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SCIENTIFIC ARTICLE

Gorham-Stout disease and generalized lymphatic anomaly—clinical, radiologic, and histologic differentiation

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Abstract
Purpose Gorham-Stout disease (GSD) is a rare vascular disorder of lymphatic origin characterized by progressive osteolysis. Generalized lymphatic anomaly (GLA) is a multisystem disorder that also commonly affects bone. We hypothesized that Gorham-Stout disease is different from other osseous lymphatic anomalies. We proposed to discriminate these entities by analyzing findings on skeletal imaging.
Methods Clinical data, imaging studies, and histopathologic findings were retrospectively reviewed in patients presenting to our Vascular Anomalies Center with lymphatic anomalies of bone.
Findings Within a cohort of 51 patients with lymphatic disorder and radiological evidence of bony involvement, two distinct categories emerged. Nineteen patients met the imaging criteria for GSD: progressive osteolysis with resorption and cortical loss. Thirty-two were categorized as GLA: Discrete radiolucencies and increasing numbers of bone affected over time, but without evidence of progressive osteolysis. The ribs were the most common site in both groups, followed by the cranium, clavicle, and cervical spine in GSD, and thoracic spine, humerus, and femur in GLA. Fewer bones were involved in GSD, with relative sparing of the appendicular skeleton. Associated infiltrative soft tissue abnormality was seen in 18 in GSD, but only six with GLA. Macrocystic lymphatic malformations were identified in 14 with GLA, but none with GSD.
Conclusions There are significant radiological differences between GSD and GLA, although there are some overlapping features. The major distinguishing characteristic is the progressive osteolysis seen in GSD. Findings suggestive of GLA are more extensive involvement, particularly of the appendicular skeleton, presence of discretemacrocystic lymphatic malformations and visceral organ lesions.

Keywords Imaging · Lymphatic malformation · Gorham · Lymphangiomatosis

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Introduction

Gorham-Stout disease (GSD), also known as massive osteolysis or vanishing bone disease, is a rare disorder characterized by progressive osteolysis. This condition is purported to be originally described by Jackson in 1838 as a case of a "boneless arm" in a 12-year-old boy [1]. In 1954, Gorham described two cases of "disappearing bones" in 1954, which was followed by a comprehensive review based on 24 cases by Gorham and Stout in 1955 [2, 3]. They reported that the massive osteolysis was "usually associated with an angiomatosis of blood vessels and sometimes of lymphatic vessels". It has been recognized that GSD is developmental rather than neoplastic in origin, with slow endothelial cell turnover and association with cutaneous lymphatic malformations [4]. Pathologically, the disease is

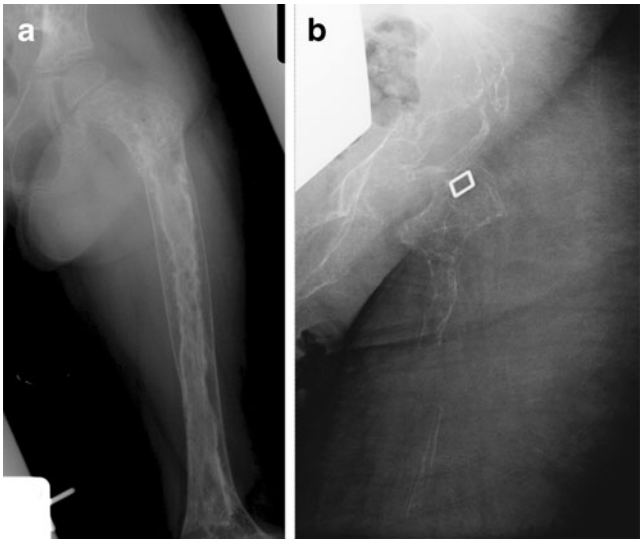

Fig. 1 Frontal radiographs of the femur in a female patient with Gorham-Stout disease. **a** At age 5 years: Lytic lesions are seen in the left pelvis and femur, with evidence of endosteal scalloping and cortical thinning **b** At age 18 years: There is massive progressive osteolysis with almost complete resorption of the left femur, ischium, and ilium

characterized by proliferation and dilatation of lymphatic vessels [5]. Tissue samples also test positive for lymphatic endothelial cell markers, suggesting that GSD is primarily a disease of disordered lymphangiogenesis [6, 7].

In the years since Gorham and Stout's original paper, there have been multiple case reports and small series describing the clinical, pathological, and radiographic findings of this eponymous disorder [8]. These have further emphasized the varied nature of the presentation and natural history of the condition. Johnson and McClure divided the disease into an early stage with intramedullary and cortical lucencies, and a later stage characterized by destruction and resorption of bone [9]. However, we have identified many patients with evidence of osseous involvement that did not appear to progress to the progressive osteolysis characteristic of GSD. We hypothesized that, although both conditions are lymphatic disorders of bone, Gorham-Stout disease is different from generalized lymphatic anomaly (GLA) with bony involvement.

We retrospectively reviewed the imaging of patients with the diagnosis of either GSD or GLA to determine whether these conditions had different imaging characteristics.

Materials and methods

The study was approved by the Committee on Clinical Investigation. A retrospective review of the Vascular Anomalies Center and Department of Pathology databases was performed from 1990 to 2010 to identify patients who had been diagnosed with Gorham-Stout disease or generalized lymphatic anomaly (including diagnoses of lymphangiomatosis and diffuse lymphatic anomalies).

Patient demographics, clinical presentation, and type of imaging were recorded. The imaging was reviewed independently by two pediatric radiologists (S.L and G.C). In instances of discrepancy, a final decision was reached by consensus. The findings included: the number and distribution of bones involved and the type of osseous involvement (bone resorption, cortical loss, and discrete lytic lesions). The presence of soft tissue abnormalities, pleural effusions, and visceral involvement (splenic and hepatic cysts) was also documented in each patient. As the key feature of the condition described by Gorham and Stout was osteolysis and "disappearing" bone [2, 3], only patients with evidence of cortical loss and/or progressive bone resorption were categorized as GSD. The remaining patients were categorized as GLA. Discrepancies were resolved by consensus. Statistical analysis was performed using the Fisher's exact test and the unpaired *t* test.

Microscopic slides of biopsies of bone were available for review in 15 patients with generalized lymphatic anomaly

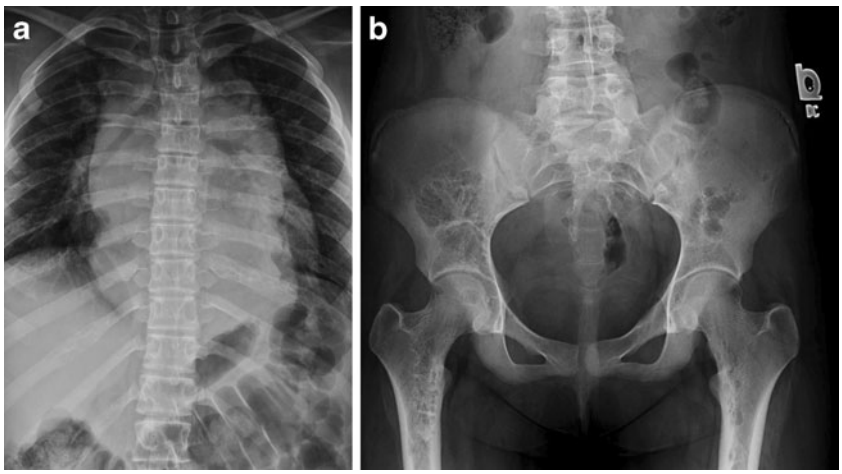

Fig. 2 A 14-year-old girl with generalized lymphatic anomaly. Multiple lytic lesions are seen in the ribs (**a**), proximal femur, and iliac bones (**b**) bilaterally. There is preservation of the bony framework with no evidence of cortical resorption

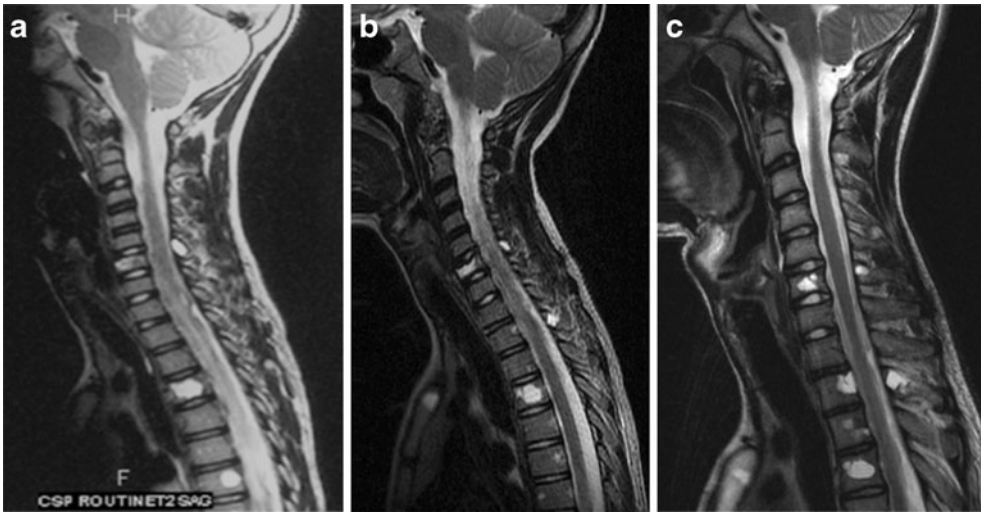

Fig. 3 Male patient with generalized lymphatic anomaly. Sagittal T2 image of the cervical spine obtained at the age of 6 (**a**), 9 (**b**), and 13 (**c**) years of age. There is a slight increase in the size and number of the hyperintense lesions in the cervical and thoracic spine, but no evidence of progressive osteolysis

(GLA) and 12 patients with Gorham-Stout disease (GSD). Some patients in both groups (ten in all) also had cutaneous, soft tissue, or visceral biopsies but only the results of the osseous biopsies are considered herein. In the majority of instances, D2-40 immunochemistry had been performed to help confirm the lymphatic phenotype of the abnormal vascular channels.

Results

Of the 104 patients with a diagnosis of GSD or GLA, 77 had imaging available for review. Of these, 26 had evidence of multifocal lymphatic anomalies consistent with GLA, but no definite bony abnormality. Therefore, 51 patients with osseous findings were included in our study group. The imaging included plain radiographs (n=32), CT (n=38), and MRI (n=32). Follow-up imaging was available in 40. The diagnosis of both conditions was primarily based on imaging, with histopathologic confirmation only available in 19 patients.

Cortical loss and/or progressive bony resorption were identified in 19 patients and these were categorized as having GSD (Fig. 1). The remaining cohort (n=32) was found to have discrete lytic lesions without cortical loss or evidence of progressive osteolysis and were categorized as GLA (Figs. 2, 3). Mean age at presentation was 12.8 years for GSD and 7.8 years for GLA. The sex distribution was equal in both groups, with 10 (52%) males in the GSD cohort and 17 (54%) males with GLA.

Table 1 Osseous findings in GSD and GLA

Radiologic findings	GSD n=19	GLA n=32	p value
Number of bones involved (mean)	7.5	30.7	<.0001
Axial skeleton involvement	17	31	0.54
Appendicular skeleton involvement	5	28	<.0001

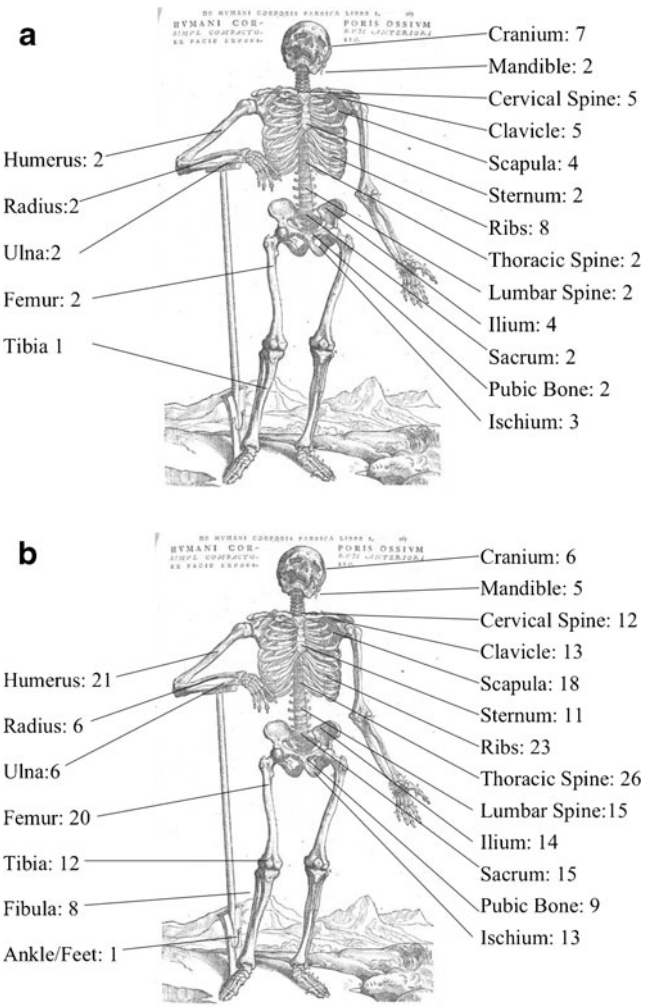

Fig. 4 Distribution of bony involvement in GSD (**a**) and GLA "Humani corporis ossium" (b). Andreas Vesalius. De humani corporis fabrica. Oporinus, Basel 1543

Table 2 Soft tissue findings in GSD and GLA

Radiologic finding	GSD $n=19$	GLA $n=32$	p value
Infiltrative soft tissue abnormality	18	6	<0.001
Visceral: splenic or hepatic cysts	4[a]	19[a]	0.014
Pleural effusions	8	16	0.77
Macrocystic lymphatic malformation	1	14	0.004

[a] Imaging of the upper abdomen was performed in 17 patients with GSD and 30 with GLA

In patients with GSD, the mean number of affected bones was 7.5, while the mean number of bones in GLA was 30.7 (Table 1). Disease of the axial skeleton (cranium, facial bones, rib cage, sternum, and the vertebral column) was seen in 17 of the 19 patients with GSD, and 31 of the 32 patients in patients with GLA. However, involvement of the appendicular skeleton (shoulder girdle, pelvic girdle, upper and lower extremities) was only seen in five (26.3%) patients with GSD compared to 28 patients (87.5%) of patients with GLA. The ribs were the most common site of osseous changes in both groups, followed by the cranium, clavicle, and cervical spine in GSD, and thoracic spine, humerus, and femur in GLA (Fig. 4).

An infiltrative soft tissue abnormality adjacent to the area of osseous involvement was identified in 18 (94.7%) patients in the GSD cohort and 18 (56.2%) patients in the GLA cohort (Table 2). The soft tissue lesion was of high T2 signal in 13 of the patients who were imaged with MRI ($n=14$) and demonstrated intense enhancement following administration of gadolinium contrast (Fig. 5). In the remaining five patients in the GSD cohort, CT was the only cross-sectional imaging performed and showed ill-defined fluid attenuation stranding seen adjacent to the osseous changes.

Cross-sectional imaging was available in 31 patients with GLA (MRI in 22), but a similar infiltrative soft tissue lesion was only identified in six patients. Fourteen of the GLA cohort also had evidence of a macrocystic lymphatic malformation (Fig. 6); however this abnormality was not seen in any of the patients with GSD.

Pleural effusions were identified in eight patients with GSD and 16 with GLA. Cross-sectional imaging of the upper abdomen was performed in 17 patients with GSD and 30 with GLA. Of these discrete splenic and/or hepatic cysts were identified in 19 with GLA (63%) and four with GSD (21%).

On examination of the pathology slides, some biopsies were small and crushed making it difficult to reconstruct architecture and histopathologic details so much so that in three patients with GLA and two patients with GSD, the biopsies were non-diagnostic. Periosteum and adjacent soft tissue were not present in every biopsy.

In GLA, variably sized lymphatic channels were present in both the medulla and cortex. These were lined by an inconspicuous flattened endothelium with their thin walls devoid of a smooth muscle coat and their lumens were either empty or contained protein or blood. Endothelial immunopositivity for D2-40 was present in most vessels although in the larger ones, it was sometimes faint and focal. The larger channels and bony trabeculae moulded against each other and often were separated only by osteoblasts. The latter were only minimally prominent and overlay early lamellar bone. Osseous surfaces were only minimally irregular with osteoclasts and Howship's lacunae being rare. Both the cortical and medullary trabeculae were thinned with osteocytes seemingly larger than usual. The intertrabecular stroma had delicate fibrosis with a minor infiltrate of lymphocytes and occasionally plasma cells and mast cells and hematopoiesis was diminished or absent (Fig. 7).

Abnormal lymphatic vessels were observed in periosseous soft tissue in nearly half of the biopsies. They were most often small with flat, cuboidal, or hobnailed endothelial cells and without a smooth muscle coat. The growth pattern was usually anastomotic with channels insinuating themselves between individual skeletal muscle and collagen fibers.

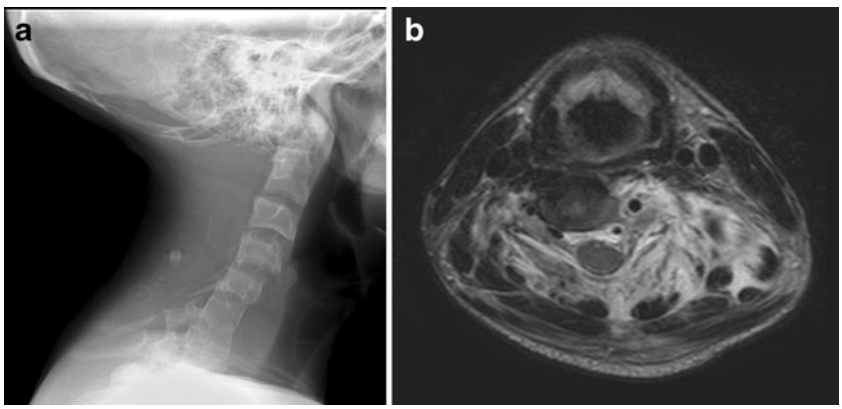

Fig. 5 A 15-year-old boy with GSD involving the cervical spine and skull base. **a** Lateral radiograph of the cervical spine shows almost complete resorption of the posterior elements with extension to the occiput. **b** Axial T2 image of the cervical spine demonstrates hyperintense soft tissue surrounding the cervical spine. **c** Post-gadolinium axial T1 fat-saturated image of the cervical spine shows intense soft tissue enhancement

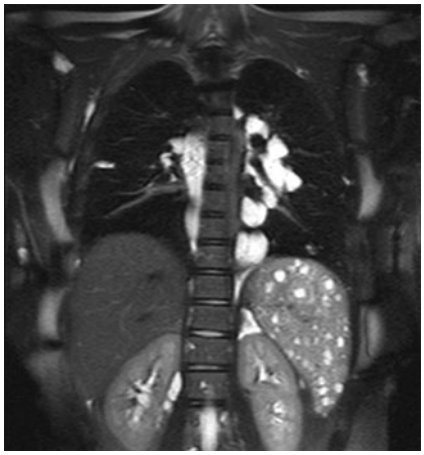

Fig. 6 A 10-year-old girl with GLA. Coronal inversion recovery sequence demonstrates multiple cystic lesions in the spleen and a macrocystic lymphatic malformation of the posterior mediastinum

In GSD, the histopathology had many features in common with GLA. Abnormal lymphatic channels were numerous and the cortical ribbon was partially or totally destroyed. Abnormal lymphatic channels were also present in periosteum and soft tissue in more than half of the biopsies. Osteoclastic and osteoblastic activity with new bone formation and marrow fibrosis were often greater than in GLA. In some biopsies, there was callus and pseudarthrosis and it was unclear to what extent a presumed vicinal fracture may have contributed to the brisk osteoclastic and osteoblastic activity (Fig. 8)

Discussion

Gorham-Stout disease (GSD) is a rare vascular anomaly disorder characterized by proliferation of thin-walled sinusoidal channels of lymphatic origin resulting in progressive bony destruction [4]. Lemuel Whittington Gorham was Professor of Medicine of the Albany Medical College and had an abiding interest in pathology. Following his initial description of "massive osteolysis", he invited his old college friend Arthur Purdy Stout, Professor of Surgery and Director of the Laboratory of Surgical Pathology at the Columbia-Presbyterian Medical Center to co-author another paper that tabulated 24 published reports of disappearing bones and reviewed the histopathology of eight cases [2, 3]. Radiographic analysis demonstrated slow but progressive, partial

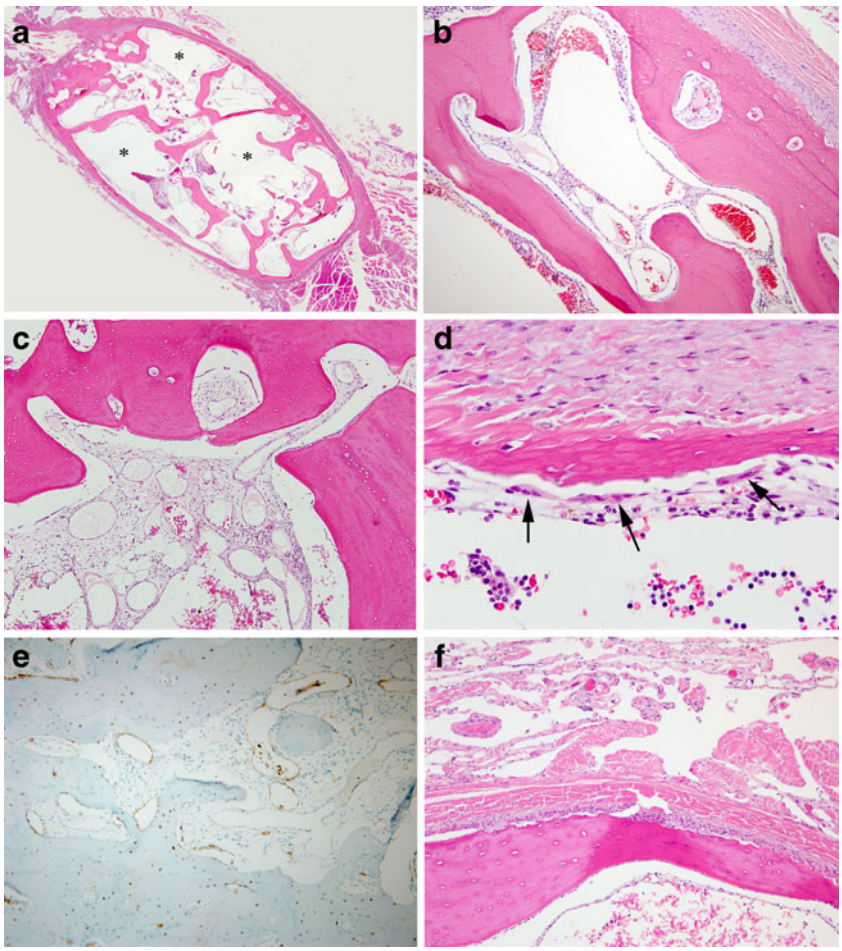

Fig. 7 Generalized lymphatic anomaly. **a** Cross section of rib with many enlarged medullary lymphatic channels (*asterisks*). Note thin cortical ribbon and medullary trabeculae. **b, c** Cortex and medulla contain large thin-walled and variably sized lymphatic vessels. **d** Thin cortex with osteoclasts (*arrows*) and dilated lymphatic vessel inferiorly. **e** D2-40 immunostain (*brown*) highlights the endothelium of medullary lymphatic channels. **f** Network of abnormal lymphatic vessels in periosteal soft tissue (superiorly)

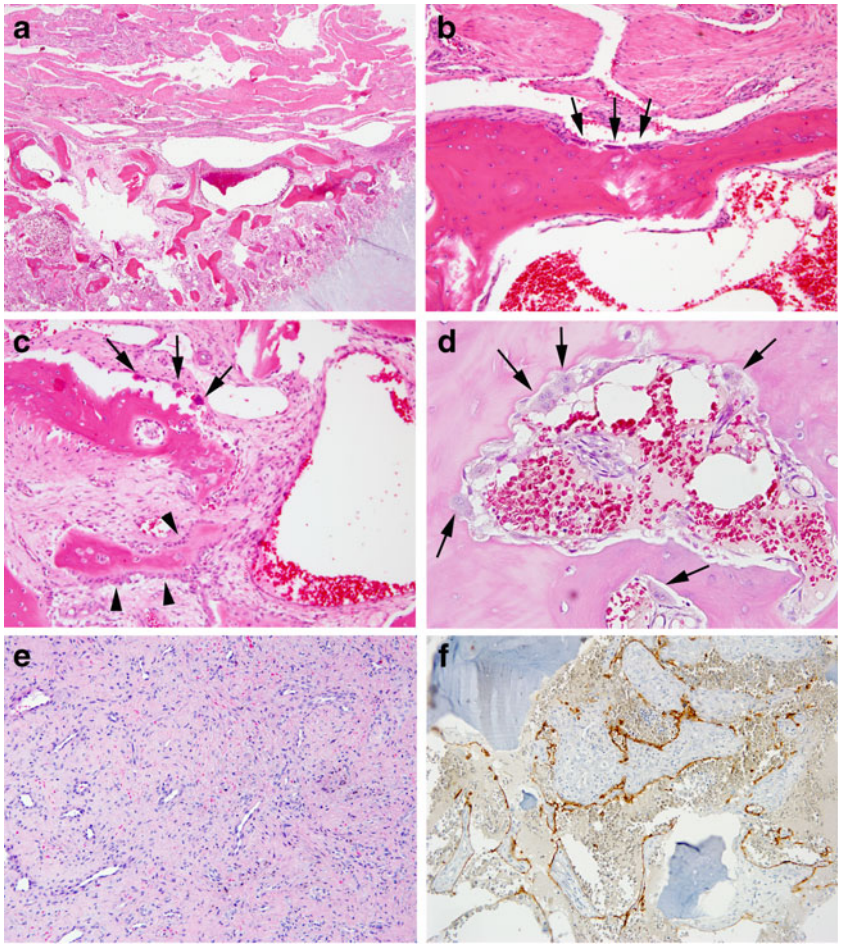

Fig. 8 Gorham-Stout disease. **a** Dilated lymphatic channels in soft tissue (superiorly) and bone (inferiorly) with loss of cortex and some medullary trabeculae. **b** Thinned cortical ribbon apposed by lymphatic channels in periosteum (superiorly) and medulla inferiorly). Surface osteoclasts present (*arrows*). **c** Medullary lymphatic channels are thin-walled and vary in size. Osteoclasts (*arrows*) and osteoblasts (*arrowheads*) are present. **d** Numerous osteoclasts (*arrows*) with underlying Howship's lacunae. **e** Focus of medullary fibrosis with admixed small lymphatic and venous channels. **f** D2-40 immunostain (*brown*) delineates the endothelium of lymphatic channels within bone

or complete, bony resorption involving one or more bones [3]. Their histologic examination showed that progressive osteolysis was associated with "angiomatosis of blood and sometimes of lymphatic vessels" [3].

Generalized lymphatic anomaly, which is synonymous with "generalized cystic lymphangiomatosis", "cystic angiomatosis", or "lymphangiomatosis", was initially described by Rodenber in 1828 [10]. Consistent with the International Society for the Study of Vascular Anomalies (ISSVA) classification, we avoid using the term lymphangiomatosis as the suffix -oma implies increased endothelial cell turnover. This is a multisystem disorder that is characterized pathologically by a persistence of dilated lymphatics [11]. GLA also demonstrates evidence of osseous involvement and, clinically, both of these conditions can present with skeletal pain and pathologic fractures.

As shown in our study, the pattern and type of bony involvement in these two conditions appears to be different. GSD is characterized by cortical resorption and progressive, often extensive, osteolysis. In contrast, the common radiographic appearance of skeletal involvement in GLA is multiple lytic areas confined to the medullary cavity; although these lesions can increase in number and in size over time, there is no cortical destruction [12]. In addition to these distinct types of osseous changes, we identified additional characteristics that help to further differentiate these disease entities.

The first of these features is the distribution of osseous abnormalities. The data from Gorham and Stout's original series showed that the axial and appendicular skeleton was equally involved [3]. In our study, while there was axial skeletal involvement in the vast majority of patients in both groups, only five patients with GSD demonstrated concurrent appendicular skeletal changes. In addition, the appendicular osteolysis was contiguous with adjacent axial skeletal disease in four of these patients and thus tended to involve the proximal long bones. In contrast, involvement of the appendicular skeleton with non-contiguous lesions was seen in the majority of the patients with GLA. Axial skeletal involvement has been reported to be more common than appendicular in patients with "multiple cystic lesions", with pelvis, ribs, and cranium being the commonest sites [12]. A review of the literature also shows that osseous lesions of the tibia, radius, and ulna are less common than those of the humerus and spine in GLA [12]. In our group, there was no significant difference between appendicular and axial

skeletal involvement in GLA. Gorham and Stout found the most common site of involvement in their cohort to be the carpal bones [3]. In our study, we found that the most common sites were the ribs in both groups, followed by the cranium, cervical spine, and clavicle in GSD and the thoracic spine, humerus, and scapula in GLA.

Soft tissue changes adjacent to the site of skeletal involvement have previously been reported in case reports of GSD [2, 13]. This is believed to represent extension of proliferating sinusoidal channels into soft tissue [14, 15]. In our study, we found that almost all of the patients with GSD had associated soft tissue changes, all of which were adjacent to the site of osseous abnormality. Infiltrative involvement of the soft tissue was seen, characterized on MRI by high signal intensity on fluid-weighted sequences, with evidence of intense enhancement on administration of contrast. Similar soft tissue changes, immediately adjacent to osseous findings, were only seen in six patients with GLA. However, the incidence of macrocystic lymphatic malformation was much higher in the latter cohort, likely reflecting the multisystem nature of the disease.

Chylothorax has also previously been reported in patients with GSD [16]. This is thought to be related to disruption of thoracic duct or pleural lymphatics by adjoining osteolysis [16]. There were pleural effusions in eight of our patients with GSD, six of whom had concurrent evidence of costal osteolysis. Of the remaining two patients, one developed a chronic pleural effusion following a rib biopsy, while no cause was identified in the other. Nevertheless, pleural effusions do not appear to distinguish between the two conditions, as these were also identified in half of our GLA cohort. One of GLA patients also developed a pleural effusion as a complication of a biopsy procedure. Wunderbaldinger et al. found that pleural effusions are associated with mediastinal involvement in patients with GLA [17]. They speculated that the pleural effusions in these cases are related to lymphatic obstruction caused by a mediastinal mass [17]. A concurrent mediastinal lymphatic malformation was only found in just over half of our patients with pleural effusion and GLA. The remainder had evidence of extensive osseous involvement of their ribs.

Visceral lesions, specifically splenic and/or hepatic cysts, were seen in both disorders, although the incidence was greater in patients with GLA. However, the multifocal nature of the involvement in a few of the patients with GSD suggests a degree of overlap between the two conditions. This was confirmed on histopathology with many common features between the two conditions. However, there does appear to be evidence of greater osteoblastic and osteoclastic activity in GSD.

The major limitation of our study is its retrospective design. The lack of consistent imaging protocols and modalities probably contributed to an underestimation of both soft tissue and osseous findings. The imaging obtained was also focused on sites of clinical concern and symptoms and therefore may have overlooked remote sites of involvement.

In conclusion, there appear to be significant differences in imaging and histology of Gorham-Stout disease and generalized lymphatic anomaly, although there are some overlapping features. GSD is characterized by cortical resorption, progressive osteolysis, adjacent soft tissue changes, and relative sparing of the appendicular skeleton. GLA appears to be a much more insidious condition, preserving the bony framework. Reflecting the systemic nature of the disease, there is a significantly greater number of bones involved in GLA and higher incidences of both visceral involvement and associated discrete macrocystic lymphatic malformations.

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