

CASE REPORT

Diagnostic challenges in a patient with calciphylaxis – a case report

VIOLETA CLAUDIA BOJINCĂ¹⁾, MIHAI BOJINCĂ²⁾, CRISTINA-ILEANA IOSIF³⁾, ȘERBAN MIHAI BĂLĂNESCU⁴⁾, ANDRA RODICA BĂLĂNESCU¹⁾

¹⁾Department of Internal Medicine and Rheumatology, "Sf. Maria" Hospital, Bucharest, Romania; Research Center in Rheumatic Diseases, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

²⁾Department of Internal Medicine and Rheumatology, "Dr. Ion Cantacuzino" Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

³⁾Department of Pathology, "Sf. Maria" Hospital, Bucharest, Romania

⁴⁾Department of Cardiology, "Elias" Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Abstract

Calciphylaxis is a condition with unclear etiopathogeny with vascular calcifications and thrombotic occlusion that lead to necrotic lesions. It is usually described in patients with end-stage renal disease (ESRD), but also in other conditions. The mortality rate is high, due to sepsis and internal organ failure. We present the case of a patient with multiple comorbidities (ESRD, diabetes, hypertension, Mönckeberg's sclerosis) with problems of differential diagnostic due to the necrotic lesions that mislead initially to systemic lupus erythematosus (SLE) with necrotizing vasculitis.

Keywords: calciphylaxis, Mönckeberg's sclerosis, renal failure.

Introduction

Calciphylaxis is a rare and potentially lethal condition of unknown cause with development of vascular calcifications, peripheral gangrene and skin necrosis, due to progressive calcification and thrombotic vaso-occlusion of media in small- and medium-sized arteries. The lesions are distinct from medial calcinosis and intimal atheroma [1, 2].

Chronic renal failure and end-stage renal disease (ESRD) and dialysis are the conditions associated most frequently with calciphylaxis, possible due to secondary hyperparathyroidism. Increased parathyroid levels, vitamin D, calcium, and phosphate may serve as sensitizers in humans. Hans Selye was the first to introduce the term "calciphylaxis" as a "sensitization by endogenous parathyroid hormone" [3].

The name calcific uremic arteriolopathy (CUA) is considered more appropriate in connection with patients having ESRD, while calciphylaxis should be used for the disease in non-ESRD. There are some risk factors thought to play a role in the development of calciphylaxis: diabetes, obesity, corticotherapy, immunosuppressive agents, (Methotrexate, Cyclophosphamide), anticoagulants (Warfarin), protein C or S deficiency, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome [4, 5].

Lesions of calciphylaxis are produced by concomitancy of vascular calcification and thrombosis [6]. Calciphylaxis could be considered a common endpoint of a variety of conditions. Activation of nuclear factor κ B (NF- κ B) is thought to be the end-piece of the joint pathway that determines the calcification of vessels [7]. Other hypothesis

is that in uremic patients the impairment in system receptor activator of nuclear factor κ B/RANK ligand/osteoprotegerin (RANK/RANKL/OPG) (with implications in skeletal and extraskelatal mineralization) is a factor that predispose to calciphylaxis [8]. In chronic inflammatory conditions, there might be a reduction of serum levels of fetuin-A, an important inhibitor of calcification produced in the liver [9–11]. Calciphylaxis was also considered as an active form of osteogenesis, with up-regulation of bone morphogenic protein-2 (BMP-2), Runt-related transcription factor 2 (Runx2), its target gene, and its indirect antagonist sclerostin [12].

Aim

We present the case of a 61-year-old patient, smoker, obese, admitted in the hospital for intense pain on left foot, muscle weakness, necrotic lesions on the skin of the calf, on both sides, with a history of important comorbidities (arterial hypertension, diabetes, dyslipidemia, hyperuricemia, ESRD).

Case presentation

The patient was diagnosed in 2002, with idiopathic thrombocytopenic purpura (autoantibodies to platelet surface positive) and was treated with glucocorticoids, with complete remission. In 2005, the patient was diagnosed with arterial hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, kidney stones (extracorporeal shockwave lithotripsy and endoureteral lithotripsy, in 2010) and stage 5 of chronic kidney disease with secondary hyperparathyroidism.

In April 2014, in another hospital, the presence of

arthralgia, proteinuria, anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies slightly elevated (but without the presence of other autoantibody and with normal values of C3 and C4), raised the suspicion of systemic lupus erythematosus (SLE) with renal and vasculitis involvement. Thus, the patient begun treatment with Cyclophosphamide (four monthly administrations) and Methylprednisolone, followed by oral Prednisone, with no improvement of clinic and biological manifestations (at admission, he had 20 mg Prednisone daily). Serum creatinine values varied between 4–6 mg/dL, glomerular filtration rate (GFR) 14–15 mL/min, patient had anemia, mild biological inflammatory syndrome, persistent leukocyturia, hematuria and subnephrotic proteinuria.

In 2014, he was diagnosed with pyelonephritis – chronic infection with *Klebsiella* – and treated with antibiotics (Ceftriaxone, Co-trimoxazole).

On admission on our Clinic, in March 2015, he was obese, with important pain on the left ankle, unable to walk and using a wheeling chair, necrotic lesions on the skin of both calves and abdomen, no detectable pulse on both anterior tibia arteries, *livedo reticularis* aspect on calves.

He was treated with Enoxaparin (low-molecular-weight heparin – LMWH), antihypertensive drugs (Lercanidipine, Rilmenidine, Furosemide), antibiotics, Prednisone 20 mg daily, Esomeprazole 20 mg daily, Paricalcitol for secondary hyperparathyroidism. The evolution was unfavorable, so he was admitted in the Intensive Care Unit (Figures 1 and 2).

Laboratory examination revealed high levels of acute phase reactants [erythrocyte sedimentation rate (ESR) 60 mm/h, C-reactive protein (CRP) 28.7 mg/L], leukocytosis ($21\,960/\text{mm}^3$) with neutrophilia (19 910 – 90.7%), mild anemia [hemoglobin (Hb) 11.3 g/dL, hematocrit (Ht) 33.4%], high value of creatinine 4.59 mg/dL (in evolution 6.72 mg/dL), urea 287.5 mg/dL (in evolution 304 mg/dL), Na^+ 119 mmol/L, K^+ 5.28 mmol/L, Cl^- 84 mmol/L, normal value of serum complement C3, C4, no antibodies detected and elevated levels of procalcitonine (2 – elevated).

Radiographic examination of pelvis and left foot showed extensive calcification of arteries (Figure 3, a and b) and computed tomography (CT) examination of abdomen showed massive aortic calcification (Figure 4).

Renal biopsy and renal artery biopsy showed nephro-angiosclerosis, and calcifications of the media of the renal arteries (Figures 5–7).

In evolution, the patient rapidly developed extensive necrotic lesions on both hands and feet, with intense pain and worsening of the general condition despite treatment. He was admitted in the Intensive Care Unit and treated with complex measures (antibiotics, antihypertensive therapy, volemic equilibration, major analgesics, Sodium Thiosulphate and local treatment of necrotic lesions) but he developed respiratory failure and he was intubated and mechanically ventilated. Despite intensive care and multiple therapeutic attempts, the evolution was unfavorable, with exitus.



Figure 1 – Necrotic lesions on the skin.



Figure 2 – Ischemic lesions on the hand.

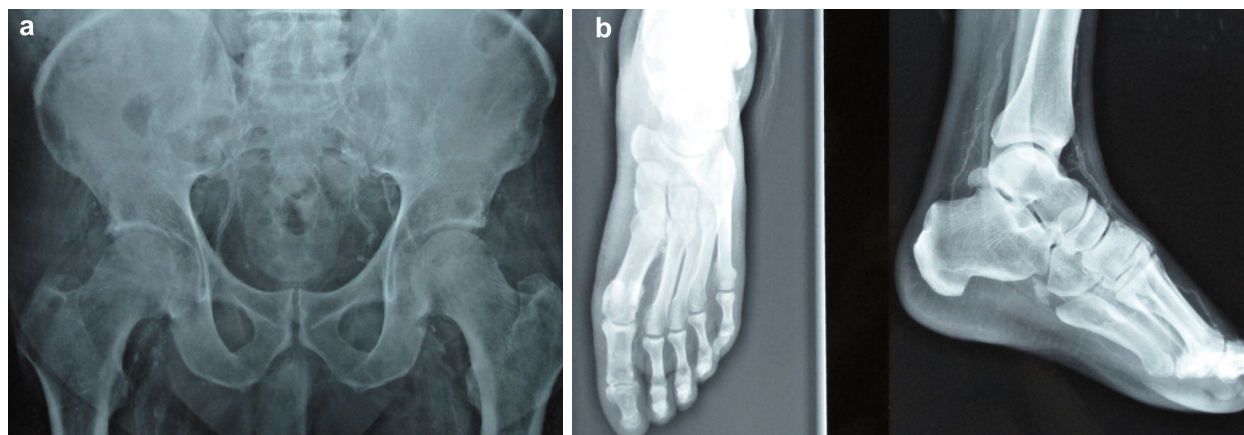


Figure 3 – (a and b) Extensive arterial calcification on radiographic examination ("pipestem appearance").

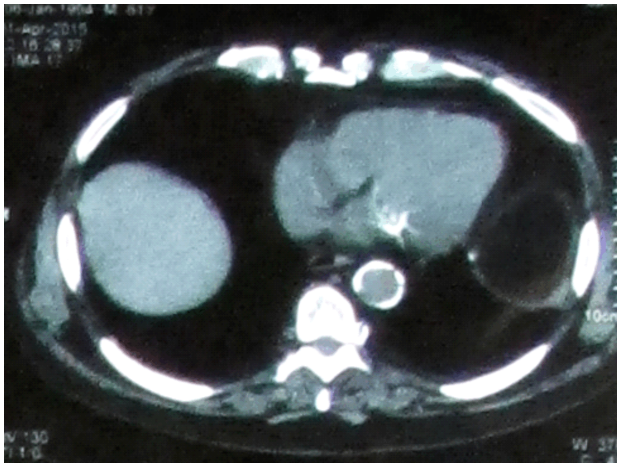


Figure 4 – CT examination with aortic wall calcification.

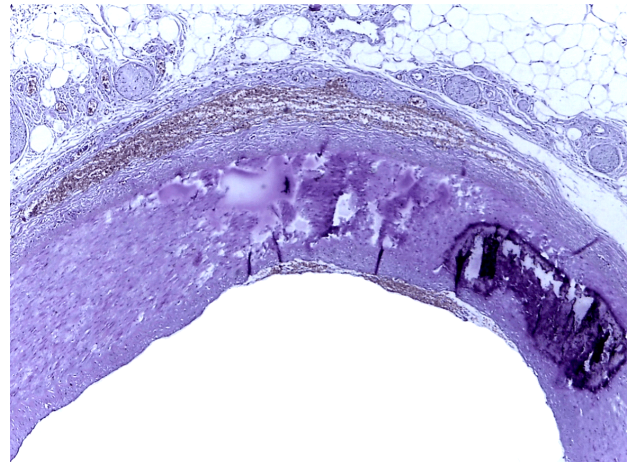


Figure 5 – Medial calcification of the renal artery [Hematoxylin–Eosin (HE) staining, $\times 100$].

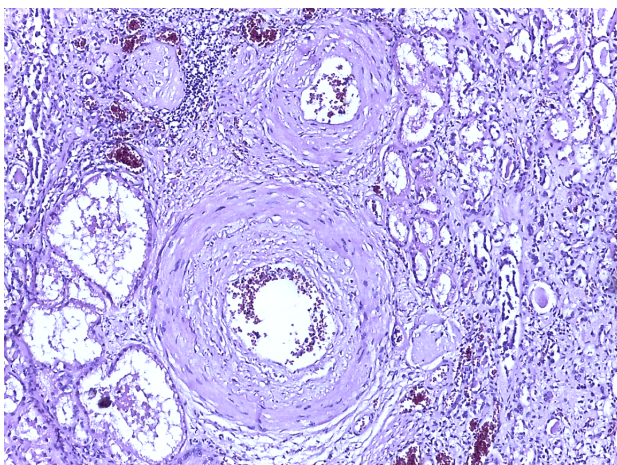


Figure 6 – Nephroangiosclerosis with vascular calcification (HE staining, $\times 200$).

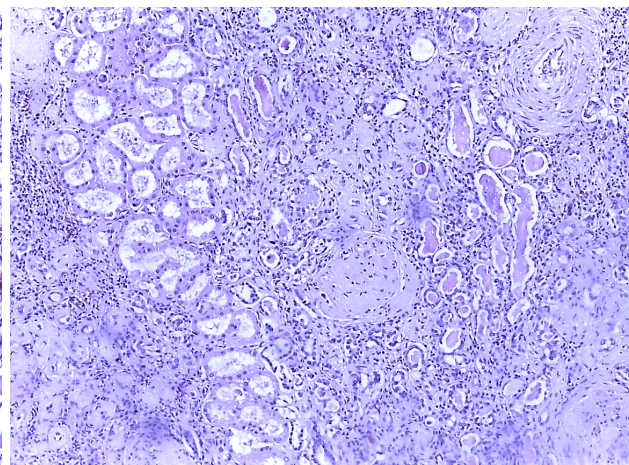


Figure 7 – Focal glomerulosclerosis (HE staining, $\times 100$).

Discussions

We presented the case of a patient with multiple severe conditions that involve arteries. This obese and smoker patient had diabetes, dyslipidemia, ESRD, diffuse vascular calcifications and was treated with glucocorticoids and immunosuppressive drugs for cutaneous lesions initially diagnosed as necrotizing vasculitis associated with SLE.

CUA is a condition characterized by systemic calcification of arterial media, narrowing and occlusion of subcutaneous vessels due to calcific deposits in media and internal lamina that might be accompanied by intimal fibrous proliferation. Thrombotic lesions induced cutaneous necrosis with poor prognosis (difficulty/impossibility of healing).

Glucocorticoids, aluminum, hyperparathyroidism, liver disease, chronic inflammatory conditions may be associated with calciphylaxis [6, 7].

Mönckeberg's syndrome is characterized by arteriosclerosis with calcific deposits found within the media of muscular arteries (usually of medium and small caliber), while the intima is left intact (no vascular obstruction) – “dystrophic calcification”. The calcification is diffuse and circumferential along the vessel. On conventional radiological film, it has a “pipestem appearance”. Although there is no definite cause for Mönckeberg's sclerosis, elders are predominantly more affected, while

both chronic renal disease and diabetes may play a role as well in the pathogenesis of the disease [13].

It is discovered by accident or by chance. It is usually asymptomatic until complicated with atherosclerosis or calciphylaxis. Ultrasonography of the feet or hands, though not diagnostic, might be, sometimes, revealing for the vessel changes and in the same time can clarify the structure involved [14, 15]. The complex involvement of arteries generated severe obstruction with extensive necrosis of hands, feet and abdominal wall with sepsis and fatal evolution despite sustained measures of intensive care.

Infection, necrotic skin lesions, internal organ failure might be fatal in patients with calciphylaxis, the mortality rate reported being 60–80% [6].

Treatment is difficult, with combined and complex measures, with the necessity of proper wound care [16, 17]. Systemic antibiotics are indicated, as sepsis is frequent. For the intense pain, opioid pain medication is useful. Parathyroidectomy is a method of treatment, but remains controversial [18], hyperparathyroidism being one of its primary indications.

For the normalization of calcium–phosphorus homeostasis and for lowering the parathyroid hormone levels, a calcimimetic drug called Cinacalcet can be used, as it interacts with the calcium specific receptors found on the main parathyroid cellular component [19].

Bisphosphonates (Etidronate Disodium) can be used for calciphylaxis patients, as it may have an anti-calcification effect on arteries [20].

In patients with hemodialysis, Sodium Thiosulfate was reported to be useful (unknown mechanism of action, but possible role in chelating calcium from tissue deposits) [21–23].

Hyperbaric oxygen therapy can sometimes be used in treating cutaneous ulcers associated with calciphylaxis [24].

✉ Conclusions

Calciphylaxis is a rare, severe condition, sometimes difficult to diagnose. The differential diagnosis with necrotizing vasculitis might be challenging. Simple vascular calcification should not always be labeled as calciphylaxis, even though it is a form of vascular calcification. The evolution and prognosis of calciphylaxis is unfavorable, especially in the presence of other factors that are deleterious on arterial wall (chronic renal failure, atherosclerosis, hypertension, diabetes, use of glucocorticoids, immunosuppression). The treatment must be complex, but it is frequently disappointing.

Conflict of interests

The authors declare that they have no conflict of interests.

References

- [1] Adrogué HJ, Frazier MR, Zeluff B, Suki WN. Systemic calciphylaxis revisited. *Am J Nephrol*, 1981, 1(3–4):177–183.
- [2] Kent RB 3rd, Lyerly RT. Systemic calciphylaxis. *South Med J*, 1994, 87(2):278–281.
- [3] Selye H, Gabbiani G, Strebel R. [Sensitization to calciphylaxis by endogenous parathyroid hormone]. *Endocrinology*, 1962, 71(4):554–558.
- [4] Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol*, 2008, 3(4):1139–1143.
- [5] Ozbalkan Z, Calguneri M, Onat AM, Ozturk MA. Development of calciphylaxis after long-term steroid and methotrexate use in a patient with rheumatoid arthritis. *Intern Med*, 2005, 44(11):1178–1181.
- [6] Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol*, 2007, 56(4):569–579.
- [7] Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B. *J Am Acad Dermatol*, 2008, 58(3):458–471.
- [8] Haas M, Leko-Mohr Z, Roschger P, Kletzmayer J, Schwarz C, Domenig C, Zsontsich T, Klaushofer K, Dellling G, Oberbauer R. Osteoprotegerin and parathyroid hormone as markers of high-turnover osteodystrophy and decreased bone mineralization in hemodialysis patients. *Am J Kidney Dis*, 2002, 39(3):580–586.
- [9] Rogers NM, Teubner DJ, Coates PT. Calcific uremic arteriopathy: advances in pathogenesis and treatment. *Semin Dial*, 2007, 20(2):150–157.
- [10] Slough S, Servilla KS, Harford AM, Konstantinov KN, Harris A, Tzamaloukas AH. Association between calciphylaxis and inflammation in two patients on chronic dialysis. *Adv Perit Dial*, 2006, 22:171–174.
- [11] Swanson AM, Desai SR, Jackson JD, Andea AA, Hughey LC. Calciphylaxis associated with chronic inflammatory conditions, immunosuppression therapy, and normal renal function: a report of 2 cases. *Arch Dermatol*, 2009, 145(6):723–725.
- [12] Kramann R, Brandenburg VM, Schurgers LJ, Ketteler M, Westphal S, Leisten I, Bovi M, Jähnen-Dechent W, Knüchel R, Floege J, Schneider RK. Novel insights into osteogenesis and matrix remodelling associated with calcific uremic arteriopathy. *Nephrol Dial Transplant*, 2013, 28(4):856–868.
- [13] Magro CM, Simman R, Jackson S. Calciphylaxis: a review. *J Am Col Certif Wound Spec*, 2011, 2(4):66–72.
- [14] Gutierrez M, Pineda C, Salaffi F, Raffener B, Cazenave T, Martinez-Nava GA, Bertolazzi C, Vreju F, Inanc N, Villaman E, Delle Sedie A, Dal Pra F, Rosemffet M. Is ankle involvement underestimated in rheumatoid arthritis? Results of a multi-center ultrasound study. *Clin Rheumatol*, 2016, 35(11):2669–2678.
- [15] Vreju FA, Ciurea ME, Popa D, Popa F, Parvanescu CD, Chisalu BA, Barbulescu AL, Parvanescu V, Rosu A, Ciurea PL. Ultrasonography in the diagnosis and management of non inflammatory conditions of the hand and wrist. *Med Ultrason*, 2016, 18(1):90–95.
- [16] Wilmer WA, Magro CM. Calciphylaxis: emerging concepts in prevention, diagnosis, and treatment. *Semin Dial*, 2002, 15(3):172–186.
- [17] Don BR, Chin AI. A strategy for the treatment of calcific uremic arteriopathy (calciphylaxis) employing a combination of therapies. *Clin Nephrol*, 2003, 59(6):463–470.
- [18] Hafner J, Keusch G, Wahl C, Sauter B, Hürlimann A, von Weizsäcker F, Kräyenbühl M, Biedermann K, Brunner U, Helfenstein U. Uremic small-artery disease with medial calcification and intimal hyperplasia (so-called calciphylaxis): a complication of chronic renal failure and benefit from parathyroidectomy. *J Am Acad Dermatol*, 1995, 33(6):954–962.
- [19] Robinson MR, Augustine JJ, Korman NJ. Cinacalcet for the treatment of calciphylaxis. *Arch Dermatol*, 2007, 143(2):152–154.
- [20] Hanafusa T, Yamaguchi Y, Tani M, Umegaki N, Nishimura Y, Katayama I. Intractable wounds caused by calcific uremic arteriopathy treated with bisphosphonates. *J Am Acad Dermatol*, 2007, 57(6):1021–1025.
- [21] Zitt E, König M, Vychytil A, Auinger M, Wallner M, Lingenhel G, Schilcher G, Rudnicki M, Salmhofer H, Lhotka K. Use of sodium thiosulphate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients. *Nephrol Dial Transplant*, 2013, 28(5):1232–1240.
- [22] Meissner M, Kaufmann R, Gille J. Sodium thiosulphate: a new way of treatment for calciphylaxis? *Dermatology*, 2007, 214(4):278–282.
- [23] Hayden MR, Tyagi SC, Kolb L, Sowers JR, Khanna R. Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis—calcific uremic arteriopathy: the emerging role of sodium thiosulfate. *Cardiovasc Diabetol*, 2005, 4:4.
- [24] Basile C, Montanaro A, Masi M, Pati G, De Maio P, Gismondi A. Hyperbaric oxygen therapy for calcific uremic arteriopathy: a case series. *J Nephrol*, 2002, 15(6):676–680.

Corresponding author

Mihai Bojincă, Associate Professor, MD, PhD, Department of Internal Medicine and Rheumatology, “Dr. Ion Cantacuzino” Hospital, 3–5 Ion Movilă Street, 020475 Bucharest, Romania; Phone +40723–302 501, e-mail: vmbojinca@yahoo.com