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Case Report

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Medical mystery. Deposition of calcium oxalate and phosphate stones in soft tissues: A case of cutaneous stone calciphylaxis?

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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 pannucilitis is defined as small vessel calcification mainly affecting blood vessels of dermis and sub-cutaneous 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 reveal 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 racemosa, and ultimately retiform purpura.

In our clinical case we describe about a patient with multiple risk factors for calciphylaxis, intense widespread calcification (vessels, tendons, joints) and with 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 lower limbs.

Medical history

Chronic renal failure since young age from suspected vitamin D intoxication; no renal histological examination. Caesarean section in 1991. In 1998 start of haemodialysis for 14 months until cadaveric renal transplantation occurred in 1999. A few months after transplantation rupture of Achilles tendon. 2001 bilateral cataract surgery. In 2010 Non-Hodgkin's lymphoma interesting uterine cervix 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.

The beginning of clinical history we are going to describe was July 2013: Patient developed a small ulcer (history of trauma) on outer malleolus right leg. After six months occurrence of spontaneous ulcer on right leg below the knee. The patient, following the finding at the angiology assessment of critical ischaemia in the arteries of the right lower limb and the positivity of the skin ulcer swab for Psudomonas aeruginosa, was admitted to hospital to undertake targeted antibiotic therapy (meropenem) and underwent peripheral angiography and angioplasty: "subocclusive calcific stenosis in series of right superficial femoral artery; mid-distal occlusion of superficial femoral artery and right deep femoral artery. Effective balloon PTA on the right superficial femoral artery".

In July 2014 she underwent four sessions of hyperbaric oxygen therapy chamber (HBO_2) suspended due to worsening of 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 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. This lesions later turned into infected ulcers (more then ten) from which purulent exudate and granular millimetric stones came out (Figure 2). Stone's chemical analysis revealed: 90% calcium oxalate, 10% phosphates (Figure 3).

Laboratory findings

Erythrocytes (RBC) 3.65 x 10^9/L, hemoglobin 110 g/L (r.v. RBC 3.80-5.00 x 10^9/L, Hgb 120-160 g/L). White blood cell (WBC) count 17.31 x 10^9/L(differential count: 91% neutrophils, 3% lymphocytes, 2% monocytes) Platelet count 209 x 10^9/L (r.v. PLT 150-400 x 10^9/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, pCO_2 6.9 kPa, HCO_3 24 mmol/L, base excess 0 mmol/L, pO_2 6.8 kPa, SO_2 96%. Serum calcium 8,5 mg/dl, serum phosphorus 2,5 (mg/dl) Serum PTH 56 pg/ml, Anti-ARS antibodies (aminoacyl-tRNA synthetases), Anti-Jo-1 antibodies, Anti-PL-7 antibodies, Anti-PL-12 antibodies, ANA, anti-dsDNA antibodies resulted negative. No signs of lymphoma's recurrence.

Home therapy

Cyclosporine 50+25 mg, methylprednisolone 8 mg, Lansoprazole 15 mg, Enalapril 5 mg, acetil salicylic acid 100 mg, B-vitamin complex, Beta-erythropoietin 5000 twice a week, opioid patch for pain.

Radiological finding

CT LEFT LEG CT LEFT KNEE: Examination of the left lower limb from the distal third of the femur to the tibio-tarsal joint. Numerous calcifications of apparent vascular relevance as well as extensive calcific plaques drawing 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.

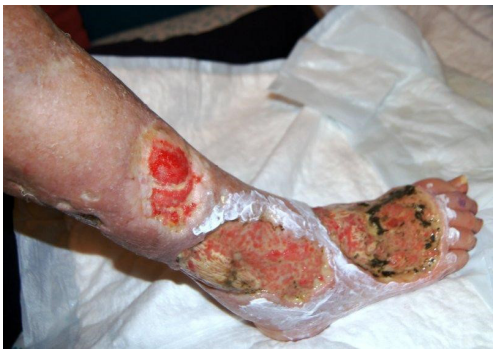

Figure 1: Cutaneous lesions extended on the dorsum of the foot, with exposure of all the extensor tendons, the external malleolus with exposure of the tibialis anterior tendon and another ulcer on the heel.

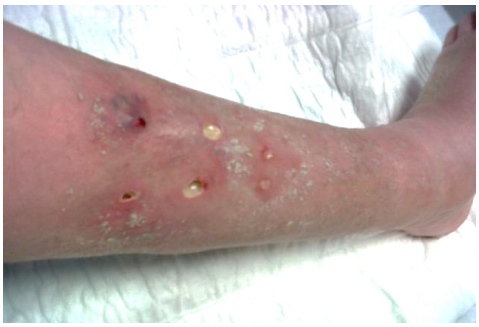

Figure 2: Infected ulcers (approx. 10) of the left leg from which purulent exudate and granular millimetric stones came out.

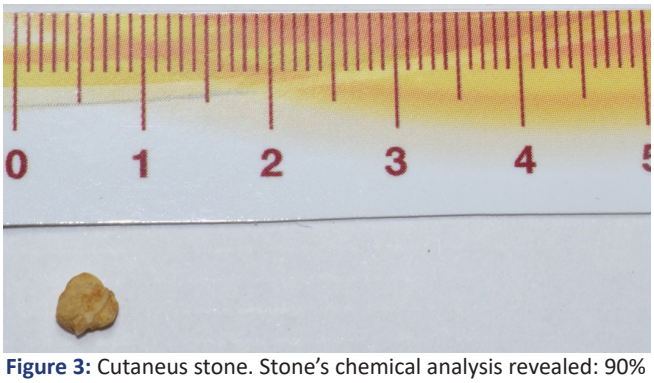

Figure 3: Cutaneus stone. Stone's chemical analysis revealed: 90% calcium oxalate, 10% phosphates (figure 3).

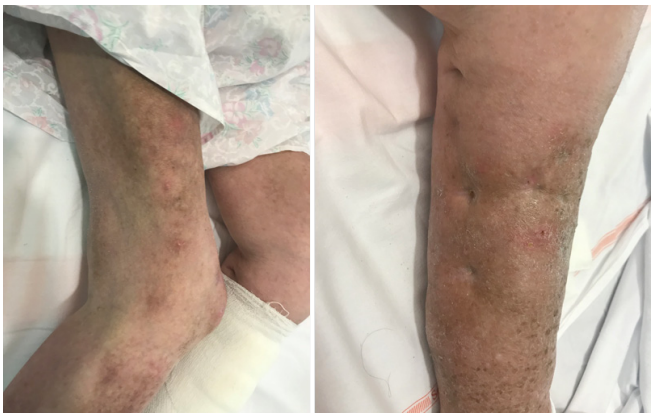

Figure 4: Complete healing of the skin lesions.

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, kidney transplant. One potential link between transplantation and calciphylaxis could be the use of systemic corticosteroids. Two articles found that corticosteroid use was present as a predisposing factor in 61% [5] and 80% [6] of patients with nonuremic calciphylaxis.

Derangements of receptor activator of NF-B (RANK), RANK ligand, and osteoprotegerin may also be involved in the pathogenesis of CUA because this system is involved in regulation of extraskeletal mineralization [7]. 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-B or degrading the inhibitory protein of NF-B (or a combination of these) [8].

One should also work-up to rule out collagen vascular disease, as dystrophic CC is caused usually by connective tissue disease. Calcinosis is sometimes present in dermatomyositis, scleroderma and even it can be seen in lupus erythematosus [9]. In our case markers of dermatomyositis, scleroderma and lupus erythematosus were negative. Possibly oxalosis was excluded because of negative history of kidney stones [10].

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.

Disclosures

Conflict of interest: The author declares no conflict of interest.

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