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Gorham-Stout Disease(GSD): A Rare Disease with A Differential Diagnostic Dilemma

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Abstract

Gorham-Stout disease (GSD) or "Vanishing/Phantom bone disease" is an extremely rare and poorly understood disorder which consist of intraosseous abnormal lymphatic and blood vessels proliferation, which results in progressive bone resorption/osteolysis. The disease has been described as early as in 1838, but until now the aetiology of GSD is not well understood with no concrete evidence of genetic or environmental factors. It also has no obvious race or age predilection. The management is difficult with no established curative treatment and mainly focused on symptomatic and palliative care.

Keywords
Gorham-Stout disease (GSD), Vanishing/Phantom bone disease, lytic bone lesion, Diffuse Pulmonary Lymphangiomatosis (DPL), Langerhans cell histiocytosis (LCH).

Introduction

GSD is characterized by progressive massive osteolysis affecting one or more bones and overgrowth proliferation of lymphatics and blood vessels. Other conditions that can present similarly include Langerhans cell histiocytosis (LCH) and Diffuse Pulmonary Lymphangiomatosis (DPL). LCH is an inflammatory myeloid neoplasia due to genetic alteration. It causes excess of Langerhans cells and accumulates in certain areas of the body. DPL is another rare disease where the proliferation of lymphatic vessels occurs in the lungs and the mediastinum. All these diseases shared a common pathology, namely excessive proliferation of lymphatic vessels, thus posing diagnostic challenges due to overlapping clinical, radiological, and histopathological features and the rarity of these conditions. We report a case of a young

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adolescent with persistent chylothorax and generalized lytic bone lesions with cortical destruction, a diagnostic dilemma before arriving at an accurate diagnosis.

Case Report

A 16-year old Malay boy with no significant past medical illness, was referred for massive right pleural effusion. He presented to the local healthcare clinic with history of progressive shortness of breath (SOB) of one-week duration, associated with chronic chesty cough for 15 months. There was no history of fever, loss of appetite, loss of weight, bleeding tendencies, bone pain, or rash. There was no exposure to tuberculosis-infected patient and he is non-smoker, has no high-risk behaviour and has completed Covid-19 vaccination. He was afebrile with evidence of respiratory distress upon ward admission. His oxygen saturation under room air was ranging 80-85% which improved with facemask 10L/min oxygen supplement. He was slightly tachycardic with heart rate of 101/min with normal blood pressure of 108/71mmHg. Lung examination revealed massive right sided pleural effusion, evidenced by markedly reduced breath sound and stony dullness to percussion with mediastinal shift to contralateral side. There was also non-tender palpable firm right supraclavicular swelling which measures approximately 3.0 x 4.0cm (AP x W).

The patient was subjected to various investigations. The blood investigation revealed a mildly raised white blood cell count of 12.55 x 10^9/L with neutrophil predominance along with normal haemoglobin and platelet level. Peripheral blood film analysis showed normocytic normochromic haemoglobin with neutrophilia and no abnormal mononuclear cells. Electrocardiogram (ECG) was normal. Chest radiograph on arrival reveals massive right hydropneumothorax, confirmed via a contrast-enhanced computed tomography (CECT) thorax. CECT revealed a massive right-sided pleural effusion and pneumomediastinum. There was multiple enlarged lymph nodes and lymphatic mass at the neck and mediastinum. Multiple hypodense splenic lesions were also noted. A skeletal survey revealed extensive multiple lytic bone lesions with cortical destruction involving the cranium vault, long bones, ribs, pelvis and spine. An echocardiogram showed good cardiac contractility with no regional wall abnormality or pericardial effusion.

A right chest tube drained a massive amount of pleural fluid, initially milky orange in colour (as mixed with blood) but subsequently milky in colour . The pleural fluid is confirmed to be chylothorax with high Triglyceride (661mg/dl) and low cholesterol (54mg/dl) and Cholesterol to Triglyseride ratio was < 1 (unfortunately, pleural fluid lymphocytes percentages was not examined). Pleural fluid biochemistry showed exudative fluid with high protein and cytology examination showed atypical mononuclear cells with histiocytes and scattered eosinophils. Blood and pleural fluid culture showed no growth.

The chylothorax was persistent despite continuous drainage, therefore he underwent pleuroscopy examination which revealed septate pleural effusion, haemorrhagic pleural fluid, thickened pleura, irregular mucosa and whitish patches. Histopathology examination (HPE) of the pleural biopsy showed no atypical cells, granulomatous inflammation or malignant cells. Immunohistochemistry of the pleural biopsy, including CD1a, S100, and Ziehl Nielsen stain, yielded negative results. The patient then underwent a right mini-thoracotomy, pleural, chest wall and rib biopsy by cardiothoracic team as multiple lytic rib lesions were noted during examination. Despite 1.8 L of pleural drainage, only the right upper and middle lobes were expanded to about 70% and the right lower lobe remained chronically trapped. Initial impression was loculated effusion with thickened parietal pleural, suggestive of grade lll empyema (before biochemistry result which was consistent with chylothorax was known). Rib bone histopathological examination (HPE) showed thick fibroadipose tissue fragments lined by granulation tissue and fibrinoid material. Diffuse proliferation of complex, irregular, and dilated lymphatic channels lined by a single layer

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of flat endothelial cells. Lymphatic channels are seen dissecting through adjacent adipose tissue. Immunochemistry staining showed that the proliferating endothelial cells are positive for D2-40 and CD31. Initially, the patient was thought to have LCH or DPL, however after multidisciplinary discussion involving various subspecialists, a diagnosis of Gorham Stout Disease (GSD) was made based on clinical presentation, radiological and HPE findings. As there is no consensus about the treatment of this extremely rare disease, our multidisciplinary team discussion decided to start on Sirolimus (0.8mg/m^2 twice daily while keeping the concentration in the blood between 5-15ng/ml). Sirolimus, an immunosuppressant agent that inhibits mTOR, acts by having anti-angiogenic and anti-tumour effects. Intravenous bisphosphonates (Zometa 4mg once every 3weeks) was also commenced. Bisphosphonates reduce the quantity of osteoclasts precursor cells as well as reducing osteoclastic activity. For management of refractory chylothorax, the patient was initially keep nil orally (NBM), supported by total parenteral infusion (TPN), intravenous infusion Octreotide 50mcg/hour (a long acting somatostatin analogue that acts on the vascular somatostatin receptors which assists in reducing chyle excretion), immunoglobulin replacement therapy (as ongoing loss via chylothorax) and the patient was dependent on Bilevel Positive Airway Pressure (BiPAP) using oronasal mask. The patient subsequently underwent decortication and pleurodesis of the right lung which resulted in full right lung expansion. We subsequently were able to off the right chest tube and BiPAP support. We gradually off his TPN, octreotide and immunoglobulins and introduce special high protein and medium chain triglyceride (MCT) diet/milk formula as he still has residual mild right chylothorax. He has mild residual tachypnoea (respiratory rate of 24/min) but able to maintain SpO2 of > 95% in room air and his weight has increased favourably on discharge.

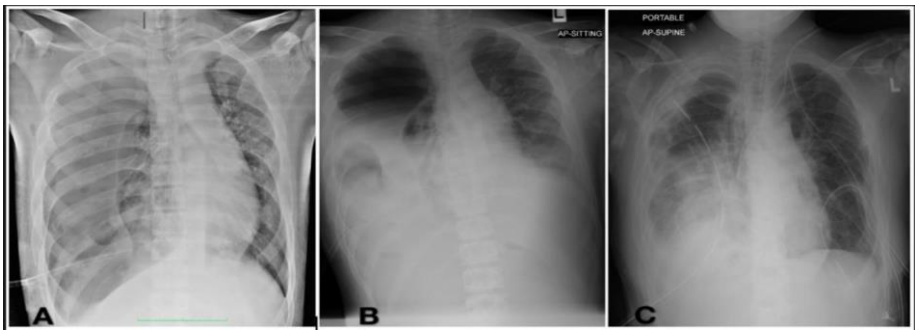

Figure1: Chest x-ray of the patient
A - Right chest tube inserted with the radiograph showing hydropneumothorax causing mediastinal shift to the left.
B - Right chest tube in-situ with bilateral pleural effusion.
C - Right chest tube with left pigtail in-situ. Right pleural effusion still persist with residual left pleural effusion.

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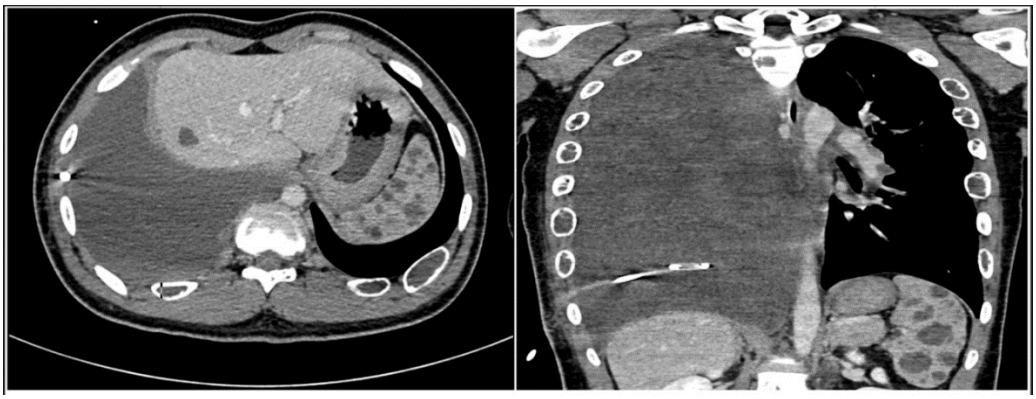

Figure2: Massive right pleural effusion with chest tube in-situ. Multiple hypodense splenic lesions with segment Vlll hypodense liver lesion.

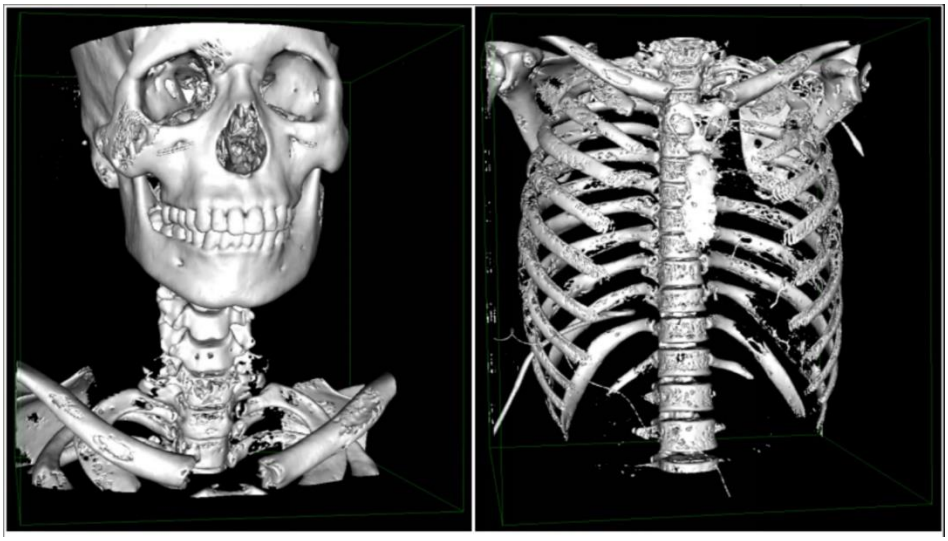

Figure3: 3D reconstruction images from CECT shows similar multiple bone lesions.

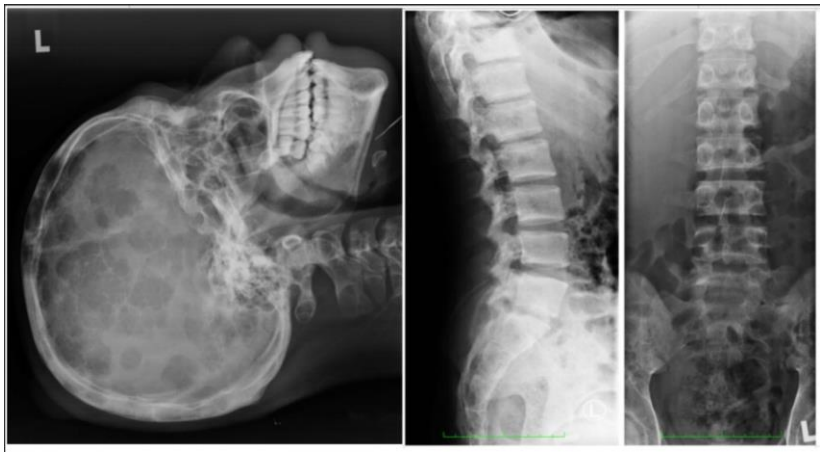

Figure4: Skeletal survey radiograph shows multiple lytic bone lesions.

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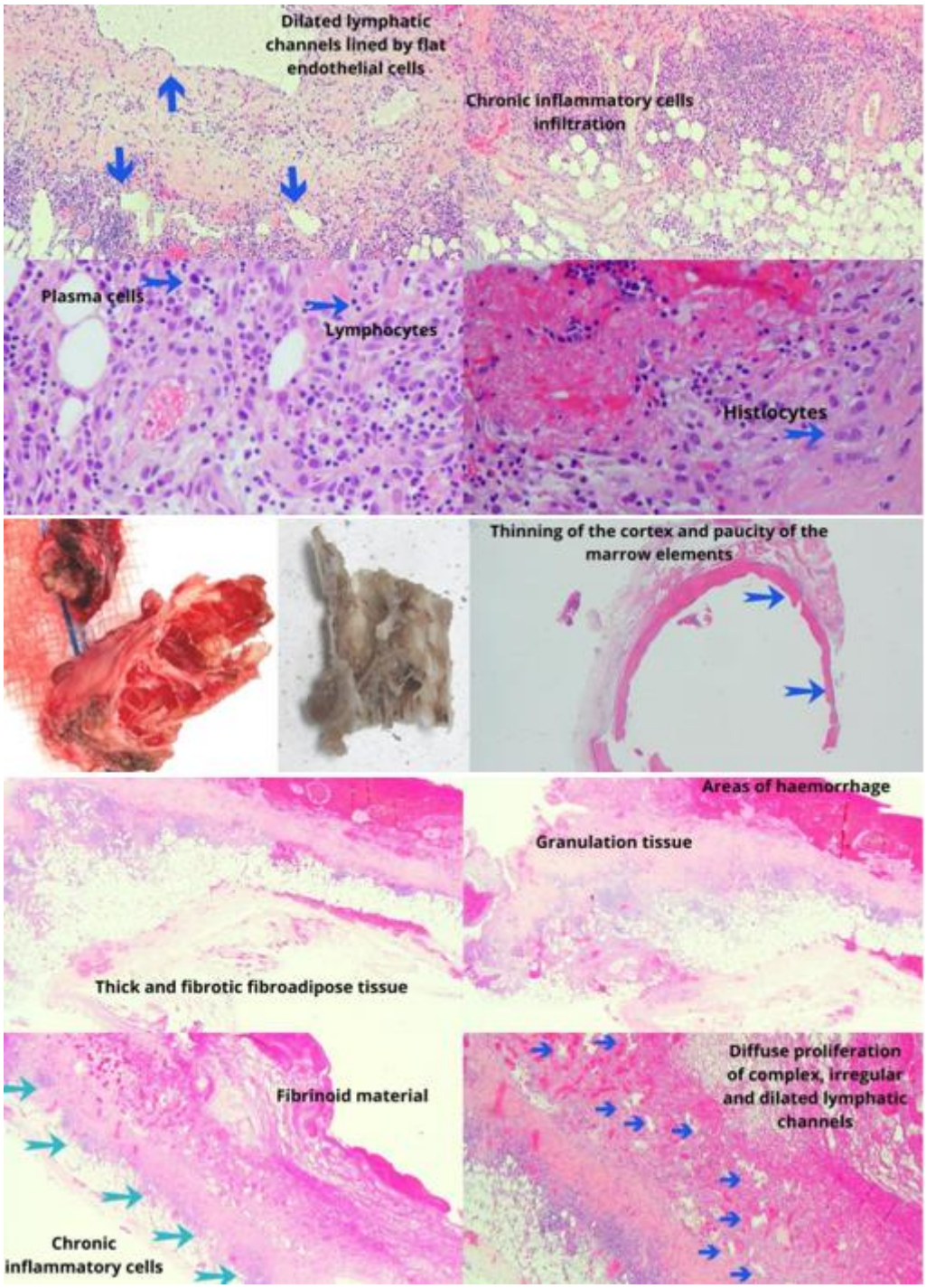

Figure 5: HPE of the bone and chest wall.

Discussion

This case highlights a diagnostic dilemma as Gorham-Stout Disease (GSD) is an extremely rare condition and has overlapping features with other Lymphatic Malformations (LM), especially Intractable LMs known as Complex Lymphatics Anomalies (CLA). The main differentiating features of cortical bone resorption accompanying extensive osteolytic bone lesions and adjacent soft tissue destruction, distinguish GSD and

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other General Lymphatics Anomalies (GLD), including CLA and DPL (Diffuse Pulmonary Lymphangiomatosis), as illustrated in this patient.

Diffuse pulmonary lymphangiomatosis (DPL) is a another rare disease characterized by infiltration of the lung, pleura and mediastinum with thin-walled lymphangiomas. DPL can presented as mass effect from infiltrative disease, restrictive and obstructive pulmonary physiology, chylous effusions and respiratory failure (1). It is commonly seen in children and young adults with no gender preponderance. However, there are no CT findings of pleural thickening, ground glass opacities, peribronchovascular thickening or increased interlobular septal thickening which are usually present in DPL (1,2).

Another differential diagnosis considered initially with multiple punch-out lytic bone lesions, pleural effusion, splenomegaly and lymphadenopathy is systemic Langerhans Cell Histiocytosis (LCH). Nonetheless, the skeletal manifestation of LCH is mostly asymptomatic. Bones manifestations may be solitary or multiple punched-out lytic lesions. Pulmonary LCH (PLCH) is commonly seen in older age group between 20 to 40 years old who are typically smokers and presented with shortness of breath and cough. Imaging of the chest with high resolution chest CT scanning may show characteristic nodular and cystic abnormalities, which are absent in this patient (3). Lung biopsy is diagnostic with the pathologic hallmark of PLCH is the accumulation of Langerhans and other inflammatory cells in small airways, resulting in the formation of nodular inflammatory lesion (3).

The underlying mechanisms of osteolysis in GSD remain unclear. It is postulated that activation of osteoclasts and lymphangiogenesis is essential in the development of GSD. The disease is first described by Dr Jackson in 1838 in a 12-year-old boy who presented with idiopathic osteolysis of the humerus. In 1955, Dr Gorham and Dr Stout published a paper correlating massive type IV osteolysis (osteolysis with hemangiomatosis without nephropathy). Destruction and absorption of bone are the result of osseous matrix destruction and vascular structure proliferation. The bone lesion is frequently seen in the long bones, shoulder and pelvis though it can affect any bones in the body(4). The few radiological findings that can be seen are the slow bone destruction, minimal bone repair and absence of periosteal reaction(5). Dr Resnick described radiographic findings with initial stages of radiolucent foci. These foci resemble patchy osteoporosis and occur in the subcortical or intramedullary regions. This is followed by progressive fragmentation and, finally, dissolution of the bone(6).

The diagnosis of GSD is extremely difficult, particularly in the early stage of the disease. The diagnosis is often based on clinical manifestation, age, radiological findings and confirmed with bone biopsy. In our patient, the chylothorax is probably due to lymphangiectasia extension into the pleural cavity or thoracic duct invasion (7). The presence of multiple osteolytic bone lesions with cortical bone resorption, chylothorax and splenic lesions and histological findings of abnormal proliferation of lymphatic systems is diagnostic of GSD. This patient also has positive special immunostains Anti CD31 and Anti D2-40 on bone biopsy, which is also diagnostic for GSD(7,8).

Kotecha et al. (2012) promote using quantitative computed tomography (QCT) bone densitometry to enable quantification of cancellous and cortical bone mineral densities, which may help to decide treatment initiation and monitor disease response to treatment (9) (10). It was not done in or patient due to unavailability of the service. A Thallium scan scintigraphy is excellent for differentiating GSD (benign bone lesions) from malignant bone lesions as the latter has increased Thallium intake. In patient with GSD who were subjected for 3-phase bone scan scintigraphy showed a decreased activity in the arterial phase (due to the absent normal remodelling of osteoclasts and osteoblast), a slight activity increment (in the

blood pool phase) and significant activity increment in the delayed phase (due to the chronic nature of the disease)(10).

Currently, there is no established treatment for GSD. The treatment options include pharmacological treatments (Interferon, Sirolimus, Bisphosphonates, Calcium, and Vitamin D), supportive treatments for chylothorax and surgical treatments. Several studies showed Sirolimus stabilizes and reduces signs and symptoms of GSD and improve quality of life of those affected. In one of the case series, overall positive response rate with Sirolimus was 83.3% (20/24 cases)(11). In this patient, Sirolimus prevent further progression of chronic right chylothorax and enable to remove dependency to oxygen and BIPAP, hence facilitate discharge. Whether it can halt progression of osteolytic remains to be seen. Surgical options include resection of bony lesion, reconstruction by the use of bone grafts or prostheses and ligation of lymphatic system (11,12), which currently are not indicated in this patient.

Conclusion

GSD should be considered in any patients who presented with multiple osteolytic bone lesions, chylothorax, soft tissue involvement and splenic lesions. High index of suspicion, coupled with CT imaging of the bone and other organs involved and histopathological examination of bone biopsy facilitates early diagnosis and thus may improves outcome with early treatment.

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