires decompression. Rare cases may warrant even more aggressive management, including total spondylectomies (12).

Chylothorax is a frequent complication of GSD in the thoracic region with a reported mortality rate of 52% (4). Although the pleural effusion in our patient did not include triglycerides – hence, it was non-chylous – the massive protein-rich pleural effusion alone was a life-threatening condition. In such a case, repetitive pleural aspirations lead to hypoalbuminemia, edema, and reduced healing capacity of tissues, while loss of immunoglobulins and lymphocytes increases the risk of sepsis. In 1994, Tie *et al*. advocated an aggressive treatment of GSD with chylothorax, including total parenteral nutrition and bowel rest, thoracic duct ligation, and/or pleurodesis (7).

Pleuro-peritoneal shunt has been used in the management of persistent pleural effusions, especially with advanced malignancies (13). It is a possible option when surgical pleurectomy and talc pleurodesis proves impossible due to a limited expansion capability of the lung, or the patient is too weak for more extensive surgery. Mini-invasive surgery is a valuable option for cachectic patients with an increased risk for infections. We found no previous report of pleuro-peritoneal shunting in patients with GSD and chylothorax. We regard this method worth considering in the management of this life-threatening complication of GSD.

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Conclusion

This is the first report of pleuro-peritoneal shunting in the management of pleural effusion associated with GSD. We consider this a valuable option in the treatment of this serious condition. Further, IL-6 and bone resorption markers appear useful in measuring the disease activity. We consider a multidisciplinary approach crucial in the management of rare and serious diseases, such as GSD.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
The patient gave a written informed consent for publication of this report.

Author contribution statement
L T wrote the manuscript. M N, T S, P I, and S M participated in the writing and were responsible for the patient care.

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