Alexandria Journal of Medicine

ISSN: 2090-5068 (Print) 2090-5076 (Online) Journal homepage: https://www.tandfonline.com/loi/tajm20

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To cite this article: H. Hasan Yeter (2017) Gorham–Stout disease or new entity on the basis of vasculopathy, Alexandria Journal of Medicine, 53:2, 193-196, DOI: 10.1016/j.ajme.2016.03.006

To link to this article: https://doi.org/10.1016/j.ajme.2016.03.006

Alexandria Journal of Medicine (2017) **53**, 193–196

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Alexandria Journal of Medicine

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Gorham–Stout disease or new entity on the basis of vasculopathy

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Received 24 December 2015; revised 11 February 2016; accepted 29 March 2016
Available online 25 May 2016

KEYWORDS

Gorham–Stout disease;
Vanishing bone disease;
Vasculitis;
Thrombosis

Abstract Gorham–Stout disease (GSD) is a rare osteolytic bone disease also known as vanishing bone disease. The pathogenesis of GSD is not well understood. Studies showed that lymphatic and blood endothelial cells in addition to macrophages secrete TNFα and IL-6 that stimulate osteoclast formation with osteolysis. Also TNFα secretion inhibits osteoblast differentiation and new bone formation. It is known that cytokines such as TNFα, IL-1 and complement system activation are responsible for inflammation and necrosis in the vessel wall at vasculitis. Both diseases have similar pathogenesis. Here, we presented a case of Gorham's disease with involvement of bilateral humerus, systemic arterial thrombosis and mesenteric vasculitis.

1. Introduction

Gorham–Stout disease (GSD) is a rare osteolytic bone disease also known as vanishing bone disease. It is an musculoskeletal disorder characterized by spontaneous and progressive osteolysis, angiomatous proliferation and soft tissue swelling without new bone formation, although first description of a humerus osteolysis in 1838 by Jackson. Moreover, in 1955, Gorham and Stout published a paper, which correlated the massive osteolysis noted in the disease with hemangiomatosis.[1] The pathogenesis of GSD is not well understood. Studies showed that lymphatic and blood endothelial cells in addition to macrophages secrete TNFα, IL-1β and IL-6 that stimulate osteoclast formation with osteolysis.[2,3] Also TNFα secreted by macrophage and endothelial cells inhibits osteoblast differentiation and new bone formation. Additionally, the signaling pathway of the receptor of the lymphangiogenic growth factor Platelet Derived Growth Factor BB(PDGFR-b) and vascular endothelial growth factor (VEGF) family has the critical role that could play in the pathogenetic mechanism of the disease.[4,5] Besides the bone disease, also lymphatic vascular malformations involving the skin and the soft tissues can be adjacent to the diseased bone.[4] It can affect any part of the skeleton. The sites most affected are the cranium, shoulder and pelvis.[6] GSD shows no preference for gender or race and occurs more often in children and young adults. Although dissolution, fracture, fragmentation and disappearance of a part of a bone are typical at X-ray diagnosis of GSD is based on exclusion of other causes of osteolysis, such as infection, cancer, inflammatory and endocrine disorders.[7]

Herein, we report a 50 years old female patient who had been presented with osteolysis of bilateral humerus, systemic thrombosis and mesenteric vasculitis.

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Peer review under responsibility of Alexandria University Faculty of Medicine.

http://dx.doi.org/10.1016/j.ajme.2016.03.006

2. Case report

A 50 year-old woman was admitted to the hospital having abdominal pain and anemia to find etiology of osteolysis of humerus. Her shoulder pain had started five years earlier with progressive loss of range of motion. She did not have any previous history of trauma but she was treated because of soft tissue infection. There were no document neither tissue nor blood culture positivity.

At the objective examination she presented with pain upon palpation of bilateral shoulder. She also could not raise left upper arm and right upper arm was limited to internal and external rotation, abduction and adduction. At her abdominal examination she had diffuse defence without rebound.

She underwent X-ray examination with the right and left shoulder (Fig. 1). X-ray showed the right humerus radiolucent foci (osteolytic lesions) and loss of tissue and left humerus proximal resorption of bone. MRI on bilateral humerus (Fig. 2) also showed complete bone resorption of left humerus head and neck and scapula's glenoid process and partial bone resorption of right humerus. Bilateral shoulder muscles widespread lipoid atrophy was seen. Her blood chemistry, parathyroid and thyroid hormone levels, serum immunoglobulins, complement levels, and tumor markers were all normal (Table 1). She had iron deficiency anemia and mild leukocytosis. Sedimentation rate was high and also she had anti nuclear anticor (ANA) positivity (1/320 titer). Lupus anticoagulants and hereditary thrombophilia tests were negative except for PAI heterozygosity (Table 2). Her Schirmer test was negative and salivary gland biopsy was normal. Her upper and lower endoscopy was normal except for gastritis.

Thorax CT showed thrombus in right subclavian artery and aorta and third costa focal bone destruction with normal pulmonary parenchyma. Abdominal CT angiography showed thrombus in left common iliac artery, mesenteric vasculitis, ileal wall thickness and partial intestinal obstruction. To exclude hematologic malignancy bone marrow aspiration and biopsy were performed. It was negative for malignancy and dysplasia.

She underwent humerus biopsy and culture. Her biopsy was reported nonspecific minimal chronic inflammatory process. Tissue tuberculosis and aerobe culture were both negative.

We started 1 mg/kg/day metilprednizolone as a treatment of vasculitis. After one month follow-up she had no abdominal pain and her acute phase reactants were normal. The second month of discharge she admitted to emergency department with acute abdominal pain and diffuse abdominal defence and rebound. Her abdominal CT showed intestinal perforation. After surgery she died because of septic shock.

3. Discussion

GSD is a rare condition that is characterized by loss of bone matrix, which is replaced by fibrotic tissue and proliferation of vascular and lymphatic canals. There is no association between GSD and vasculitis and thrombosis in the literature. We can also not explain the bone findings of our patient with vasculitis. Patient's X-ray and MRI findings are appropriate with GSD but lymphatic malformation and nonmalignant hyperproliferation of small vessels have not seen in bone biopsy taken from the patient. Presence of multiple thrombosis, mesenteric vasculitis and ANA positivity was considered systemic lupus erythematosus (SLE) but not enough to diagnose SLE to Systemic Lupus International collaborating clinics classification criteria for systemic lupus erythematosus.[8] In SLE, lupus vasculopathy is found in up to 40% patient especially woman and typically characterized by inflammation and necrosis in the vessel wall.[9] It is known that cytokines such as TNFα, IL-1 and complement system activation are responsible for inflammation and necrosis in the vessel wall.[10] Also TNFα, IL-1β and IL-6 stimulate osteoclast formation with osteolysis and the other way is TNFα inhibits osteoblast activation and new bone formation at GSD.[2,3] Experimental animal models showed that, TNFα infusion was rapidly followed by thrombin generation and the study with the colorectal cancer patients also showed association between TNFα levels and venous thromboembolism risk.[11] Chronic inflammation or

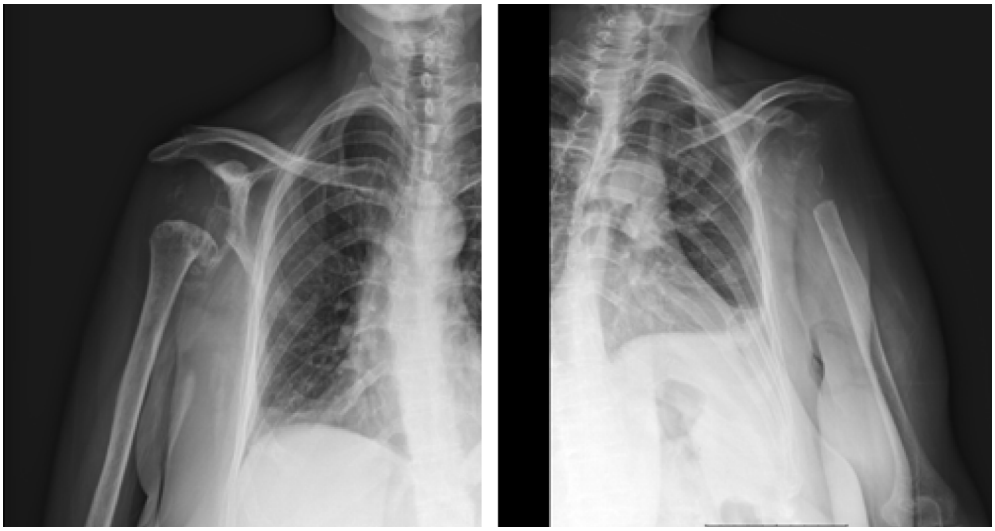

Figure 1 Bilateral humerus X-ray. X-ray showed that right humerus radiolucent foci(osteolytic lesions) and loss of tissue and left humerus proximal resorption of bone.

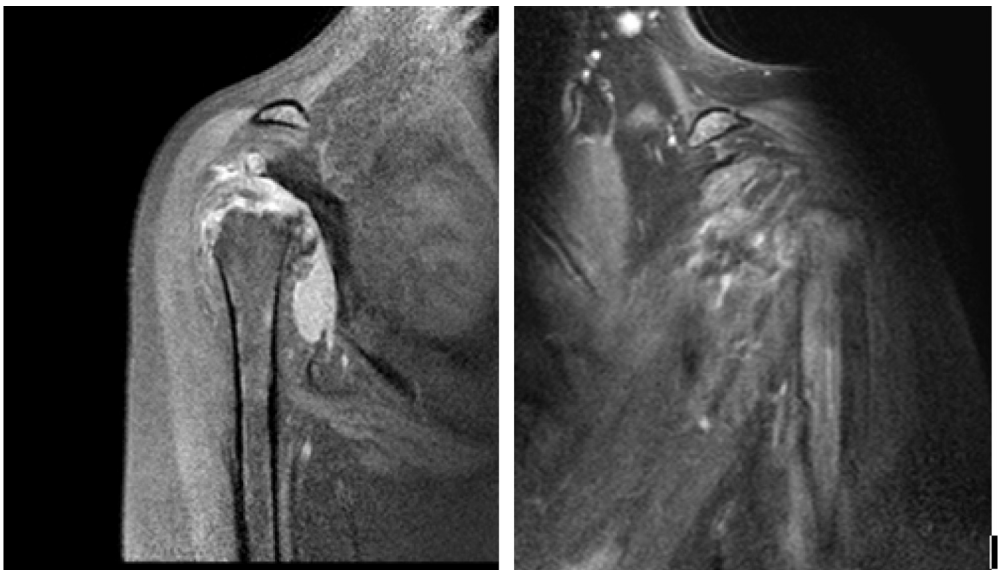

Figure 2 Bilateral humerus MRI of patients. MRI showed complete bone resorption of left humerus head and neck and scapula's glenoid process and partial bone resorption of right humerus. Bilateral shoulder muscles widespread lipoid atrophy was seen.

Table 1 Laboratory tests.

	Results	Normal range
ALT[a]	7 μ/L	< 33
AST[a]	13 μ/L	< 31
GGT[a]	24 μ/L	< 36
ALP[a]	76 μ/L	< 104
T. Bilirubin	0.4 mg/dl	0.1–1.2
Albumin[a]	3.24 g/dl	3.4–4.8
Creatinine	0.52 mg/dl	0.5–0.9
CK[a]	141 μ/L	26–192
LDH[a]	175 μ/L	240–480
TSH[a]	1.7 μIU/L	0.27–4.2
Hemoglobin	10.4 g/dl	11.7–15.5
MCV[a]	89.7 fl	80–95
Leukocyte	14×10^3 μL	$4–11.2 \times 10^3$
Neutrophil	12.9×10^3 μL	$1.8–6.4 \times 10^3$
Thrombocyte	352×10^3 μL	$159–388 \times 10^3$
Sedimentation	66 mm/h	0–25
Ca 125[a]	4.5	0–35 U/ml
Ca 19-9[a]	32.5	0–35 U/ml
Ca 15-3[a]	6.1	0–31.3 U/ml
CEA[a]	1.37	0–3 ng/mL

[a] ALT: Alanine transaminase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; CK: Creatine kinase; LDH: Lactate dehydrogenase; TSH: Thyroid stimulating hormone; MCV: Mean corpuscular volume; Ca: carbohydrate antigen; CEA: Carcinoembryonic antigen.

Table 2 Immunologic tests.

	Results	Normal range
C-rp[a]	2.18	0–1 mg/dl
ANA[a]	1/320	Negative
Anti ds-DNA	Negative	Negative
ENA-SsA[a]	Positive	Negative
ENA-SsB	Negative	Negative
ENA-Jo1	Negative	Negative
ENA-Scl70	Negative	Negative
Anti phospholipid IgM	Negative	Negative
Anti phospholipid IgG	Negative	Negative
Beta-2 glycoprotein IgM	Negative	Negative
Beta-2 glycoprotein IgG	Negative	Negative
Anti cardiolipin Antibody IgM	Negative	Negative
Anti cardiolipin Antibody IgG	Negative	Negative
ANCA profile[a]	Negative	Negative
Anti HBc total	Negative	Negative
Anti HBs	14n IU/ml	0–10
Anti HCV	Negative	Negative
TPHA[a]	Negative	Negative
Brucella agglutination	Negative	Negative
C3[a]	128 mg/dl	79–152
C4[a]	25 mg/dl	16–38
IgA	361	82–453 mg/dl
IgG	1170	751–1560 mg/dl
IgM	64	46–304 mg/dl

[a] CRP: C-reactive protein; RF: Rheumatoid factor; ANA: Anti nuclear anticor; C3: Complement 3; C4: Complement 4; ENA: extractable nuclear antigens; ANCA: antineutrophil cytoplasmic antibodies; TPHA: *Treponema pallidum* hemagglutination assay.

autoinflammatory diseases are also possible cause of thrombosis.[12]

In a study conducted by Franchi et al. to find a diagnostic marker for GSD, CD105 expression was found to be significantly higher in GSD vessels compared to control group.[13] Similarly, CD105 (endoglin) expression was significantly higher in systemic vasculitis and the expression of it correlates with disease activity.[14–16]

As a major molecule in angiogenesis, VEGF also contributes to the regulation of the immune system.[17] Significantly increased levels of VEGF were demonstrated in activation of vasculitis as well as in GSD.[2,3,18]

4. Conclusion

TNFα, IL-1β, IL-6, VEGF and CD105 have pathophysiological role both in the vasculitis and in the GSD. This common pathway increases the risk of coexistence of both diseases. Thrombosis may be the result of direct effect of cytokines such as TNFα or chronic inflammation or autoinflammation. To our knowledge this report is the first combination of GSD, arterial thrombosis and vasculitis in the literature. Perhaps it is a new entity on the basis of vasculopathy including vasculitis, thrombosis and GSD like disease.

5. Conflict of interest

The authors declare that there is no conflict of interest.

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