

Case Report

Medical mystery: Deposition of calcium oxalate and phosphate stones in soft tissues

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Abstract

Calcinosis cutis (CC) [1] is an unusual disorder characterized by calcium-phosphate deposition into cutaneous and subcutaneous tissues. There are five subtypes: dystrophic, metastatic, idiopathic, iatrogenic and calciphylaxis.

Calciphylaxis or calcifying panniculitis is defined as small vessel calcification mainly affecting blood vessels of the dermis and subcutaneous fat. Despite the predominance of cases in patients with ESRD, calciphylaxis can also be found in patients with normal renal function and normal levels of calcium and phosphate. These cases are often referred to as nonuremic calciphylaxis (NUC), a heterogeneous category with several associations. Literature reveals an association with hyperparathyroidism (28%), malignancy (22%), alcoholic liver disease (17%) and connective tissue diseases (11%) while obesity, liver disease, high-serum calcium (Ca) × phosphorus (P) levels, combined therapies of calcium salts with vitamin D, warfarin and corticosteroids have been observed to increase the likelihood of this disease [2]. The lesions in both nonuremic and uremic calciphylaxis tend to be indistinguishable from each other, initially presenting as tender subcutaneous plaques that progress into nonhealing ulcers with overlying black eschar. Skin changes often begin with a livedo reticularis pattern that can progress to livedo racemes and ultimately retiform purpura.

In our clinical case, we describe a patient with multiple risk factors for calciphylaxis, intense widespread calcification (vessels, tendons, joints) and cutaneous calcific stone of calcium and phosphate oxalate not elsewhere described before.

Case report

We report the case of a 60 years-old woman with a two years history of several painful ulcerations of the lower limbs.

Medical history

Chronic renal failure since a young age from suspected vitamin D intoxication; no renal histological examination. Cesarean section in 1991. In 1998 start of hemodialysis for 14 months until cadaveric renal transplantation occurred in 1999. A few months after transplantation rupture of the Achilles tendon. 2001 bilateral cataract surgery. In 2010 Non-Hodgkin's lymphoma involving the uterine cervix was treated with chemotherapy (CHOP - cyclophosphamide, doxorubicin, vincristine and prednisone), plus radiotherapy in remission after 1 year. Our patient also suffered from

colon diverticulosis, severe osteoporosis, and widespread chondrocalcinosis. No history of kidney stones.

Her clinical history began in July 2013 when she developed a small ulcer (history of trauma) on the outer malleolus's right leg. After six months occurrence of spontaneous ulcer on the right leg below the knee. The patient, following the finding of critical ischemia in the arteries of the right lower limb and the positivity of the skin ulcer swab for *Pseudomonas aeruginosa*, was admitted to the hospital to undertake targeted antibiotic therapy (meropenem) and underwent peripheral angiography and angioplasty: "sub-occlusive calcific stenosis in series of right superficial femoral artery; mid-distal occlusion of the superficial femoral artery and right deep femoral artery. Effective balloon PTA on the right superficial femoral artery".

More Information

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In July 2014 she underwent four sessions of hyperbaric oxygen therapy chamber (HBO₂) suspended due to worsening ulcers. Numerous infected lesions extended on the dorsum of the foot, with exposure of all the extensor tendons, the external malleolus with exposure of the tibialis anterior tendon, and another ulcer on the heel (Figure 1).

In November 2014 a new angioplasty was performed with the improvement of clinical conditions. December 2014 - Vacuum-assisted closure (VAC) therapy with poor results and necrosis of the extensor tendons of the back of the foot.

In November 2015 patient underwent the first homologous skin transplant on the right leg completed six months later, with significant improvement of the lesions (ulcer on the heel and external malleolus closed).

January 2016 - Appearance of localized swelling at the knee of the left leg. These lesions later turned into infected ulcers (more than ten) from which purulent exudate and granular millimetric stones came out (Figure 2). Stone's chemical analysis revealed: 90% calcium oxalate, and 10% phosphates (Figure 3).



Figure 1: Cutaneous lesions extended on the dorsum of the foot, with exposure of all the extensor tendons, the external malleolus with exposure of the tibialis anterior tendon, and another ulcer on the heel.



Figure 2: Infected ulcers (approx. 10) of the left leg from which purulent exudate and granular millimetric stones came out.

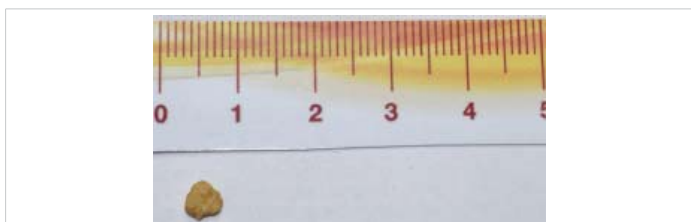


Figure 3: Cutaneous stone. Chemical analysis of stone revealed: 90% calcium oxalate, and 10% phosphates.

Laboratory findings

Erythrocytes (RBC) 3.65x10⁹/L, hemoglobin 110 g/L (r.v. RBC 3.80-5.00x10⁹/L, Hgb 120-160g/L). White blood cell (WBC) count 17.31x10⁹/L(differential count: 91% neutrophils, 3% lymphocytes, 2% monocytes) Platelet count 209x10⁹/L (r.v. PLT 150-400x10⁹/L),C-reactive protein (CRP) 7.98 mg/L (r.v.0-5 mg/l)Urea nitrogen 23.4 mg/dl, serum creatinine 0.9 mg/dl Acid-base status pH 7.48, pCO₂ 6.9 kPa, HCO₃ 24 mmol/L, base excess 0 mmol/L, pO₂ 6.8 kPa, sO₂ 96%.Serum calcium 8,5 mg/dl, serum phosphorus 2,5(mg/dl) Serum PTH 56 pg/ml, , Anti-ARS antibodies (aminoacyl-tRNA synthetizes), Anti-Jo-1 antibodies, Anti-PL-7 anti-bodies, Anti-PL-12 antibodies, ANA, anti-dsDNA antibodies resulted negative. No signs of lymphoma recurrence. Home therapy consisted of Cyclosporine 50+25 mg, methylprednisolone 8 mg, Lansoprazole 15 mg, Enalapril 5 mg, acetyl salicylic acid 100 mg, B-vitamin complex, Beta-erythropoietin 5000 twice a week, opioid patch for pain.

Radiological finding

CT left leg and knee: Examination of the left lower limb from the distal third of the femur to the tibiotarsal joint. Numerous calcifications of apparent vascular relevance as well as extensive calcific plaques draw the femoral-popliteal and tibio-peroneal arterial vascular axis. Calcific enthesopathy of the quadriceps and patellar tendons. Calcific enthesopathy of the significantly and diffusely thickened Achilles tendon.

Antibiotic therapy and local medication progressively lead to improvement of the clinical picture with complete healing of the skin lesions (Figures 4,5).



Figure 4: Complete healing of the skin lesions.



Figure 5: CT Left leg and knee: Numerous calcifications of apparent vascular relevance as well as extensive calcific plaques drawing the femoral-popliteal and tibio-peroneal arterial vascular axis (a). White arrow indicates subcutaneous stone (b).



Discussion

Calciphylaxis was first described by Selye, et al. [3] in 1961 as a systemic hypersensitivity reaction. In animal experiments, they induced calcification of various organs after animals had been exposed to one of several sensitizing agents referred to as “calcifiers” (e.g., dihydrotachysterol, vitamin D2, vitamin D3, parathyroid hormone), followed by exposure to a “challenger” (e.g., metallic salts such as iron and aluminum, egg albumin, trauma). A few years after Selye, et al. coined the term, calciphylaxis was reported in humans as a syndrome primarily seen in uremic patients characterized histopathologically by small vessel mural calcification, extravascular calcification and thrombosis leading to ischemia with skin and soft tissue necrosis and high mortality.

Kidney transplantation should theoretically improve or treat ulcers in patients with renal disease as the new kidney acts to restore the mineral balance [4], however, cases such as this one exist in which calciphylaxis arises after kidney transplant. This case is unique in the presentation with stones, more than ten, with calcium oxalate and phosphate stones arising from multiple perforating lesions of the lower limbs. Our patient had several causes for dystrophic calcifications: suspected juvenile vitamin D intoxication, history of chronic kidney disease and hemodialysis, severe vascular calcification, lymphoma, and kidney transplant. One potential link between transplantation and calciphylaxis could be the use of systemic corticosteroids. Corticosteroid use is reported as a predisposing factor in 61% and 80% [5] of patients with nonuremic calciphylaxis.

Derangements of receptor activator of NF- κ B (RANK), RANK ligand, and osteoprotegerin may also be involved in the pathogenesis of calcific uremic arteriolopathy (CUA) because they are involved in the regulation of extraskeletal mineralization [6]. Some of the factors that predispose to NUC (parathyroid hormone, corticosteroids, and liver disease) are known to increase the expression of RANK ligand and decrease the expression of osteoprotegerin, thus activating NF- κ B or degrading the inhibitory protein of NF- κ B (or a combination of these) [7].

One should also evaluate to rule out collagen vascular disease, as dystrophic CC is caused usually by connective tissue disease. Calcinosis is sometimes present in dermatomyositis, and scleroderma and even it can be seen in lupus erythematosus. [8] In our case markers of dermatomyositis, scleroderma, and lupus erythematosus were negative.

Possibly oxalosis was excluded because of negative history of kidney stones [9-11].

A peculiarity found in our patient was the presence of calcium oxalate and phosphate stones (more than 10) within skin lesions: an abnormal and not elsewhere described form of cutaneous stones calciphylaxis.

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