



# Widespread cutaneous and visceral calcification

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It is an honor to comment on the report of multiple calcifications in the skin and viscera by Li *et al.* The authors present unique findings in a 39-year-old man with an 8 year history of abdominal pain, leukopenia, thrombocytopenia, and widespread calcifications in skin and viscera associated with a missense mutation in the Wiskott-Aldrich syndrome (WAS) gene: NM-000377; exon9: p.I294T, c. T881C, a mutation associated with congenital neutropenia and thrombocytopenia. The patient tested positive for Jo-1 and ANCA and large vessel vasculitis, although specific details of the type of vessel and infiltrate are not specified. Panniculitis was seen in the skin, viscera, and mesentery of this patient and no obvious abnormality was noted in the pancreas. Panniculitis is typically divided into lobular and septal forms. The most common form of septal panniculitis is erythema nodosum, while lobular panniculitis can occur with infection, connective tissue disease, polyarteritis nodosa,  $\alpha$ 1-antitrypsin deficiency or as an id reaction to tuberculosis (Tb). The associated leukopenia and thrombocytopenia in the current patient are related to the WAS gene mutation which may also predispose to a variety of infections. The positive Jo-1 and ANCA antibodies raise the possibility of associated dermatomyositis or polyarteritis nodosa. Full evaluation of such a patient should include tissue culture, deep incisional biopsy, full connective tissue serological evaluation, gamma-release assay for Tb, and careful examination for associated renal or pulmonary disease as well as the possibility of underlying malignancy. In regard to the vasculitis, the type of vessel and inflammatory infiltrate should be specified. Arterioles are characterized by a concentric wreath-like muscularis and thick internal elastic membrane, whereas veins have a muscularis composed of small bundles of smooth muscle surrounded by fine

elastic fibers (1). Arteritis is characteristic of polyarteritis nodosa, smaller arteriolar vasculitis may be seen in Tb-associated erythema induratum and thrombophlebitis may be associated with underlying malignancy or deep venous thrombosis. Erythema induratum often demonstrates granulomatous foci as well as caseous necrosis. Suppurative and granulomatous panniculitis may be seen with infection or connective tissue disease and the presence of neutrophils within panniculitis should prompt investigation for infection as well as  $\alpha$ 1-antitrypsin deficiency. Lupus profundus presents with fibrinous necrosis of the panniculus, lipomembranous change and nodular lymphoplasmacytic infiltrates. Calciphylaxis is a unique form of calcifying panniculitis often associated with diabetes mellitus and end stage renal disease. It involves calcification and thrombosis of small capillary-sized as well as larger vessels in the fat and other organs and responds to treatment with sodium thiosulfate and thrombolytic therapy (2,3).

The widespread calcifications associated with the WAS gene are a unique manifestation in this patient and deserve comment. Calcification in the setting of pancreatic panniculitis appears as saponification of necrotic lipocytes leading to slightly basophilic ghost cells. Arteriolar calcification is a manifestation of atherosclerotic disease, whereas capillary calcification is typical of calciphylaxis. This patient presented with widespread cutaneous and visceral calcification with features of tumoral calcinosis.

Visceral calcification has also been noted in familial tumoral calcinosis associated with homozygous missense mutation in FGF23 (4). This form of familial tumoral calcinosis, termed Hyperphosphatemic Familial Tumoral Calcinosis (HFTC; MIM211900), is a rare autosomal recessive disorder with progressive calcified masses in

cutaneous and subcutaneous tissues, and elevated circulating levels of phosphate. The disease is more commonly related to mutations in GALNT3 encoding a glycosyltransferase. More recently, missense mutations in FGF23, encoding a potent phosphaturic protein, have been reported as a cause. Management includes lowering of phosphate concentration and surgical debulking of calcifications. Associated inflammatory flares can respond to anti-interleukin-1 therapy, including anakinra and canakinumab, but this may not prevent extension of calcinosis (5).

A systematic review of studies published in MEDLINE, Embase, and the Cochrane library between 1980 and July 2018, found 30 comparable studies that addressed treatment of calcinosis cutis. Several studies suggested the use of diltiazem and bisphosphonates (Level IV evidence). Rituximab has shown potential in both dermatomyositis and scleroderma patients and tumor necrosis factor alpha inhibitors may be useful in juvenile dermatomyositis (Level IV). Intralesional sodium thiosulfate is promising in all forms of calcinosis cutis (Level IV). In contrast, one small randomized controlled trial and 4 retrospective studies suggest that low-dose warfarin should NOT be used for calcinosis cutis (Level IB evidence) (6,7).

A review of patients treated with topical sodium thiosulfate for calcinosis cutis associated with underlying autoimmune connective tissue diseases at the Mayo Clinic suggested that the majority had clinical improvement (8). Apremilast has also been described as adjuvant therapy (9). Calcinosis cutis has been reported in the setting of multiple sclerosis on chronic dexamethasone and concurrent supplementation of calcium and daily cholecalciferol to prevent corticosteroid-induced osteoporosis, and normocalcaemia was restored with the use of denosumab, an agent usually reserved for hypercalcaemia of malignancy and intractable osteoporosis (10).

Li *et al.* remind us that cutaneous calcification may be associated with severe systemic disease. In their patient, abdominal pain, leukopenia, thrombocytopenia, and widespread calcifications in skin and viscera were associated with a missense mutation in the WAS gene. Clinicians should pay careful attention to the constellation of systemic manifestations in patients with calcinosis cutis in order to diagnose associated disease and provide effective management.

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