

Case report

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Calciophylaxis in chronic, non-dialysis-dependent renal disease

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Abstract

Background: Calciophylaxis cutis is characterized by media calcification of arteries and, most prominently, of cutaneous and subcutaneous arterioles occurring in renal insufficiency patients.

Case Report: A 53-year-old woman with chronic cardiac and renal failure complained of painful crural, non-varicosis ulcers. She was hospitalized in an immobilized condition due to both the crural ulcerations and the existing heart-failure state (NYHA III-IV) having pleural and pericardial effusions, atrial fibrillation and weight loss of 30 kg over the past year. Despite normalization of calcium-phosphorus balance and improvement of renal function, the clinical course of crural ulcerations deteriorated during the following 3 months. After failure of surgical debridements, multiple courses of sterile-maggot therapy were introduced at a late stage to stabilize the wounds. The patient died of recurrent wound infections and sepsis paralleled by exacerbations of renal malfunction.

Conclusions: The role of renal disease in vascular complications is discussed. Sterile-maggot debridement may constitute a therapy for the ulcerated calciophylaxis at an earlier stage, i.e. when first ulcerations appear.

Background

Calciophylaxis cutis is characterized by media calcification of arteries and, most prominently, of cutaneous and subcutaneous arterioles [1], as well as by intimal proliferation and fibrosis [2]. The pathogenesis of Calciophylaxis remains unclear as it differs from intima-based common atherosclerosis and extravascular calcium-phosphate deposits in organs such as the skin in Calcinosis cutis are not involved. However, it appears to be associated with an elevated serum calcium or phosphate concentration elicited either by hyperparathyroidism or by vitamin-D intake. Female gender appears to be a risk factor. Although singular cases associated with non-renal diseases including inflammatory bowel disease, cancer, and primary

hyperparathyroidism were reported [2], Calciophylaxis cutis mainly occurs in end-stage renal insufficiency, almost exclusively in patients undergoing kidney-replacement therapy [2–4]. The prognosis in Calciophylaxis patients is dramatically poor, with up to 6 months life expectancy after appearance of ulcerations [3]. Emphasizing its difference from intima-based atherosclerosis, it is also called calcific uremic arteriolopathy [1].

Case Report

A 53-year-old woman with a body mass index of 27.5 kg/m² having chronic renal failure and chronic heart failure complained of painful crural, non-varicosis ulcers that started 8 months previously as livid palpable plaques or



Figure 1
Calciophylaxis cutis on admission. After transfer to the dermatologic department, about 1 month after first incidence of a calciophylactic ulcer of the lower right leg.

nodules within and underneath the skin, transforming into ulcers five weeks before admission and showing little sign of healing since. While a single, 2.5-cm ulcer closed, other ulcerations appeared at the right calf (Figure 1). Hence, the patient was admitted to a dermatologic department in an immobilized, weak condition having heart failure due to hypertensive and ischemic heart disease (left ventricular ejection fraction: 30 %, NYHA III-IV). Furthermore, she had a loss of appetite and lost 30 kg during the past year. Hypertension, recurrent ascendant urinary-tract infections and renal atherosclerosis were likely causes of renal failure. In addition, the patient had regularly taken analgesics. Systemic atherosclerosis was indicated by history of a myocardial infarction 5 years previously and by limitations of walking distance. In a coronary angiogram, a single-vessel coronary-artery disease was diagnosed necessitating an elective percutaneous coronary recanalization and stent deployment as well as three more percutaneous coronary interventions for repeated late in-stent restenosis during the previous 5 years. Clinical signs of the heart-failure state included both pleural and pericardial effusions, secondary mitral regurgitation due to cardiac dilation, and atrial fibrillation. The prevalent pericardial effusion was not deemed significant for cardiac filling as determined by echocardiography. Six months before admission, an Implantable Converter/Defibrillator (ICD) was inserted because of pre-syncope, non-sustained ventricular tachycardias in the Holter-ECG and a positive electrophysiological test result.

Laboratory tests revealed a normal plasma concentration of parathyroid hormone (5.02 pmol/l, normal: 1.1–6.9),

Vitamin (1,25-OH)-D3 deficiency (7.1 pg/ml, normal: 20.2–46.2), however, slightly elevated calcium (2.66 mmol/l, normal: 2.02–2.6) concentration. Potassium (4.3 mmol/l) and phosphate (1.26 mmol/l) concentrations were normal. Glomerular filtration rate estimated by MDRD equation [5] was 25.4 ml/min (creatinine: 207 μ mol/l; urea: 30.2 mmol/l; albumin: 35.1 g/l) at admission indicative for renal failure. Further, low HDL cholesterol (0.86 mmol/l, normal: >0.9), high triglycerides (3.06 mmol/l, normal: <2.3), yet a normal LDL cholesterol (3.49 mmol/l, normal: <4.2) in absence of statins to which the patient claimed to be allergic, were found. Leukocyte count and C-reactive protein were found to be elevated at least during the 12 months prior to admission, ranging from 10–15 Gpt/l (normal: 4–9) and 60–200 mg/l (normal: <5), respectively. Ferritin was in the normal range between 200 and 300 ng/ml (normal: 13–300), neither supporting an infection as an acute-phase reactant nor being the reason for the prevalent normocytic, normochromic anemia (hemoglobin 6 mmol/l, hematocrit 31%). However, an iron deficiency could have limited further rises of ferritin due to infection. The anemia was not due to erythropoietin deficiency as reticulocytes were 15 Gpt/l. Urine tests showed a microproteinuria (0.25 g/l) and leukocyturia (25/ μ l). After cessation of coumadin therapy for atrial fibrillation, the International Normalized Ratio leveled off at 1.42 (normal: 1) in presence of low-dose heparine. Liver enzymes including serum alkaline phosphatase were between 16 and 19 μ mol/l*s (normal: <4.2) and gamma-glutamyl transferase between 9 and 14 μ mol/l*s (normal: <0.6), while transaminases were within normal range. Ultrasound examination revealed small kidneys (9 cm longitudinally) with loss of clarity of architecture and multiple cysts. The renal cortex was narrowed to 7 mm, ureters were not dilated. A whole-body bone scintigraphy was negative for bone metastases or osteomyelitis. Ultrasonographic examinations of the thyroid gland were unrevealing; parathyroid bodies were not identified. The radiologic search for nonvascular soft-tissue calcifications was negative. Systemic lupus erythematosus or other types of autoimmune diseases were ruled out by negative antibody screening tests. The diagnosis Calciophylaxis cutis was established by cutaneous biopsy.

Hypercalcaemia was readily normalized by diuretic therapy with torasemide in combination with standard heart-failure therapy including aldosterone antagonist, ACE inhibitor, beta-adrenergic blockade and digitalis over a one-month period. Possible reasons for the hypercalcaemia like hyperparathyroidism or high vitamin D serum levels were ruled out, parathyroid hormone-related peptide was not determined. Glomerular filtration rate improved to 33.1 ml/min under balanced fluid-substitution. Thus, renal function in this patient was mid-



Figure 2
Calciphylaxis cutis, 2 months after admission. Large ulcerations at both lower legs with signs of superinfection.

stage impaired with potential to recover under therapy. However, fluid overload had to be avoided because of the heart-failure condition. Once electrolytes, including plasma potassium fell, an incessant ventricular tachycardia triggered the ICD. Therefore, potassium was given to obtain a high-normal plasma concentration, and an amiodarone therapy was started.

Despite wound care on a daily basis both in hospital and in ambulatory care, the cutaneous ulcers worsened. 2 months after first admission, the patient was readmitted because of exacerbated ulcers on both lower legs (Figure 2). Hydrocolloid dressings failed because of the size and number of wounds. Instead, an active-charcoal absorbent dressing combined with repeated surgical necrectomy was applied to stabilize the wound situation in conjunction with antibiotic therapy guided by wound-secretion-derived microbiological cultures. Parathyroid function remained normal. Following a 1-month consolidation therapy the patient was discharged with a stable wound condition to continue wound care at home. However, the large extent of those ulcers affecting both lower legs remained unchanged at the time of discharge compared to admission.

About 4 months after first admission, the patient was readmitted with signs of sepsis necessitating an escalated antibiotic treatment and surgical wound care. Yet conventional necrectomy proved ineffective. Therefore, maggot debridement therapy using sterile maggots of the green-bottle fly *Lucilia sericata* was introduced. Following four courses, the wounds gradually improved, granulated and showed signs of healing, yet the large extent of those



Figure 3
Calciphylaxis cutis, 4 months after admission. Size enlargement of calciphylactic ulcerations. Maggot debridement therapy abolished superinfection to a large extent.

wounds remained, rendering the patient at high risk of reinfection (Figure 3). As an adjunct antibiotic therapy, a combination of piperacillin-combactam was given over 9 days. The subcutaneous nodule-like tumors continued to occur at new locations. The patient's overall condition remained poor. Six days after being transferred to a primary hospital, she was readmitted because of acute renal failure. In addition, she suffered from the consequences of a stroke, with right-side hemiparesis, as well as from worsened crural ulcerations and a new pre-sacral pressure-sore lesion. A urinary-tract infection with *Pseudomonas aeruginosa* was diagnosed. The patient died within 4 days of a systemic-inflammatory response syndrome primarily due to her superinfected, poorly controllable wounds.

The diagnosis of Calciphylaxis cutis was confirmed by autopsy, revealing small- and medium-sized blood-vessel calcifications within the ulcerated skin of the lower legs as previously seen in the biopsy (Figure 4 and 5). Even capillaries were found to be surrounded by calcific deposits. The patient was shown to have severe calcified atherosclerotic lesions occasionally involving the whole circumference of the aorta and the coronary arteries with an in-stent restenosis within the right coronary artery. Furthermore, the patient presented intermediate-grade atherosclerosis in renal as well as in lower-leg peripheral arteries. Unusual locations of calcifications were the wall of the left atrium of the heart (Figure 6) and pulmonary arteries.

Discussion

Here we report a case of ulcerated Calciphylaxis cutis in the presence of a moderate renal insufficiency in contrast

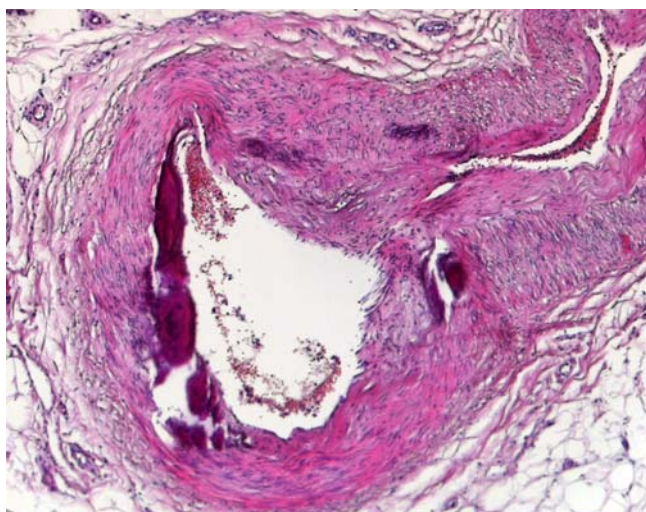


Figure 4
Calcifications of skin arteries, arterioles and capillaries. Biopsy and autopsy revealed calcifications of small arteries, arterioles and capillaries within the ulcerated skin.

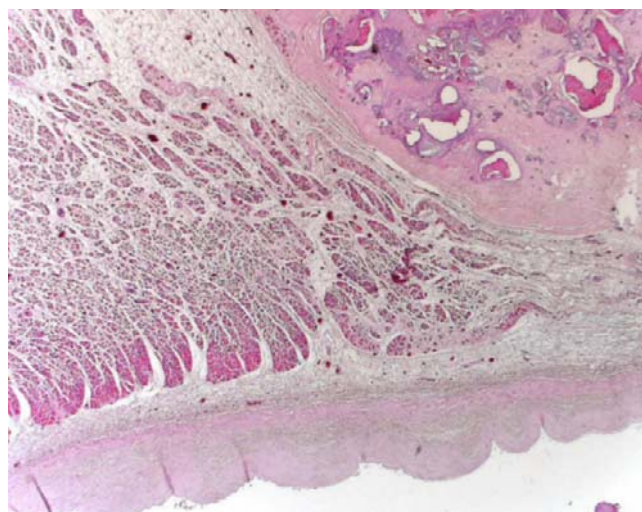


Figure 6
Calcifications of the left atrial wall of the heart. Autopsy revealed calcifications and endocardial fibrosis within the wall of the left atrium.

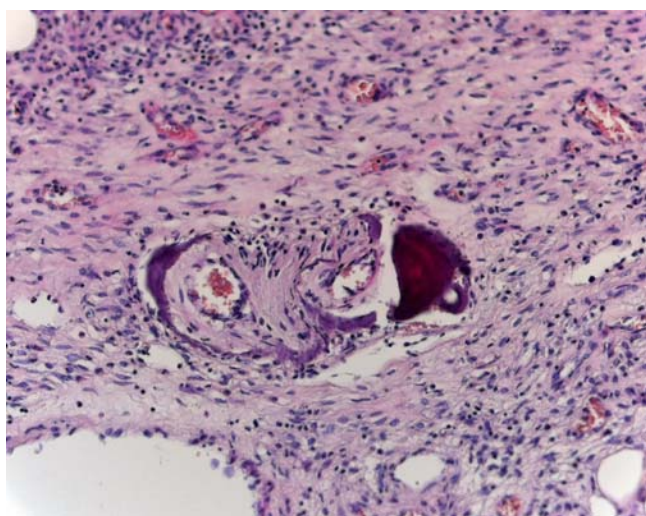


Figure 5
Calcifications of skin arteries, arterioles and capillaries. Biopsy and autopsy revealed calcifications of small arteries, arterioles and capillaries within the ulcerated skin.

to most previous observations that suggest Calciphylaxis cutis to be associated with terminal renal insufficiency [3,4]. Moreover, the actual plasma levels of calcium and phosphorus seemed to play a minor role than assumed from previous evidence [3]. However, in spite of measures to preserve renal function, the clinical course of Calciphylaxis cutis was rapidly progressive and virtually undeterred

by treatment in our patient. The skin ulcerations due to Calciphylaxis cutis constantly deteriorated over less than 6 months from first admission. Alternative therapeutic options including glucocorticoids were not deemed salutary in the presence of ulcerations [3]. Sterile maggot debridement therapy was more successful than surgical debridement in this patient. However, it was introduced late. In line with previous evidence [6], we strongly encourage its use in ulcerated Calciphylaxis cutis in combination with a broad-spectrum, *Pseudomonas* – effective antibiotic earlier on to avoid superinfections and to facilitate the granulation process. Overall, screening of renal-disease patients for Calciphylaxis cutis in the non-ulcerated stage seems to be crucial to timely address risk factors associated with the disease. Classic and putative risk factors for Calciphylaxis cutis derived from this case are summarized below.

Cardiovascular risk factors were low HDL cholesterol and high triglycerides, history of cigarette smoking during the previous 10 years (20-pack years) and arterial hypertension. The prevalent renal disease appears to be both a cardiovascular risk factor [7] and risk factor for Calciphylaxis [3]. Further, the patient may have had a genetic disposition to cardiovascular disease, as her mother died of myocardial infarction prematurely. Lipoprotein (a) and homocysteine levels were not determined. C-reactive protein elevation is likely due to the skin ulcers. However, it was high during the 12 months prior to death and was probably high even before that as her history of urinary-tract infections revealed, thus, making it eligible as a contributing factor for atherosclerosis [8]. A slight distur-

bance of calcium-phosphorus metabolism as well as a history of obesity, former coumadin use, and a possible underlying vitamin-K deficiency based on a steadily elevated international normalized ratio after coumadin discontinuation are prevalent, putative risk factors for Calciphylaxis [2]. Yet, the mechanism of these disseminated calcifications in small cutaneous arteries, and capillaries as well as in conductive arteries, pulmonary arteries and the left atrium is by far not explained. Future research will clarify whether matrix-protein dysfunction elicited by Vitamin-K deficient state is in play [9,10] which may affect both pyrophosphate and calcium metabolism [1,11] as well as wound healing [3].

Taken together, Calciphylaxis cutis is thought to arise from the arterial media layer rendering it different from intimal calcifications seen in common atherosclerosis and from extravascular organ calcifications such as Calcinosis cutis. The in-stent restenosis problem in our patient may reflect a propensity of intimal proliferation and fibrosis usually seen in Calciphylaxis [2]. Here, we speculate that the patient actually had both Calciphylaxis cutis represented by calcifications of small arteries, arterioles and capillaries of the skin as well as systemic atherosclerosis as primarily seen in conductive arteries.

List of abbreviations used

ACE = angiotensin converting enzyme

ECG = electrocardiogram

HDL = high-density lipoprotein

ICD = implantable cardioverter defibrillator

MDRD = Modification of Diet in Renal Disease (Study)

NYHA = New York Heart Association class

Competing interests

None declared.

Authors' contributions

RUP was the attending physician for this patient. He collected all results and drafted the paper. JS performed the autopsy, added his insights to all parts of the case report and helped in the process of revision. RP, head of the department, has overseen the drafting process and gave critical inputs to the manuscript. HA as the attending chief physician knowledgeably participated in the discussion and in the revision. All authors read and approved the final manuscript.

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Written consent for autopsy to further medical science and teaching was given by the patient before she died.

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