Case Report

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Double whammy: A rare disorder complicating a common infection – A case report and review of literature

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Abstract:

Gorham-stout disease (gsd), is a rare disorder of unknown etiology. although a non-malignant, non-infectious condition, gsd results in massive destruction of bones by osteolysis secondary to proliferation of blood vessels. we present a young man afflicted with this condition with coexisting tuberculous pleural effusion and the successful outcome with treatment.

Keywords:

Gorham's disease, interferon-alpha, tuberculosis

Introduction

Vanishing bone disease or Gorham–Stout disease (GSD) is a rare disorder of unknown etiology. Although a nonmalignant, noninfectious condition, GSD results in massive destruction of bones by osteolysis secondary to proliferation of blood vessels.[1] We present a young man afflicted with this condition and the successful outcome with treatment.

Case Report

A 25-year-old male presented with fever, right-sided dull-aching chest pain, radiating to the ulnar aspect of the right hand, breathlessness of 7-month duration, and weight loss. He had been on antituberculosis medicines for the past 6 months based on pleural fluid analysis from elsewhere.

He denied any history of trauma, and family history was not contributory. Physical examination showed a temperature of 37.5°C, pulse rate of 90 beats/min, blood pressure of 110/80 mmHg, and respiratory rate of 20 breaths/min. Respiratory system examination revealed right hemithoracic volume loss and moderate right-sided pleural effusion. There were no neurological deficits.

Pleural fluid aspiration revealed a straw-colored lymphocytic exudate, with low Adenosine Deaminase (ADA) of 12.5 U/L. There was no evidence of chylothorax, with pleural fluid triglycerides being 63 mg/dl.

As the patient had not responded to antituberculosis medicines, further evaluation was undertaken. Computed tomography (CT) of the thorax showed moderate pleural effusion, complete

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resorption of the 1st and 2nd ribs, and demineralization of the 3rd and 4th ribs in the right hemithorax [Figures 1 and 2]. The 6th and 7th cervical vertebrae also showed osteolytic lesions [Figure 3]. His hemogram was within the normal range; the secondary causes of osteolysis such as renal osteodystrophy and malignancy were ruled out by analyzing serum creatinine, calcium, phosphorus, and serum alkaline phosphatase levels which were within the normal range.

Biopsy of the involved rib and the pleura showed normal hematopoietic cells and focal increase in vascularity. Immunohistochemical staining of the pleural biopsy specimen showed many blood vessels highlighted by CD31 and CD34 stains.

In view of the extensive osteolysis and the benign biopsy report, a diagnosis of GSD was made. The constant usage of Philadelphia neck collar was ensured, as surgical option with spine fixation was not considered a favorable option by the surgeon. Radiation to the affected site was also considered hazardous in view of expected complication of vertebral collapse. However, the issues of an unstable spine and continuing drain from the intercostal tube (500–600 ml/day) persisted. Thus, after an extensive review of the existent literature for alternative therapeutic options, it was decided to initiate alpha-2b-interferon therapy. The fluid outflow reduced 2 weeks after initiation of interferon-alpha at a dose of 50 mcg subcutaneously. Chemical pleurodesis was done at the end of 2 weeks, once the fluid drain reduced to 50 ml/day. Other symptoms resolved gradually on treatment with alpha-2b-interferon which was continued at a dose of 50 mcg subcutaneously weekly for 8 weeks followed by monthly doses for 1 year. A repeat evaluation 1 year later showed restitution of the vertebral bones [Figures 4 and 5].

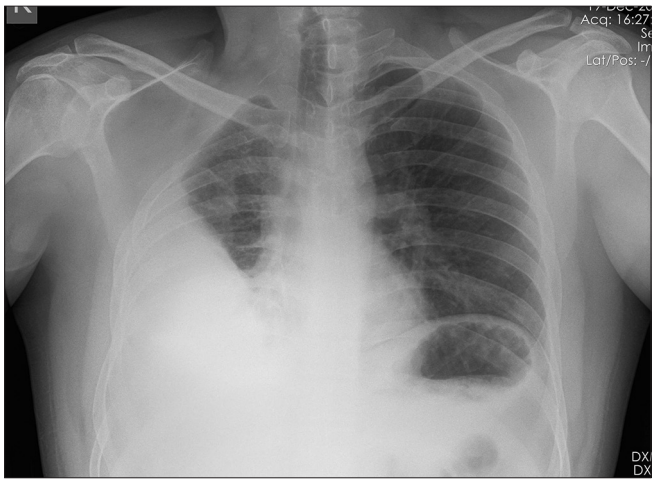

Figure 1: Chest X-ray showing moderate right-sided pleural effusion with osteolysis of the right first and second ribs

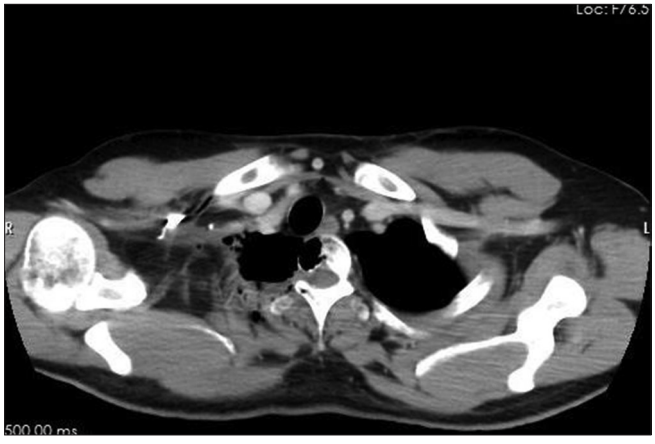

Figure 3: Computed tomography thorax showing osteolysis of the vertebrae and adjacent first rib

Discussion

GSD is a rare musculoskeletal disorder which has been described >60 years ago. However, fewer than 350 patients have been reported as suffering from the disease till date. Gorham and Stout described

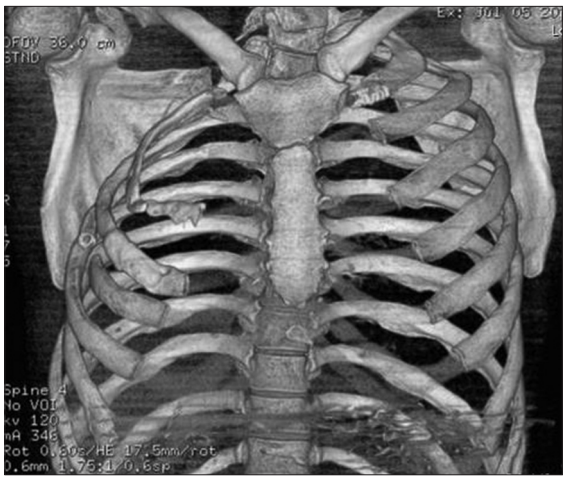

Figure 2: Computed tomography reconstruction of thorax showing bone loss

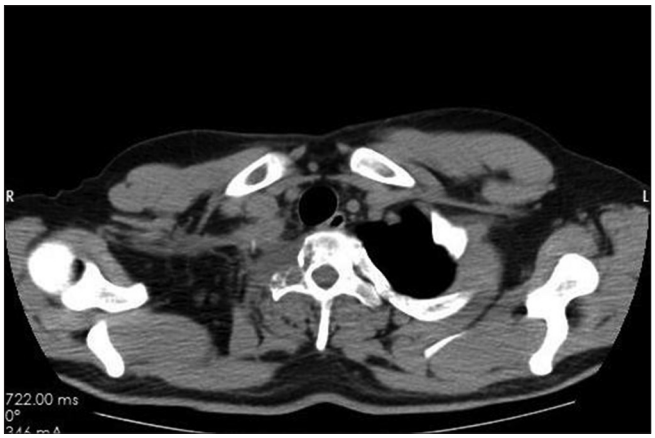

Figure 4: Computed tomography thorax: Partial restitution of the vertebra

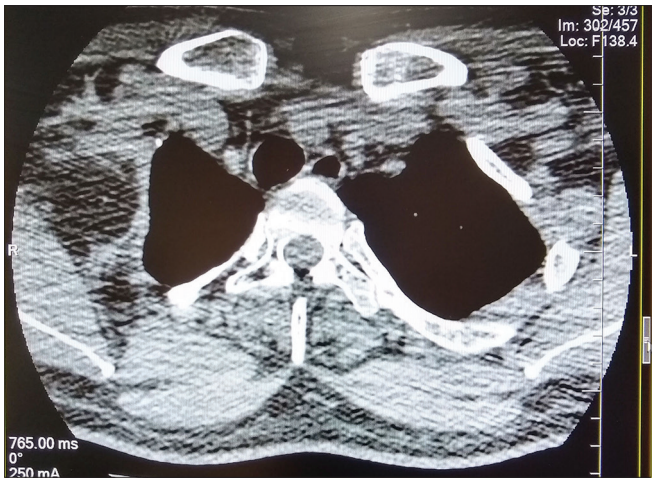

Figure 5: Computed tomography thorax: Bone regeneration in the vertebra and first rib

two patients afflicted with this syndrome in 1955 and further elaborated similar findings in 16 patients from retrospective records.[2]

Although a few hundreds of cases have been reported worldwide, the etiology remains elusive. GSD affects the musculoskeletal system, and various eponyms such as "massive osteolysis," "vanishing bone syndrome," and "disappearing bone disease" in fact describe the most evident finding in these patients.[1]

Etiology and pathogenesis

A clear etiology and pathophysiology of GSD is yet to be ascertained. The prominent feature evident in these participants is the proliferation of blood vessels and lymphatics into the bone, leading to bone loss. Many factors have been thought to promote osteoclast formation and bone resorption; some of these are described below.

Many cases report an antecedent trauma to the affected area. This lead to the theory that the vascular granulation tissue caused bone resorption.[2,3] Another theory for bone resorption suggests an inflammatory cause, as evidenced by the heightened sensitivity of osteoclast precursors to humoral factors such as interleukin-1 (IL-1)-beta, IL-6, and tumor necrosis factor-alpha.[4] This plausibility is supported by Devlin *et al*. who also suggest the role of IL-6 in enhancing the activity of the osteoclasts.[5] Other theories implicating mechanical factors such as local proliferation of endothelial-lined vessels resulting in bone loss by increasing blood flow, changing local pH, or by exerting mechanical force have fallen into disfavor.[6] It has also been purported that exuberant and uncontrolled growth of lymphatic vessels may result in osteolysis by compressing bone. This growth of lymphatic vessels is said to be driven by increased lymphangiogenic factors such as vascular endothelial growth factor (VEGF)-A, VEGF-C, and VEGF-D,[3,7,8] which also stimulate osteoclast differentiation. There is also a suggestion that there may be a lack of repair response by the osteoblast.

The characteristic feature which helps to clinch the diagnosis in GSD is nonneoplastic vascular tissue which replaces normal bone in the affected region. In the late stage of the disease, massive osteolysis is seen where the bone is replaced by fibrous tissue.

GSD has no age, race, or sex predilection, though it is diagnosed in most of the patients before the end of the fourth decade. Familial inheritance has not been proven. Some case reports point to trauma as an inciting event to GSD.[9,10] The index patient was 25 years old and did not report any trauma to the affected part of the body.

Extensive osteolysis is *sine qua non* to speculate a diagnosis of GSD. GSD can afflict the axial or appendicular region, and the clinical profile depends on the respective region. The shoulder girdle, upper arm, and mandibular bones are more commonly cited as affected regions. The massive osteolysis is notable for traversing anatomical boundaries and hence involves contiguous areas in the region.[11] Our patient had involvement of the right hemithorax and the lower cervical vertebrae.

Most of the patients with GSD present with pain at the involved site with limitation of movement, sometimes with swelling and progressive weakness of the affected limb.[12] This leads to atrophy of soft tissues and adjacent muscles.[13] The index patient had persistent right hand pain but demonstrated no weakness of the limb. On imaging, the lower cervical vertebrae and the first three ribs showed osteolysis.

The involvement of vertebral bones has been previously reported to result in paraparesis, and thoracic skeletal involvement causes pleural effusion or chylothorax.[1,14-17] Chylothorax results in high morbidity and mortality unless surgical intervention is commenced. Our patient had right massive effusion, which was lymphocytic exudate. The fluid characteristics were not suggestive of chylothorax.

Despite the bone lysis and deformity being severe and extensive, severe complications are rare in GSD. Spinal cord involvement, especially vertebral bone osteolysis, can result in paraplegia.[18] Respiratory impairment is prominent when the thoracic cage or pleura is involved. Sporadic reports of death due to relentless drainage of chylous fluid or respiratory impairment have been noted.[13]

The disease progresses inexorably over a period of years and ultimately stabilizes spontaneously. Some reports of massive osteolysis describe spontaneous recovery of some of the lost osseous tissue.

Investigations

Radiological appearance of osteolytic bones plays an important role in the evaluation of GSD. The involvement of contiguous areas, crossing the anatomic boundaries, such as an intervening joint, helps to suspect a diagnosis of GSD. Disappearance of the bones begins from subcortical or intramedullary radiolucent foci, which progresses to atrophy, fragmentation, and dissolution of part of the bone. Computed tomogram, MRI, and radioisotope bone scans have been used by various investigators to demonstrate the bone involvement.[19]

Hematological evaluation is usually within the normal limits in these participants. In some cases, elevated alkaline phosphatase levels have been reported. Osteoclastogenic (IL-6, transforming growth factor-beta-1, and IL-1-beta) and angiogenic (VEGF-A) inflammatory mediators are known to be increasingly released from cells cultured from the soft-tissue lesions in GSD.[4,8] However, clinical implications of monitoring these mediators are not evident, given the rarity of GSD.

Biopsy and histopathological evaluation play a key role in clinching the diagnosis of GSD. Demonstration of noncancerous proliferation of blood vessels and lymphatics in the absence of any osteoblastic response or calcification helps to confirm the diagnosis. GSD is a diagnosis of exclusion, once the differential diagnostic possibilities such as bone hemangioma, essential osteolysis, angiosarcoma, and hereditary osteolysis have been ruled out.[12] Conditions such as osteomyelitis, hyperparathyroidism, intraosseous malignancies or metastasis, and infection are other differential diagnoses to be considered.[20]

The options for the management of Gorham's disease are varied. The surgical options include operative resection,[21] usage of bone graft and reconstruction,[11] or a prosthesis support.[22,23] Nonsurgical therapy ranges from radiation therapy to involved site,[24] to chemotherapy,[25] anti-osteoclastic medicines (bisphosphonates),[13,26,27] denosumab,[28] sirolimus,[29-31] and alpha-2b-interferon.[13,14,32]

Treatment with low-molecular-weight heparin,[33] anti-VEGF-A antibody, bevacizumab,[34] propranolol,[35] steroids, Vitamin D, and calcitonin[1] are sparsely reported. Few reports have noted spontaneous stabilization of the disease and no further osteolysis.[1,9,12]

We considered radiotherapy as a treatment option in our patient, but the consequence of neurological impairment such as quadriplegia due to C6 and C7 vertebral bone destruction led to withholding this therapy. Surgical fixation was also considered hazardous.

He was stared on interferon-alpha-2b 50 mcg subcutaneously weekly for 8 weeks followed by monthly doses for 1 year. He showed clinical improvement within 2 weeks of therapy as the daily drain from intercostal tube reduced considerably and permitted to discontinue the drainage. The patient tolerated the treatment well, though he had a febrile response to interferon during the initial doses.

A repeat CT scan after 1 year showed not only stable disease but also partial regeneration of the cervical vertebrae. The patient is off treatment at present and continues to be on follow-up with no further progression of the disease.

Conclusion

Our understanding about the disease characteristics and pathology has been increasing since the original description of GSD by the eponymous authors in 1955. The available data have clarified our understanding of the disease process, the vascular and lymphangiogenic biomarkers, and the potential curative therapeutic options for this rare disease. However, the cause of regional but massive osteolysis in the presence of systemic inflammatory markers, the inciting event, or genetic cause has been so far undetermined.

The prospect of these patients is looking bright with improved understanding of the disease process and basic science research which is transforming into bedside therapy.

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We would like to thank the patient for agreeing to publish this manuscript.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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