Calcific Uremic Arteriolopathy in Hemodialyzed Patients

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Abstract
In the present article, we discuss the case of 67-year-old female patient diagnosed with inferior limbs calciphylaxis and hemodialyzed since 2006. The clinical manifestations and pathological lab findings are typical for this rare and extremely severe complication in chronic hemodialyzed individuals. The favorable treatment response to sodium thiosulfate, not often used as elected therapy in international studies, represents the particularity of the case.

Key words: calciphylaxis, hemodialysis, treatment

Introduction
In the last decade, vascular calcifications (extremely rare 30 years ago) became a common feature of chronic kidney disease (CKD). Although they occur in a variety of diseases, vascular calcifications have certain pathophysiology particularities in uremic patients, affect an increased area and they are more severe compared to the general population of the same age. The estimated incidence of CUA is approximately 4% in hemodialyzed patients and less than 1% in pre-dialysis CKD patients (1,2).

Bryant and White described calciphylaxis (calcific uremic arteriolopathy = CUA) for the first time in 1898 (3). It represents a rare, life-threatening form of vascular calcification, which is seen more often in chronic hemodialyzed (HD) or recently transplanted patients (1,4-8) and it is characterized by arteriolar media calcification, presenting or not endovascular fibrosis, vaso-occlusive thrombosis and extravascular calcifications (4-6). In the end-stage of the disease, all these structural changes can induce skin ischemia and necrosis (4).

Summarizing, CUA can be classified in 2 stages: pruritus and erythemas phase (unspecific) and the pain-related ulcerative and necrotic one (9,10).
The literature data describes several risk factors associated with calciphylaxis development in HD patients (4): female gender (11,12), body mass index > 30 (1,13), increased serum intact-parathormone (iPTH), hyperparathyroidism (9), elevated calcium-phosphorus product (Ca x P product) (14), chronic therapy with warfarin (12), calcium-phosphate binders use (8), treatment with vitamin D analogs (8) and corticosteroids (15), autoimmune diseases (15): polymyositis, Sjögren syndrome, Crohn disease, sarcoidosis, rheumatoid arthritis, and systemic lupus erythematosus (16); disorders correlated with important hypercoagulable state (17-20): protein C and S deficiency or antiphospholipid syndrome. Additionally, the deficiency of some proteins (fetuin-A, matrix Gla protein = MGP), that normally represent calcification inhibitors, can induce vascular calcifications in CKD individuals (21). Although the mechanisms of CUA development are not entirely understood, an imbalance between inducers and inhibitors of calcification of the vascular wall seems to be primarily involved (22). The occurrence of CUA in only a small proportion of hemodialyzed patients seems to be related to the magnitude of this imbalance (22).

On clinical exam, patients with CUA present progressive painful skin ulcerations (8). Furthermore, the disease is associated with high mortality (up to 80%) (8), as a result of skin lesion infections or septicemia (5) and/or simultaneous cardiovascular events (4).

The treatment of calciphylaxis is based on the same measures used for preventing progression of vascular calcifications (4):

1. prophylaxis management:
   • avoidance of any types of skin traumas (including subcutaneous treatments);
   • an adequate control of phosphocalcic metabolism (P = 3.5 – 5.5 mg/dL; Ca = 8.4 – 9.5 mg/dL; iPTH = 150 – 300 pg/mL; Ca x P product below 55 mg2/dL2) with diet, non-calcium phosphate binders or cinacalcet, decreased Ca in the dialysis fluid – below 2.50 mEq/L (23);
   • parathyroidectomy in patients with refractory secondary hyperparathyroidism (HPTH II);
   • increasing dialysis sessions in subjects with inadequate Kt/V (K = dialyzer clearance of urea; t = dialysis time; V = volume of distribution of urea) (24);
   • precaution in warfarin administration, especially in patients presenting severe hypercalcemia (25);
   • consider antioxidant therapy (26).

2. drug and/or surgical options:
   • early administration of broad spectrum antibiotics;
   • surgical treatment of skin lesions and grafts, if necessary;
   • sodium thiosulfate; several studies reported decrease of pain intensity after 2 weeks of treatment (27) and lesion resolution after 6 months (27,28);
   • bisphosphonates; recent reports showed that intravenous pamidronate (29) and oral etidronate disodium (30) improved CUA patients’ symptomatology;
   • decreasing immunosuppression doses in recently transplanted individuals with persistent typical skin lesions;
   • replacing warfarin therapy with heparin immediately after lesion development; vitamin K administration (experimental phase) (31);
   • other options: hyperbaric oxygen treatment (90 minute session at 2.5 atm) (32,33); ozonated auto-hemotherapy (O3-AHT) (34); corticotherapy only in early phase, before ulceration has developed (8); lower limbs revascularization, but with poor results (35).

It is essential to underline that the treatment of already installed calciphylaxis is difficult, long and often inefficient. Therefore, prophylaxis is mandatory to prevent this extremely severe complication of chronic dialyzed patients (36).

**Case report**

A 67-year-old female patient was admitted in the Department of Nephrology and Dialysis for severe lower limbs algic symptomatology, secondary to ulcerations localized at the same level.

Since 2006 the patient had been hemodialyzed on arterio-venous fistula, 3 sessions per week, 4 hours each. Autosomal dominant polycystic kidney disease was the primary renal disease, but the patient also associated nephrolithiasis, ischemic coronary heart disease, left bundle branch block and hepatitis C. She was under treatment with 75 mg qd aspirin, 35 mg b.i.d. trimetazidine, 50 μg/week darbepoetin α.

At admittance, the clinical exam revealed lower limbs ulcerative infected lesions (posterior and anterior regions of both legs), well delimited, associating necrotic and hemorrhagic areas (Fig. 1). The lesions were extremely painful, spontaneously or when touched; therefore, the patient was unable to sleep (night or day) causing her anxiety.

The laboratory tests indicated: calcaemia = 9.4 mg/dL

![Figure 1. Ulcerative lesions – well delimited black leathery wounds surrounded by violaceous areas highlighting the necrotic and hemorrhagic process: (A) anterior region of left leg, (b) lateral region of left leg, (C) anterior region of right leg, (d) lateral region of right leg](image-url)
(after correction = 9.8 mg/dL), phosphatemia = 4.2 mg/dL, serum iPTH = 1702.95 ng/mL, hemoglobin (Hb) = 9.6 g/dL, hematocrit (Ht) = 28.50%, urea = 57 mg/dL, creatinine = 4.2 mg/dL, serum albumin = 3.9 g/dL, serum bicarbonate = 25 mEq/L, alkaline phosphatase = 224 UI/L, serum K = 2.94 mmol/L, erythrocyte sedimentation rate (ESR) = 24 mm/h, C-reactive protein (CRP) = 96 mg/L, international normalized ratio (INR) = 1.06, activated partial thromboplastin time (APTT) = 37.30/s; the rest of usual investigations were in normal range (glycemia, hepatic enzymes, serum sodium (Na) and chlorine (Cl)). Echocardiography highlighted calcifications of aortic valves and first-degree aortic regurgitation. Profile lumbar X-ray indicated a Kauppila score (37) (it measures aortic calcifications) of 14.

The patient’s present illness conditions and the history of bone mineral disorders were highly suggestive, so that CUA diagnosis was rapidly established. Data from the Dialysis Center showed that, in the last 4 years, the patient had an inadequate high level of phosphatemia (average value = 5.84 mg/dL), Ca x P product (mean level = 58.43 mg²/dL²) and serum PTH (~1193.79 ng/mL), despite of a correct hypophosphatemic diet and treatment – Renagel (1600 – 3200 mg qd). After the development of skin lesions (1 year before the admittance), besides HPTH II therapy, the patient also received antibiotics, antalgic therapy and local antiseptic treatment, without an obvious improvement. Her condition progressively aggravated. It is important to mention that the patient repeatedly refused parathyroidectomy as a viable option.

The differential diagnosis of skin lesions etiology was extremely facile, because the patient did not associated congestive heart failure (trophic ulcerations were excluded), lower limbs varices (varix ulceration was excluded), cryoglobulinemia (the lesions were not typical for this disease) (4,18), diabetes mellitus; additionally, there were no specific lesions for erysipelas, nodular lesions of erythema nodosum or systemic anomalies due to pyoderma gangrenosum and vasculitis (4,18). Contact dermatitis and other forms of skin allergies were also rapidly excluded.

Furthermore, the lesions’ bacterial cultures indicated the presence of E. Coli and Staphylococcus aureus. Initially, antibiotics according to the antibiogram and local wounds’ treatment (antiseptic solutions, multiple surgical ulcerations debridement) were administered, but after almost 3 weeks no improvement was noted. Therefore, sodium thiosulfate (25%, 50 mL) was indicated after each HD session for 3 months. The treatment proved its efficiency inducing skin lesion cicatrisation and pain relief. During the therapy, dialysis fluid with Ca = 1.25 mmol/L was used. The patient performed several skin graft procedures, because of important skin substance loss. The results are further showed (Fig. 2).

**Discussions**

Although the pathophysiology of the disease is not clearly understood, in patients with CUA, what can be noticed is an increased expression – in vascular smooth muscle cells – of osteopontin and bone morphogenetic protein 4, both inducers of vascular calcification (22). There is a tendency for the vascular smooth muscle cells to transform into express bone-related proteins (osteocalcin, bone sialoprotein, type 1 collagen, osteopontin) (22). Furthermore, the production of the inhibitors of vascular calcification (fetuin A, osteoprotegerin) is decreased as a result of proinflammatory state of dialysis (22) and the actions of the matrix Gla protein \( \gamma \)-carboxyglutamate protein (MGP) can be inhibited by the use of coumarin anticoagulants with increased vascular calcifications (15,38). The use of vitamin D analogues, hyperparathyroidism, ischemia and deficiencies of proteins C and S are associated with loss of pyrophosphate (which inhibits mineralization) from endothelial and vascular smooth muscle cells and may predispose to the development of CUA in uremic patients with CKD (39).

In accordance with several international studies, our case also supports the idea of successful recovery from CUA after sodium thiosulfate (an inorganic pentahydrated salt) administration and the use of this drug as first-line therapy (27,28,40-43), especially in dialyzed patients (44-47). In contrast with literature data (40,44,48), no side-effects (e.g.: hypotension, nausea, vomiting) have been described.

Another important aspect, emphasized by our case, was the positive and differential diagnosis, which were in agreement with international medical data (4): female patient (11,12), increased iPTH, hyperphosphatemia (9), elevated Ca x P prod-
duct (14), and the exclusion of different possible causes (4): congestive heart failure, lower limbs varices, cryoglobulinemia (18), diabetes mellitus, erysipelas (18), erythema nodosum (18), pyoderma gangrenosum (18), vasculitis (18), contact dermatitis.

Once again, we should highlight the importance of prophylaxis measures to avoid CUA development in hemodialyzed patients (36), and the importance of patient’s compliance regarding medical recommendations (our patient repeatedly refused parathyroidectomy) (4); avoidance of any types of skin traumas, an adequate control of phosphocalcic metabolism (23), parathyroidectomy in patients with refractory HPTH II, increasing dialysis sessions in subjects with inadequate Kt/V (24), precaution in warfarin administration (25), antioxidant therapy (26).

Conclusions

The present case represents a typical CUA form (localized at lower limbs) in a chronic HD patient. The particularity of the case is the unfavorable evolution despite adequate treatment and diet, as recommended by guidelines; this fact highlights the limits of present understanding regarding the mechanisms of renal osteodystrophy. Another particularity is represented by therapy success after sodium thiosulfate administration, without any known side-effects.

In addition, it is essential to emphasize the importance of a continuous interdisciplinary approach in these rare, but extremely severe cases in order to establish both the differential diagnosis (nephrologist collaboration with dermatologist, gastroenterologist, and cardiologist physicians) and an adequate long-term treatment management (nephrologist collaboration with general or plastic surgeon).

Authors contribution

I.A. Checheriță, the corresponding author, conceived and drafted the study, conducted the diagnosis and therapy management. A. Ciocâlteu, D. Râdulescu, D. Smarandache I. A. Checheriță, the corresponding author, conceived and drafted the study, conducted the diagnosis and therapy management. A. Ciocâlteu, D. Râdulescu, D. Smarandache

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