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CASE REPORT

Acral gangrene as a presentation of non-uremic calciphylaxis

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ABSTRACT

We are describing a case of 55-year-old obese female with significant history of uncontrolled rheumatoid arthritis, who recently had decreased her immune-suppression medications. She presented with extensive acral gangrene involving multiple fingers and toes. Clinical picture and laboratory findings were suggestive of vasculitis; however, skin biopsy established diagnosis of calciphylaxis, in settings of normal kidney function. Patient was treated with sodium thiosulfate with gradual improvement in her skin lesions.

Key words: Acral gangrene, calciphylaxis, non uremic, sodium thiosulfate, vasculitis

CLINICAL PRESENTATION

A 55-year-old, morbidly-obese Caucasian woman with a history of severe rheumatoid arthritis (RA) presented with a 3-week history of painful, black lesions on the tips of fingers and toes.

The patient's medical course during the preceding six months had been extensive. She first developed a severe abdominal wall infection, which necessitated stopping her disease-modifying anti-rheumatic drug and biological agent (methotrexate and etanercept). Two months later, she was diagnosed with mononeuritis multiplex with right wrist drop attributed to rheumatoid vasculitis. The patient then suffered a left MCA territory ischemic stroke, from which she was recovering at the time of her presentation. Physical exam was remarkable for dry gangrene of multiple fingertips, toes, and the left forefoot with complete anesthesia of the gangrenous areas [Figure 1]. All peripheral pulses were palpable.

The acral distribution of the lesions suggested an arterial etiology-either embolic or secondary to vasculitis, especially considering her history of RA and the recent discontinuation of immunosuppressive medications. Initial work-up revealed an elevated Rheumatoid-Factor, CRP, ESR, and antibodies against cyclic-citrullinated-peptide [Table 1]. Arterial pulse volume recordings were normal, and a transesophageal-echocardiogram revealed no potential source of emboli. Pending biopsy results, patient was started on high-dose methylprednisolone and received a single dose of rituximab for a presumptive diagnosis of rheumatoid vasculitis. Three days later, the skin biopsy results showed significant calcium deposits in the media of the subcutaneous arterioles, confirming the diagnosis of calciphylaxis with no evidence of vasculitis. Interestingly, our patient had normal renal function and calcium-phosphorus product. She was started on treatment with sodium-thiosulfate with noted improvement of necrotic skin lesions.

DISCUSSION

Calciphylaxis is a rare disorder that primarily affects patients with ESRD.[1-3] A few cases of non-uremic calciphylaxis (NUC) have been reported[4-6] and have been attributed to diverse etiologies such as hyperparathyroidism, malignancies,[5] connective tissue disease,[7-10] warfarin-induced protein C and S deficiency,[11] chronic steroid use, and rapid weight loss.[4] The pathogenesis of NUC is not completely known, but disruption in the calcium-phosphate-byproduct has been implicated. Patients with disturbances in calcium and vitamin D metabolism such as hyperparathyroidism[12]

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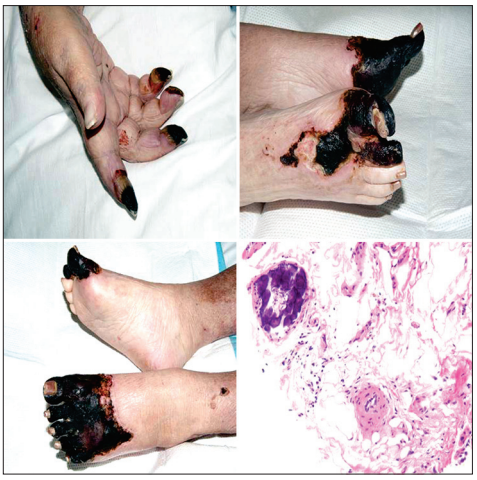

Figure 1: Dry gangrene secondary to non-uremic calciphylaxis involving finger and toe tips. Skin biopsy showing focal calcium deposit within a subcutaneous blood vessel with absence of vasculitis

or lymphoma can be affected by NUC.[4] A recent study suggested that calcium deposits in the arterial media in calciphylaxis are caused by dysregulation of the factors that regulate calcium deposition and removal from arterial walls.[13] These deposits cause vascular occlusion leading to ischemic necrosis of the skin and subcutaneous tissue.[4,14] Intractable lower extremity pain and cutaneous ulcers are the most common presentations, but indurated nodules, violaceous skin lesions, and livedo-reticularis may also occur. Extra-cutaneous manifestations of calciphylaxis include myopathy, cardiomyopathy, and mesenteric ischemia.[4] A skin biopsy is essential for diagnosis, especially in patients with normal kidney function. NUC usually has poor prognosis with mortality up to 50%, mostly secondary to sepsis.[4,15] Medical treatment aims to normalize mineral metabolism to reduce the serum concentration of calcium-phosphate-byproduct and thus prevent precipitation and calcification. Bisphosphonates, phosphate-binders, cinacalcet, and sodium-thiosulfate have been used with variable success.[6,16]

Several cases of NUC in settings of connective tissue disease have been reported.[7-10] Chronic immune suppressive therapy, rather than underlying skin injury because of vasculitis, was found to be the most important trigger of calcium deposition in these patients.[7-10] Obtaining skin biopsy, in our patient before starting immune-suppressive medications, makes the possibility of calcium deposition in setting of resolving vasculitis to be less likely.

Calciphylaxis presenting with dry gangrene of multiple fingers and toes is exceedingly rare, and to our knowledge, has not been reported in the literature. Our patient's presentation with acral lesions, high inflammatory and rheumatoid markers, and recent discontinuation of immuno-modulatory therapy all suggested a vasculitic disorder but was not consistent with the skin biopsy. While our patient did not have renal impairment, or an elevated calcium phosphate product, her longstanding rheumatoid arthritis, chronic glucocorticoid therapy, obesity, and rapid

Table 1: Admission laboratory results

Component	Reference range	Lab value
Rheumatology panel		
ANA	<1.5 OD Ratio	9.1
Rheumatoid factor	<20 IU/mL	1749
CCP Antibody, IgG	<20 Units	>250
Cryoglobulin quant, blood	0-50 ug/mL	39
Sm antibody	<1.0 AI	<0.2
RNP antibody	<1.0 AI	0.2
SSA antibody	<1.0 AI	<0.2
SSB antibody	<1.0 AI	<0.2
Centromere Ab	<1.0 AI	<0.2
Scleroderma Ab, IgG	<1.0 AI	0.2
Jo 1 antibody	<1.0 AI	<0.2
Ribosomal RNP	<1.0 AI	<0.2
Chromatin antibody	<1.0 AI	0.9
MPA IgG, serum	717-1411 mg/dL	2720
MPA IgA, serum	78-391 mg/dL	775
MPA IgM, serum	53-334 mg/dL	513
Inflammatory markers		
WSR	0-15 mm/hr	57
CRP	0.0-1.0 mg/dL	8.5
Ferritin	18.0-300.0 ng/mL	605.5
LD	100-220 U/L	208
CK	30-220 U/L	17
C3	68-260 mg/dL	87
C4	12-46 mg/dL	16
Hypercoagulable panel		
Cardiolipin Ab, IgG	0-9 GPL	13
Cardiolipin Ab, IgM	0-11 MPL	<9
Cardiolipin Ab, IgA	0-11 APL	<9
PT Sec	8.4-13.0 sec	11.2
PT INR	0.8-1.2	1
APTT	23.0-32.4 sec	24
Protein C fun	76-147%	125
Protein S clottable	59-131%	66
Anti-thrombin assay	84-138%	87
Infectious work up		
WBC	3.70-11.00 k/uL	5.25
HIV Ab	Non-reactive	Non-reactive
HCV Ab	Non-reactive	Non-reactive
HBsAg	Non-reactive	Non-reactive
HBcAb	Non-reactive	Non-reactive
Blood culture		Negative
CMP		
Protein, Total	6.0-8.4 g/dL	7.3
Albumin	3.5-5.0 g/dL	2.0 (L)
Phosphorus	2.5-4.5 mg/dL	3.4
Calcium	8.5-10.5 mg/dL	8.2
Bilirubin, Total	0.0-1.5 mg/dL	0.1
Alkaline phosphatase	40-150 U/L	102
Creatinine	0.70-1.40 mg/dL	0.41

ANA: Antinuclear antibody, CCP: Cyclic citrullinated peptide, RNP: Ribonucleotide protein, MPA: Myeloperoxidase antibodies, CRP: C-reactive protein, LD: Lactate dehydrogenase, PT: Prothrombin time, APTT: Activated partial thromboplastin time, WBC: White blood cells, HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, CMP: Comprehensive metabolic panel, HBsAg: Hepatitis B surface antigen, HBcAb: Hepatitis B core antibody

weight loss are risk factors that may have predisposed her to develop calciphylaxis.[13]

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