


“A case of vanishing bone disease complicated by chylothorax- diagnosis and treatment”

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Abstract

A 16-year old girl with Gorham-Stout disease is presented. She had progressive replacement of the bones of her left arm and shoulder girdle by fibroadipose tissue and numerous proliferated, non-neoplastic, lymphatic channels. The clinico-pathologic features of this condition are discussed, as are its possible complications and available therapeutic modalities.

Keywords

Case report of vanishing bone disease, complicated by chylothorax- diagnosis and treatment

Case report

This lady had a long history of repetitive fractures of the left arm, after minor trauma, since early childhood. Her mother noticed that her left arm grew at slower rate than the right and, at the age of ten, she developed coalescent angiomatic papules on the dorsum of her left hand. At the age of 16, she was admitted to emergency service because of shortness of breath, a dry cough and chest pain on inspiration. On examination, her left arm was much shorter than the right, with a valgus deviation and semiflexion of the elbow (Figure 1A). On the skin at the base of the left thumb, index and middle finger, there was a purple, nodular, elongated plaque, measuring 4 × 1.2 cm (Figure 1B). Peripheral pulses were normal. Plain radiographs of the left arm and hemithorax (Figure 1C) showed that all bones of the left upper limb were shortened and distorted by coalescing cystic lesions; the scapula, several ribs and the acromial end of the clavicle were affected as well. A bone biopsy, obtained from the left humerus (Figure 1D), showed fibroadipose tissue with numerous proliferated dilated vascular channels replacing bony trabeculae. These vessels were lined by endothelial cells expressing CD31 (a pan-endothelial cell marker) (Figure 2D), and podoplanin, a marker for lymphatic vessels (Figure 2C).

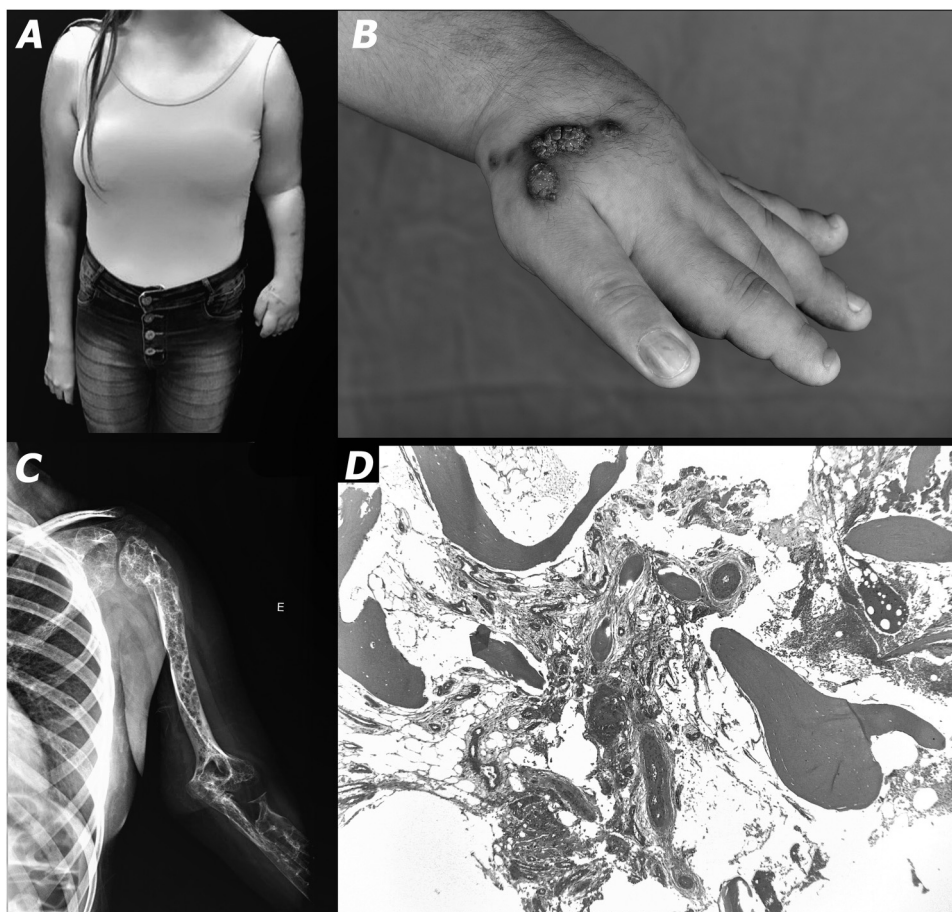
A punch biopsy of the skin (Figures 3 A, B) showed slit-like spaces filled with red blood cells and lined by elongated cells that expressed both CD31 and podoplanin (Figures 2A, B). Due to the similarity to Kaposi's sarcoma, sections were stained for human herpesvirus-8 and resulted negative. Chest tomographic scan (Figure 3C) showed bilateral pleural effusion. Thoracocentesis was performed and the fluid analysis revealed triglyceride values of 3.96 mmol/L, diagnostic of chylothorax. Blood tests were all normal. The patient was diagnosed with Gorham-Stout disease, complicated with chylothorax. She was started on a low-fat diet, and on alendronate and sirolimus. Close monitoring was instituted to detect recurrence of the pleural effusion, and consultation with the surgical team was requested, to consider pleurodesis or thoracic duct ligation.

After two years of treatment, the patient shows residual purple macules on the left forearm. The comparison between the 2020 (Figure 4A and 4B) and 2022 (Figure 4C and 4D) shows not only stabilization of osteolysis, but also bone formation.

Discussion

Gorham-Stout disease (GSD), also known as vanishing bone disease is a condition characterized by the progressive destruction of osseous matrix due to aggressive proliferation of non-neoplastic lymphatic vessels. This can lead to complete bone resorption. GSD can present at any age, but most patients are young adults of either gender. The site of involvement is variable, and the clinical presentation will depend on the affected area, with swelling, impairment of function and pain, that can be incapacitating. Cases of vertebral involvement imply serious risk, with instability of the spine and para/quadruplegia. Chylothorax can occur, secondary to occlusion of the large lymphatic vessels in the thorax. Some cases of GSD, however, are asymptomatic, and come for consultation because of a fracture, spontaneous or after minor

Figure 1. Gorham-Stout disease: shortened left arm, mild valgus deviation and semi-flexion of the elbow (A); hyperpigmented and purple elongated plaque, constituted by coalescing nodules at the base of the left thumb, index and middle finger (B); left arm and hemithorax plain radiograph: numerous, coalescing cystic lesions affecting all left upper limb bones, the scapula, several ribs and the acromial end of the clavicle (C); left humerus biopsy: fibroadipose tissue with vascular proliferation among rarefied bone trabeculae (D).



trauma.¹ The cause of GSD is unknown, but it has been suggested that it might be triggered by trauma, followed by an imbalance between osteoclastic and osteoblastic activities, with progressive bone resorption. The diagnosis of the condition is one of exclusion, based on clinical features, imaging and histological data. Heffez *et al.*² have established eight criteria for the diagnosis of GSD, as follows: 1-Minimal/no osteoblastic response; 2-Bone biopsy showing vessel proliferation and osteolysis; 3-Absence of endothelial cell atypia; 4-Evidence of local progressive osseous resorption; 5-Non-expansile, non-ulcerative lesion; 6-Absence of visceral involvement; 7-Osteolytic radiographic pattern; 8-Absence of hereditary, metabolic, neoplastic, immunological or infectious diseases. In their original publication, Gorham and Stout¹ described a marked proliferation of blood vessels in the medullary and cortical osteolytic areas. Immunohistochemistry showed

that these are lymphatic vessels, not normally present in bone tissue, identified using the markers lymphatic endothelial hyaluronan receptor-1 and D2-40 (podoplanin).³ It was found that vascular endothelial growth factor (VEGF)-A was elevated in the serum or plasma of four GSD patients and VEGF-C, in one GSD patient, compared with those of controls.⁴ Both cytokines are produced by macrophages; VEGF-C stimulates lymphatic endothelial cells directly, whereas VEGF-A and C stimulate osteoclasts, which will then stimulate lymphatic endothelial cells themselves by also producing VEGF-C. Also, GSD patients show a deficient osteoblastic response to injury and bone destruction is replaced by fibrovascular tissue rather than newly formed woven bone. Surviving osteoblasts often show signs of degeneration, as pyknotic nuclei, and decreased synthetic activity. This is surprising, considering that VEGF-A stimulates bone repair. It has been proposed that

Figure 2. Left hand skin biopsy: dermal coalescent nodules of monomorphic spindle cells forming fascicles (A) of slit-like channels containing red blood cells (B); hematoxylin and eosin staining, original magnification $\times 100$ (A) and $\times 400$ (B). Computerized tomographic scan of the thorax: bilateral pleural effusion (C).

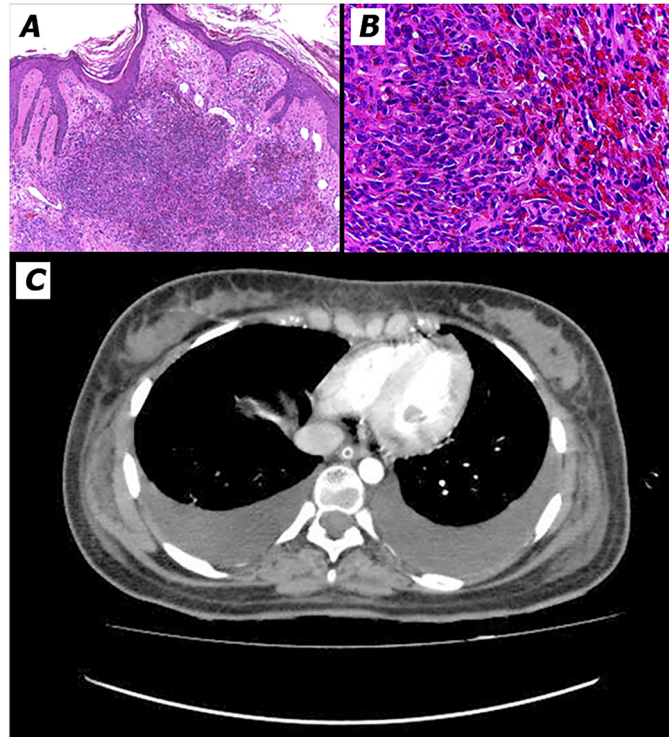


Figure 3. Gorham-Stout disease. A and B: Skin biopsy. Spindle-shaped cells in the dermis heavily stained with lymphatic endothelial marker D2-40 (A) and pan-endothelial marker CD31 (B). C and D: Bone biopsy. C: Dilated thin-walled lymphatic vessels stained with marker D2-40 within fibroadipose tissue, with a residual (arrow) bony trabecula, and D: Endothelial cells are stained with cell marker CD31. Original magnification $\times 100$.

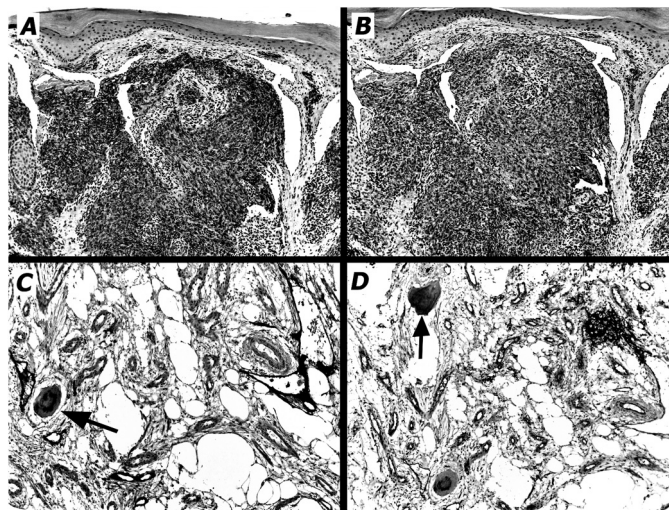


Figure 4. Comparing the radiographic findings obtained in January 2020 (A, B) and March 2022 (C, D), not only stabilization of osteolysis but bone formation was found post-treatment. Left hand and wrist (A, C, D), left hand, wrist and forearm (B). Anteroposterior (A, B, D) and oblique view (B).



osteocytes, that regulate osteoblast differentiation and activity, are inhibiting these functions in GSD, through mediators, as sclerostin.⁵ GSD tends to progress if left untreated. Several treatment modalities have been proposed, including radiotherapy, surgical excision with bone grafting or prosthesis, calcium plus vitamin D, systemic glucocorticoids, low molecular weight heparin and interferon alpha-2b, but the effectiveness of each remains controversial. Bisphosphonates seem to be more effective than other regimens, although there is no consensus about the best dose and duration of treatment. After several months of treatment with bisphosphonates, regression of lytic lesions and reossification are observed in radiographs; the borders become well defined with a sclerotic rim.⁶

Because osteolysis in GSD seems to occur secondarily to local proliferation of lymphatic vessels, sirolimus, as an inhibitor of lymphangiogenesis, has been proposed as a therapeutic agent. Despite the relatively few treated patients and the lack of established therapeutic guidelines, results seem encouraging. This option could be particularly useful in younger patients, who might not tolerate well other therapeutic regimens, as radiotherapy, bisphosphonates or interferon.⁷ Hou *et al.*⁸ have shown, through lymphoscintigraphy, that chylous effusion, observed in up to a quarter of patients with this condition, occurs because of occlusion of the thoracic duct and lymphatic hyperplasia in the pleura and thoracic bones. Chylothorax carries a 69% mortality rate, due to massive protein loss, in those treated with medical management alone, and a 36% rate if surgical intervention is attempted.⁹

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