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CASE REPORT

A lethal form of Gorham disease associated with extensive musculoskeletal pneumatosis: case report and review of the literature

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Abstract We report here the imaging findings of a rare case of a lethal form of Gorham disease in a young female patient. Multimodality imaging findings over 13 year-follow-up demonstrated progressive wide spread skeletal and soft tissue abnormalities with permeative osteolysis, pathological fractures and severe skeletal deformities. Unusual extensive osseous and soft tissue pneumatosis was illustrated on cross-sectional studies. The progressive nature of this form of Gorham disease and the subsequent complications eventually culminated in patient's death.

Keywords Essential osteolysis · Pathological fracture · Chylothorax · Computed tomography · Magnetic resonance imaging

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Introduction

Gorham disease (GD) is a rare disease characterized by replacement of the normal bone by aggressive proliferation of a non-neoplastic neovascular tissue [1]. The exact etiopathological mechanisms associated with GD are poorly understood. While GD is generally perceived as a focal self-limiting disorder [2], it occasionally presents with more extensive polyostotic distribution. We describe an unusual case of a young adult female who was diagnosed with a severe form of GD associated with the development of diffuse pneumatosis of the affected areas.

Case report

A young female patient was referred to our tertiary medical center at the age of 13 years for further management of multiple complicated fractures, skeletal deformities, and pain. She was a product of full-term pregnancy with normal prenatal history. Symptoms started at the age of four when she fractured her left femur. This was followed by multiple fractures of the left lower extremity, which were complicated by nonunion. Severe deformity of the leg resulted and the limb was eventually disarticulated at the knee level at an outside hospital at the age of nine. She was treated symptomatically with analgesics, iron and vitamin D supplies. Previous bone biopsy was histopathologically consistent with Gorham disease. At the age of 5 years, she developed chronic bilateral chylothoraces, which persisted throughout the rest of her life. At presentation, the patient was ambulating with crutches and could not use a leg prosthesis due to poor quality of the supporting bone. Physical examination revealed severe thoracolumbar scoli-

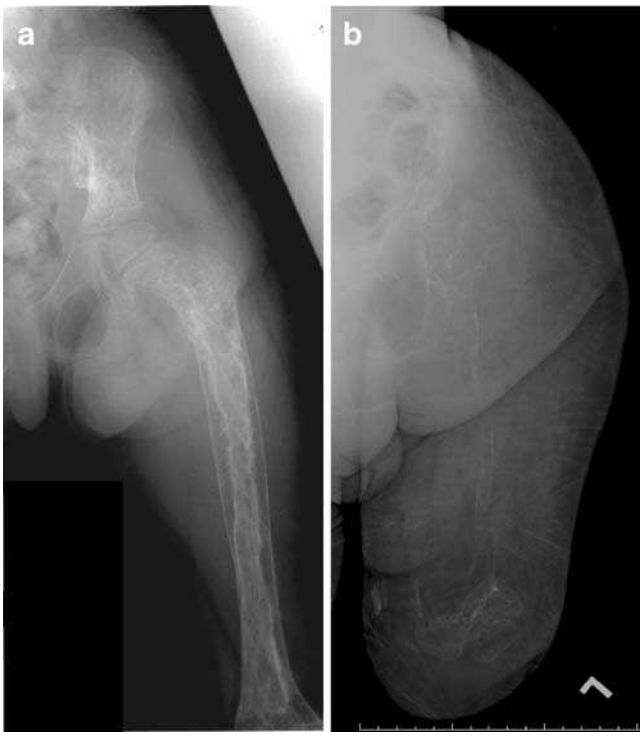

Fig. 1 Radiographs of the left thigh at the age of five (Fig. 1**a**) and 18 years (Fig. 1**b**). Initially, numerous small lucencies were seen throughout the left femur and pelvic bones (Fig. 1**a**). After 13 years, bone is reduced to a gracile, deformed cortical frame with multiple fractures (Fig. 1**b**). Note the heterogeneously low soft tissue density due to gross fatty infiltration

osis and flexion deformity of the left femur. Metabolic and biochemical surveys showed no evidence of parathyroid, hepatic or renal dysfunction.

Imaging studies showed that the disease involved the lower extremities, pelvis, vertebrae, and ribs. The upper extremities and the skull, at least on plain films, were spared. Over the next 13 years of follow-up, the disease slowly but continuously progressed.

A skeletal survey demonstrated progressive osteolytic changes, thinning and deformity of the bony structures of both femurs, pelvic bones, and ribs. Wedge facture/collapse of upper lumbar vertebral bodies resulted in severe angular kyphoscoliosis at the thoracolumbar junction (Figs. 1 and 2).

Magnetic resonance imaging (MRI) study at the age of 13 showed a diffuse corticomedullary hyperintense signal and gross deformity of the affected bones on T2-WI with asymmetrical involvement of the femora and vertebral bodies (Fig. 3). There was muscle atrophy of the left thigh with fatty replacement. The adjacent soft tissue showed irregular hyperintense reticular pattern. These osseous and soft tissue lesions were hypointense on T1-WI and enhances heterogeneously after contrast administration.

Computerized tomography (CT) scan also confirmed the diffuse progressive permeative resorption of bone, with hypodense changes gradually coalescing to nearly replace the entire affected bone. The process started in the medulla and eventually extended to the cortex resulting in the

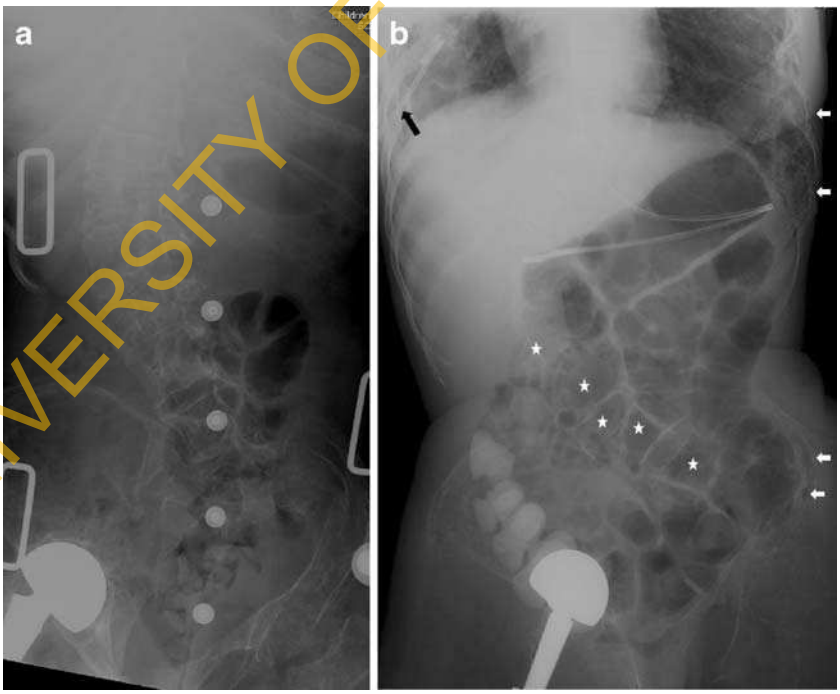

Fig. 2 Abdominal radiograph at the age of 15 (Fig. 2**a**) and 18 years (Fig. 2**b**). In addition to severe bony demineralization and deformities, there is a progressive marked right thoracolumbar scoliosis. The lumbar vertebral bodies are barely visible through bowel gases on Fig. 3**b** (The center of each lumbar vertebra is marked by a *white star*). There are widespread intraosseous pneumatosis involving multiple ribs and left hemipelvis (*white arrows*) and a right chest tube (*black arrow*)

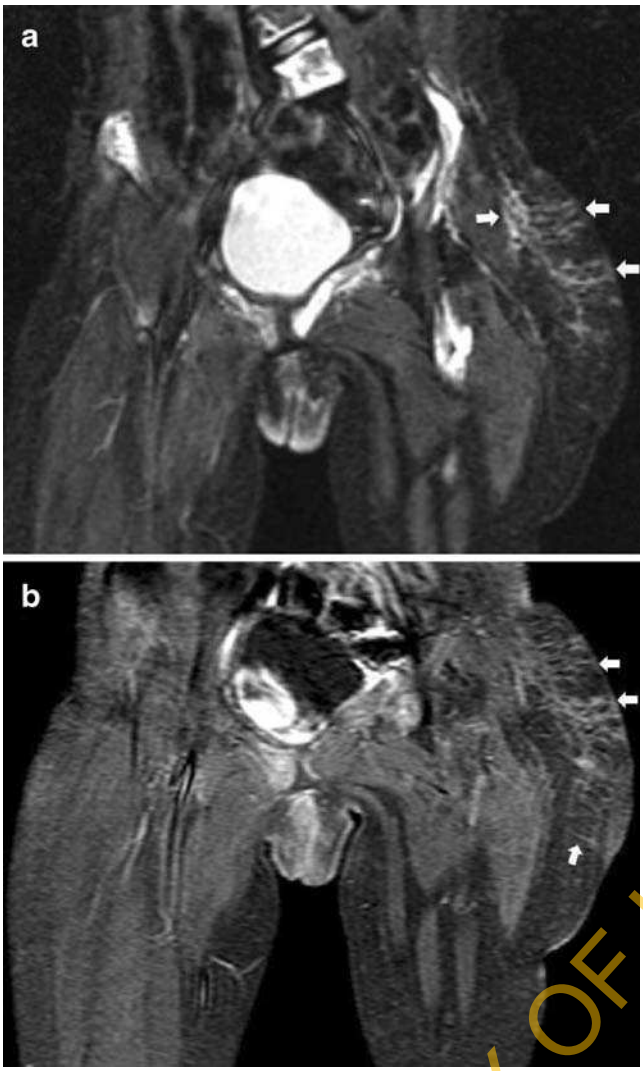

Fig. 3 MRI at the age of 13 years. The progression of the hyperintense changes is evident on the coronal T2-WI sequences (Fig. 3**a**). The involvement and the progression of the disease in the upper femora and vertebrae are asymmetrical. The surrounding soft tissue component in the left gluteal area displays a hyperintense reticular pattern on coronal T2-WI with fat saturated image (*arrows* on Fig. **a**), and enhances heterogeneously after contrast administration on coronal T1-WI with fat saturated image (*arrows* on Fig. **b**)

known "phantom bone" phenomenon. (Fig. 4) Similar to the MRI findings, there were ramifying abnormal densities within the periosseous soft tissue, muscle atrophy, and fatty replacement.

Thoracic findings, in addition to the osseous changes, included pleural thickening, bilateral chylothoraces, complex pneumothorax, and fine subpleural septal thickening (Fig. 5).

Following placement of a right chest tube for increasing chylothorax, a chest CT scan incidentally demonstrated the presence of an extensive pneumatosis. The involved bones

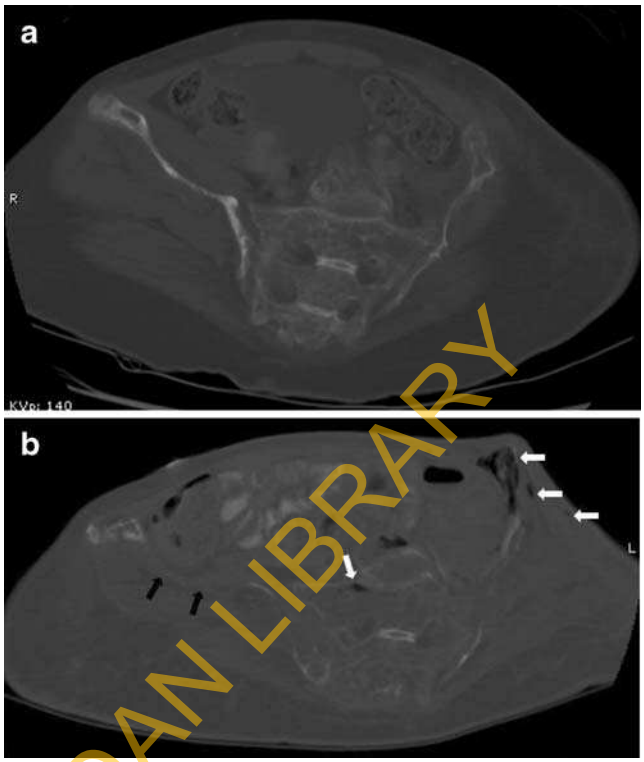

Fig. 4 CT scan images demonstrate the progressive osteolysis and bone deformity at the age of 15 (Fig. 4**a**) and 18 years (Fig. 4**b**). In certain areas, the full thickness of the bone is replaced by soft tissue density (*black arrows* in Fig. 4**b**). Osseous and periosseous pneumatosis is also seen (*white arrows* in Fig. 4**b**)

and soft tissue contained air pockets in a distribution that corresponds to the expected distribution of the abnormal lymphatic channels. This included multiple vertebrae, ribs, left femur, pleural space (pneumothorax), and soft tissue

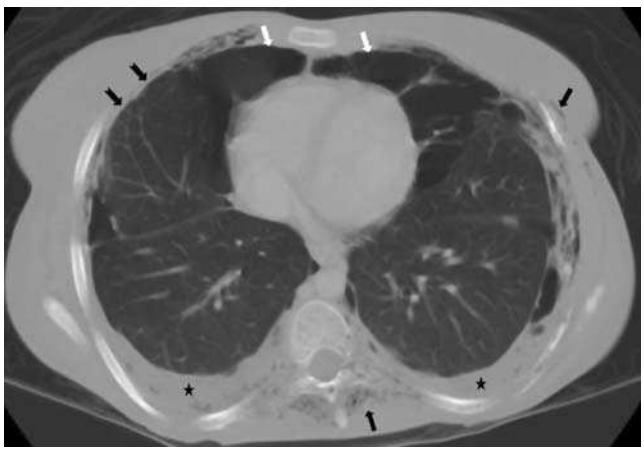

Fig. 5 Chest CT scan demonstrates complex loculated anterior mediastinal pneumothorax (*white arrows*), soft tissue emphysema (*black arrows*) and fine subpleural septal thickening (*notched black arrows*) and pleural thickening and effusions (*stars*)

emphysema (Figs. 2b, 4b, Fig 5 and Fig 6). Interestingly, this was not associated with any change of the patient's clinical status.

At the age of 15, she was involved in a motor vehicle accident and she suffered a displaced femoral neck fracture. Urgent open reduction and internal fixation were done and tissue specimens obtained during this procedure confirmed the presence of advanced changes of GD (Fig. 7). Two-months follow-up CT scan failed to demonstrate any evidence of fracture healing with complete nonunion (Fig. 8). Subsequent plain films demonstrated that the internal fixation device has broken out of the femoral head and impinged on the lateral aspect of the acetabulum. On a nuclear scans in the same admission, neither SPECT nor pinhole imaging showed any significant tracer uptake.

A Dual energy X-ray absorptiometry scan preformed at the age of 16 showed a markedly low bone mineral density of 0.317 g/cm^2 (Z-score of −6.1 SD) for the of the L1–L4 vertebrae and 0.422 g/cm^2 (Z-score of −4.5 SD) for the right femur. Compared to age-matched controls, these findings indicated a significant low bone mass and an increased risk of fracture.

At the age of 18, the patient presented to the hospital with several-month history of increasing dyspnea and nonproductive cough. Chest x-ray showed bilateral pleural effusions, the larger right effusion was drained with a pigtail catheter and large amount of chyle was drained at the rate of 0.5 to 1 l per hour. An enteric tube was placed to replace the fluid and nutritional losses. During the same admission, she had increasing marked weakness and loss of sensation in the right lower extremity, which was attributed to worsening of the spinal compression from advanced vertebral disease. At the request of the patient and after many interdisciplinary discussions among the clinical teams, no further imaging studies were performed since therapeutic options would be very limited. The patient was discharged to palliative care services closer to home, where she passed away few weeks later from respiratory complications.

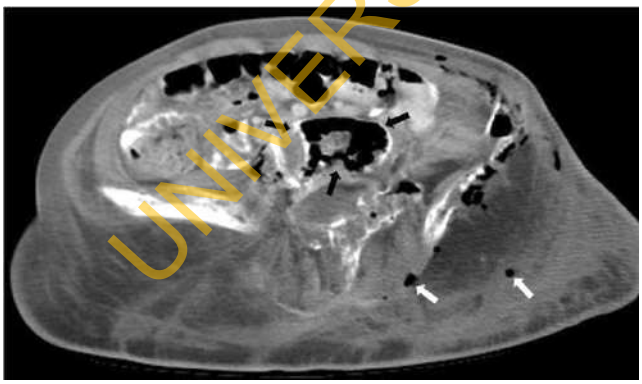

Fig. 6 Pelvic CT scan shows intraosseous pneumatosis casting an entire lumbar vertebral body (*black arrows*). Note that the vertebra is anteriorly rotated into a horizontal orientation. The periosseous soft tissue, including the muscles, shows marked fatty infiltration with reticular and coalescing densities and pneumatosis (*white arrows*)

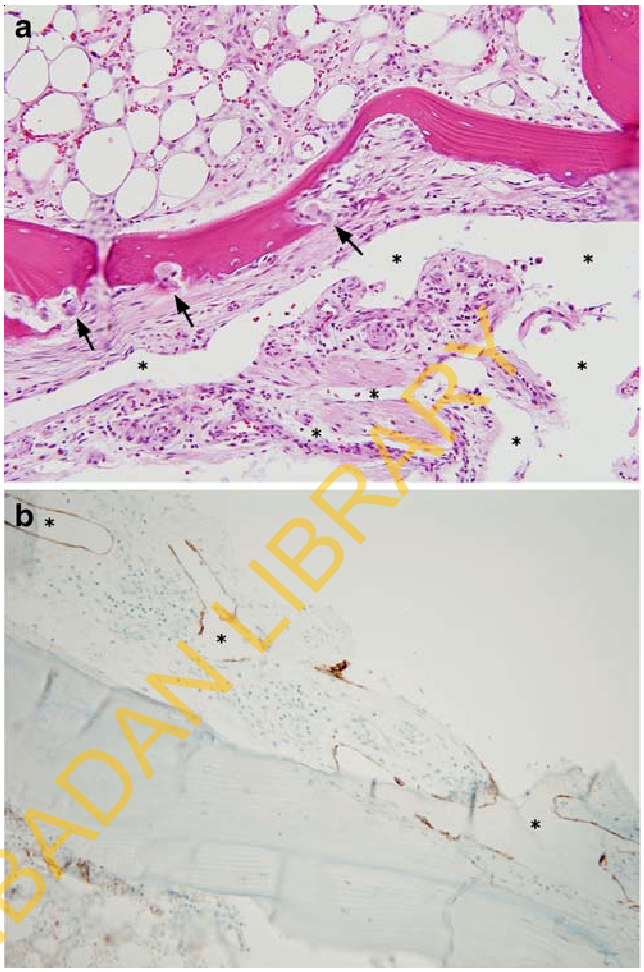

Fig. 7 Histopathological specimen from the cortex of the femoral neck. **a** The surface of the cortex of femoral neck shows enlarged, thin-walled, anastomosing lymphatic channels with resorption of underlying bone. *Asterisks* are in the lumens of the lymphatic channels and *arrows* indicate osteoclasts in Howship lacunae (H&E, ×100). **b** D2–40 immunostain highlights the endothelium of numerous enlarged lymphatic channels on cortical surface of femoral neck. *Asterisks* are in lumens of lymphatic channels. (D2–40, ×100)

Discussion

Gorham disease (also known as essential osteolysis, disappearing bone disease, vanishing bone disease, and Gorham-Stout disease, OMIM # 123880) is a rare disorder of variable degree of osteolysis. This disorder is sporadic with no race or sex predilection [1, 3, 4]. The etiopatho-

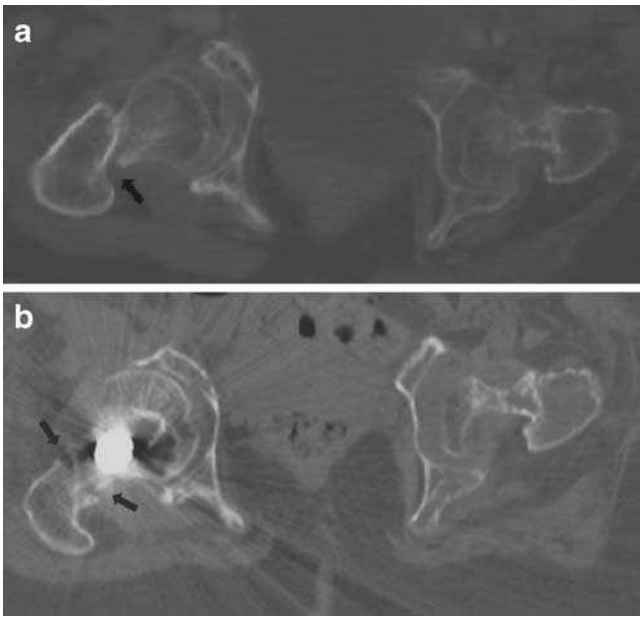

Fig. 8 CT scan images demonstrate a displaced right femoral neck fracture at the time of the presentation (*arrow* on Fig. 8**a**) and 2 months following open reduction and internal fixation (Fig. 8**b**). No evidence of significant callus formation is seen (*arrows*). The deformity, thinning and osteolysis are marked in the left hip area. Streak artifacts in the right side are due to the metallic fixation device

genesis of GD is still largely unknown [1, 3, 5, 6]. Osteoclastic resorption and lining cell activation are likely mediated via local lymphatic tissue factors resulting in osteolysis [7]. Histopathologically, there is vascular-lymphatic proliferation with or without fibrosis. GD often produces polyosteotic lytic lesions and periosseous soft tissue abnormalities with extension into the pulmonary, pleural, and solid abdominal organs [8]. The disease has a predilection to affect the clavicle, scapula, ribs, and vertebrae as well as the spleen and the lymph nodes [9]. A subtype of GD has been reported in which there is dysplasia of the lymphatic system with absence of the proximal thoracic duct and significant lymphangiectatic abnormalities of the pleural, peritoneal, diaphragmatic, splenic, and small bowel tissue [7].

The diagnosis of GD can be made based on clinical, imaging, and histological findings [10], although imaging findings are sufficient to established the diagnosis in some cases, particularly in advanced stages [1].

Plain films of the affected bones, as found in our patient, show progressive intramedullary and subcortical and cortical lucencies eventually resulting in thinning and tapering of the involved long bones. The advanced appearance resembles a "licked stick of candy" [2]. Lytic changes progressively coalesce within affected bone eventually replacing almost completely it; hence the name "vanishing bone disease" for this stage. Other osseous imaging characters include lack of periosteal reaction, involvement of multiple contiguous bones, pathologic fractures, and deformities.

Thoracic involvements such as costovertebral osteolysis and chylothorax, as displayed early in the courses of the disease in our patient, are common presentations of GD. Tie et al. reviewed 146 cases of GD and found that 25 patients (17%) had chylothorax [11]. The mortality rate among this group of patients was high.

CT scan provides an excellent evaluation of degree and extent of bony resorption and soft tissue involvement [10]. In addition, pneumatosis can be clearly depicted and delineated on CT images, as seen in the case we presented.

MRI findings of affected bones typically demonstrate characteristic increased signal intensity on T2-weighted images and low signal intensity on T1-weighted images [1, 5, 6], although Damron and colleagues reported high signal intensities on both T1- and T2-weighted images of a case of Gorham's disease of the scapula [12].

Nixon and colleagues described several abnormalities of the lymphatic system with osseous lymphatic malformation in three pediatric patients using lymphangiography [13]. Both the affected bone and the adjacent soft tissue were involved with dilated lymphatic channels, delayed drainage, paucity of lymph nodes, and the presence of large lymphatic along the lymphatic pathway and reflux. Similar findings were reported by Tsyb et al. [14]. While the lymphangiographic findings are invaluable to understand the anatomical derangements in the disease, we believed that the potential benefits from this test were not sufficient to justify the minimal morbidity associated with this procedure.

The associated soft tissue component in this case was predominantly located in the periosseous and subcutaneous fatty regions. On the cross-sectional studies, the soft tissue reticular changes are essentially similar to changes seen with other disorders of the lymphatic system, such as lymphedema [15] and microcystic lymphatic malformations".

Angiography is not indicated in GD, since it will likely show absence of neovascularity in the affected area [4, 16].

Bone scintigraphy is reported to be negative in advanced stages of GD, as it was in our case. However, some increase in the tracer uptake in early stages and other variable results have been reported [1, 4]. Due to lack of sufficient data in the published literature, the exact role of bone scintigraphy in the diagnosis and follow-up of GD is still unclear.

Intraosseous pneumatosis is an extremely rare imaging finding [17]. In addition to GD and diffuse lymphatic anomalies, the differential diagnosis of this phenomenon includes osteomyelitis, bone biopsy, osteonecrosis, and neoplasms [17]. Brown et al. reported three children with lymphatic anomalies of the bone who developed asymp-

tomatic pneumatosis which was found incidentally at imaging. Associated soft tissue emphysema was seen in two cases. In all three cases, intraosseous gas developed after biopsy or surgery in the diseased areas [18]. The mechanism of this rare complication is unclear. However, in our case, the only intervention prior to the development of pneumatosis was the placement of a right chest tube. No bone biopsy or surgical resection were performed in the interim. Brown et al. suggested that air refluxes from the abnormal pleuropulmonary lymphatics, which communicate directly with the abnormal lymphatic channels of the bone [18]. Imaging findings in our patient demonstrating the extension of the pneumatosis to anatomically remote but diseased areas, such as the lower extremities, support this theory.

Since the distribution of pneumatosis matched that of the abnormal lymphatic channels within the osseous and periosseous components, we propose the name "pneumolymphaticum". This name captures the "benign" pathological process of air dissecting into lymphangiectatic channels and potentially can enable clinicians to distinguish the mechanism of pneumatosis in GD from other more serious acute etiologies, such as infection. The presumed mechanism of intraosseous pneumatosis in infection involves anaerobic metabolism and production of hydrogen and carbon dioxide gases as a result of anaerobic infection by gas-forming bacteria. This highly morbid complication requires surgical treatment. Following orthopedic surgery, small amounts of air may be trapped within the bone and the surrounding soft tissues and air is usually resorbed within a few days [19].

Currently, there is no known effective therapy for GD. While many reports of successful medical (such as the use of bisphosphonates and interferon), surgical (such as resection of focal lesions, bone grafting, and ligation of the thoracic duct), and radiation therapy can be found in the literature, these treatment modalities provides inconsistent or little effect [20]. Treatment is still largely symptomatic and palliative and limited to stabilize the affected skeleton and control pain and chylothorax.

In summary, we presented the clinical and imaging findings of a case of lethal form of GD. The progressive course of this disease illustrated the relentless natural history of this disease. In addition, we proposed to name the exceedingly rare phenomenon of extensive musculoskeletal pneumatosis seen in this case "pneumolymphaticum".

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