



### Calciphylaxis Causing Digital, Gangrene in End Stage Renal Disease: A case report and review

*Calciphylaxie: une cause rare de Gangrène du Doigt Complicant une Maladie Rénale en Phase Terminale (MRPT): Cas clinique et revue de la Littérature*

A. A. Sanusi, F. A. Arogundade\*, A. I. A. Udo, M. O. Hassan, O. Oyewole, T. Kolawole, A. Akinsola

#### ABSTRACT

Calcific uraemic arteriopathy (CUA), a potentially life-threatening vasculopathy of the skin and subcutaneous tissues is rarely associated with advanced chronic kidney disease (CKD) particularly in patients on haemodialysis. It is more frequently reported in whites than in blacks and commonly accompanies hyperphosphataemia, elevated calcium-phosphate product and marked secondary hyperparathyroidism. We report a rare case of CUA that complicated end stage renal disease secondary to obstructive uropathy in a 68 year old Nigerian. The risk factors for CUA, diagnosis, management and our peculiar limitations were reviewed and discussed. **WAJM 2013; 32(1): 68–72.**

Keywords: Calciphylaxis, calcium, phosphore, ESRD, gangrene, blacks.

#### RÉSUMÉ

L'artériopathie calcifiée urémique (ACU), une vasculopathie de la peau et du tissu sous cutané potentiellement létale, est rarement associée à une maladie rénale chronique (MRC) avancée particulièrement chez les patients en hémodialyse. Elle est plus fréquemment rapportée chez les blancs que chez les noirs et accompagnent habituellement une hyperphosphatasémie, une élévation des composés phosphocalciques et une hyperparathyroïdie secondaire. Nous rapportons un cas rare d'ACU compliquant une maladie rénale en stade terminal secondaire à une uropathie obstructive chez un homme Nigérien de 68 ans. Les facteurs de risque d'ACU, le diagnostic, la prise en charge et nos limites spécifiques sont revues et discutées. **WAJM 2013; 32(1): 68–72.**

Mots clés: Calciphylaxie, calcium, phosphore, ESRD, gangrène, noirs.

Renal Unit, Department of Medicine, Obafemi Awolowo University Teaching Hospitals Complex, P.M.B 5538, Ile-Ife, Osun State, Nigeria

\*Correspondence: Dr Fatiu A. Arogundade, Renal Unit, Department of Medicine, College of Health Sciences, Obafemi Awolowo University, P.M.B 5538, Ile-Ife, Osun State, Nigeria Email: fatiu3@yahoo.com OR fatiuaro@oauife.edu.ng

Abbreviations: ANA, Antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CKD, Chronic kidney disease; CUA, Calcific uraemic arteriopathy; DUS, Doppler Ultrasound Scan; ESR, Erythrocyte sedimentation rate; HD, Haemodialysis; MBD, Mineral and bone disease; NFkB, Nuclear factor kappa B.

## INTRODUCTION

Calciphylaxis or calcific uraemic arteriolopathy (CUA) is a potentially life-threatening vasculopathy of the skin and subcutaneous tissues that is rarely associated with chronic kidney disease (CKD). The disorder is more common in patients on haemodialysis, about 4% in reported series and commonly seen in whites than blacks.<sup>1,2</sup> Risk factors for the development of CUA include obesity, diabetes mellitus, female sex, white ethnicity, time on renal replacement therapy and the use of coumarin anticoagulants.<sup>2,3</sup> Other factors reported to be associated with CUA include the use of vitamin D analogs, calcium-containing phosphate binders, iron-substitution therapy and glucocorticosteroids.<sup>3,4</sup> We present a rare case of CUA seen in a male black Nigerian patient with end stage renal disease. To the best of our knowledge, there is no reported case of CUA in Nigeria.

## Case Report

The patient was a 68-year-old Nigerian man who was first seen a year prior to presentation with features of uraemia secondary to obstructive uropathy from benign prostatic hypertrophy. The acute uraemic syndrome was precipitated by urinary tract infection and necessitated acute haemodialysis (HD). He had five sessions of HD over two weeks with significant clinical and biochemical improvement. He also had urinary diversion during the period. The clinical improvement was sustained on maintenance HD and he was subsequently discharged home for outpatient HD while being prepared for elective prostatectomy but defaulted from follow up. His past medical history revealed that he had prostate biopsy done five years earlier which revealed benign prostatic hypertrophy. He presented again in Adult Accident and Emergency Department a year after defaulting with progressive generalized body pain of two weeks, painful bilateral leg swelling of one week duration and inability to walk for four days.

Examination revealed an acutely ill looking elderly man in painful distress. He was pale and had asterixis and bilateral pitting pedal oedema. The legs

were tender. He also had blisters on the lower leg with associated ulcers at the dorsum of the feet. Ten days into the admission there was bluish-dark discoloration of the toes with normal pulsation of the dorsalis pedis and posterior tibial arteries. Laboratory investigations revealed deranged serum chemistry, elevated serum creatinine and urea, and inorganic phosphate and low calcium (Table 1). Doppler ultrasound scan of the lower limb vessels revealed that the flow within common femoral, superficial femoral and the popliteal arteries were within normal limits and the venous system of the thigh was also patent. The anterior and posterior tibial arteries were pulsatile with normal systolic values, however, the dorsalis pedis was noted to be highly pulsatile with very high velocity peaks (103.05cm/s) bilaterally. These values fall within the range seen in the femoral vessel and signify distal stenosis.

The X-Ray of the hip revealed calcific densities in the soft tissue of the gluteal region and scrotum. Abdominopelvic ultrasonography revealed normal sized kidneys, the left kidney measured 12.7 x 5.4 x 6.7cm while the dimensions for the right kidney were 12.9 x 4.8 x 6.6cm,



**Figure 1: Showing the Patient's Feet one week after Admission**



**Figure 2: Showing the Patient's Feet 10 days after Admission**

both had poor corticomedullary differentiation. The prostate was enlarged and measured 5.0 x 5.14 x 7.3 with a volume of 97.6mls.

The treatment offered included prophylactic tetanus vaccination, antibiotics, analgesics in form of Tramadol hydrochloride 50mg thrice daily, oral active vitamin D (calcitriol) 0.25µg daily, oral calcium carbonate 500mg thrice daily, low phosphate diet, low protein diet and haemodialysis (thrice weekly, 4-hour HD sessions). On the 12<sup>th</sup> day of admission calcitriol and calcium drugs were discontinued due to rising calcium-phosphate product and non-calcium, non aluminum phosphate binder (sevelamer or lanthanum carbonate) was prescribed but was not available. The use of sodium thiosulfate as chelating agent was considered but was not available hence intensified daily HD was prescribed which unfortunately did not relieve the pain. There was rapid deterioration of the patient's clinical state with the development of gangrene of both lower limbs. Orthopedic consult was sought and suggested bilateral amputation of the lower limbs which the patient declined but rather opted for discharge from hospital care.

## DISCUSSION

Calciphylaxis or CUA is a calcification disorder of small vessels associated with the development of progressive ischaemic necrosis of the skin and soft tissues. It is an uncommon manifestation of Mineral Bone Disease in chronic kidney disease. Gipstein *et al*<sup>5</sup> published the first case series of calciphylaxis in 1976 describing 11



**Figure 3: Showing the Patient's Feet in the 3<sup>rd</sup> Week of Admission.**

**Table 1: Laboratory Results on Day 1 and 10**

Laboratory Parameter	Day 1	Day 10
Serum Na (mmol/L)	131	130
Serum K (mmol/L)	5.2	3.0
Urea (mmol/L)	21.7	25.3
Creatinine (µmol/L)	1181	1071
Bicarbonate (mmol/L)	13	18
Total Protein (g/L)	50	51
Serum Albumin (g/L)	24	22
Corrected calcium (mmol/L)	1.85	2.2
Phosphate (mmol/L)(0.65 – 1.3)	2.72	2.73
Calcium/Phosphate Product (mmol <sup>2</sup> /L <sup>2</sup> )	5mmol <sup>2</sup> /L <sup>2</sup>	6mmol <sup>2</sup> /L <sup>2</sup>
Serum Alkaline Phosphatase (IU/L) (39 – 117) Normal value	218	230
iParathormone (iPTH) (pmol/L)	N/A	N/A
Haematocrit (%age)	24	26
White Blood Cell (cells/mm <sup>3</sup> )	6000	11000
ESR (mm/hr) Westergreen	16	18
UrinalysisProteinuriaGlucosuria	+++Negative	+++Trace

**Table 2: Risk Factors for development of Calciphylaxis**

Confirmed Risk factors	Presumed Risk Factors
End Stage Renal Disease	Vitamin K deficiency-usually treatment with warfarin
Hyperphosphatemia	Fetuin deficiency
Calcium-Phosphate Product >55mg <sup>2</sup> /dl <sup>2</sup>	Deficiency of other calcification inhibiting system
Calcium based Phosphate binders	Adynamic bone disease.
Diabetes Mellitus	Heavy Proteinuria with loss of Protein C & Protein S
Obesity	Intravenous Iron therapy
Use of Vitamin D supplementation	
Use of glucocorticosteroids	
Hypoalbuminaemia	

patients with ESRD who developed medial calcinosis of small arteries and painful ischaemic ulcer. The term calciphylaxis had earlier been coined by Seyle in 1962 after an experimental model to precipitate systemic calcification and skin necrosis similar to the syndrome described by Bryant and Whyte in 1898.<sup>6</sup> The prevalence of vascular calcification in patients with uraemia is high but the vascular calcification with skin necrosis is rare. This suggests there are other

putative factors responsible for the initiation of this syndrome. The risk factors for development of CUA in patients with CKD have been grouped into two classes. Those that have been confirmed from studies are referred to as Class 1 while Class 2 are presumed risk factors (Table 2).

**Pathogenesis**

Pathogenesis of CUA is unclear but is thought to involve an imbalance

between inducers and inhibitors of calcification of the vascular wall.<sup>7-9</sup> In affected patients, the expression of osteopontin and bone morphogenic protein 4, both inducers of vascular calcification, is increased in vascular smooth muscle and dermal cells, respectively.<sup>10,11</sup> In addition, vascular smooth muscle cells in CUA transform into osteogenic (osteoblast-like cells) via expression of core-binding factor-1 and express bone-related proteins such as osteocalcin, bone sialoprotein, type 1 collagen and osteopontin.<sup>8,12</sup> In contrast to this, it has been postulated that uraemia with its powerful inflammatory changes suppress the inhibitors of vascular calcification (e.g. fetuin A and osteoprotegerin) possibly through the nuclear factor kappa B (NFkB) cascade.<sup>13</sup> The use of coumarin in CKD can be potentially lethal because the actions of the matrix  $\gamma$ -carboxyglutamate (Gla) protein on the action of coumarin induce inhibition of vitamin-K-dependent carboxylation will result in increased vascular calcification.<sup>14</sup> Another factor that promotes vascular calcification in CKD patients is loss of pyrophosphate from endothelial and vascular smooth muscle cells; this pyrophosphate inhibits mineralisation of the bone thus promoting bone resorption.<sup>15</sup> The vascular calcification is further augmented by the existing disturbance of calcium and phosphate metabolism, the use of vitamin D analogs, elevated PTH hormone, ischemia and deficiencies of proteins C and S that accompanied heavy proteinuria. Also, very low protein C or protein S activities are encountered in patients on haemodialysis, a reflection of protein loss during haemodialysis.<sup>2</sup> The state of uraemia should generally provoke CUA but is seen in only a fraction of CKD patients, which may suggest the active roles of procalcific factors in concert with ischemia, inflammation and endothelial injury.<sup>1</sup>

**Investigations**

There are some specific investigations that are necessary for the evaluation of CUA. These include complete renal function tests that are geared towards assessing the severity of CKD particularly the changes in relation

to mineral and bone disease (MBD). Serum calcium, phosphate, PTH, alkaline phosphatase, particularly bone specific alkaline phosphatase. This bone specific alkaline phosphatase correlates with the degree of osteoblastic activity and increases the predictive value of PTH as a measure of bone turnover. Our patient had markedly deranged serum chemistry with elevation of serum creatinine, urea, phosphate as well as alkaline phosphatase (Table 1). We were unable to assay intact PTH during the admission due to a technical hitch. Also serum level of osteocalcin, a vitamin k dependent protein produced by the osteoblasts and serum tartrate-resistant acid phosphatase 5b level which are usually increased in CUA could not be assayed.

Coagulation factors level are decreased and these include prothrombin time, activated partial thromboplastin time, protein C and S level, while the levels of aluminium, erythrocyte sedimentation rate (ESR) and C-Reactive Protein, anticardiolipin, lupus anticoagulant, factor V Leiden, homocysteine, rheumatoid factor, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) and cryoglobulins are elevated. The information from the serum level of these will not only serve as predictors of CUA but may also assist in excluding vasculitides originating from connective tissue disease. The ESR in our patient was only mildly elevated when compared with marked increases that normally characterise vasculitic diseases.

Imaging studies include plain radiograph that demonstrates vascular calcification within the dermis and subcutaneous tissue. Bone scintigraphy with a technetium-99m methylene diphosphate bone scan reveals superficial tracer localization in the subcutaneous tissues as well as visceral tracer activity.<sup>17</sup> The best radiological imaging seems to be an assessment with xerography (the X-ray technique used in mammography), this might reveal small-vessel calcifications and also provides information on transcutaneous oxygen saturation, a measurement of this can confirm underlying tissue ischemia.<sup>18,19</sup> The bone xerograph is not readily available in our centre as in many others in resource poor settings hence the use of colour flow

Doppler Ultrasound Scan (DUS) which is non-invasive and is readily accessible and affordable. DUS is an alternative investigation tool that demonstrated vascular stenosis and when this was coupled with plain radiograph that revealed calcific densities in the dermis and subcutaneous tissue a diagnosis of calciphylaxis was made. Our index patient had DUS as well as X-ray of lower limbs and pelvis which were distinctly suggestive of CUA. Skin biopsy is the reliable means of diagnosis but it is fraught with major disadvantages which include traumatization to the skin with acceleration to ulceration and subsequent infection coupled with delayed healing. Biopsy specimen typically demonstrates calcification within the media of small- and medium-sized arterioles with extension of intimal hyperplasia and fibrosis. A mixed inflammatory infiltrates are seen with subcutaneous calcium deposits, panniculitis, fat necrosis and vascular microthrombi.<sup>1,20</sup>

CUA should be differentiated from coumarin-induced skin necrosis, atherosclerotic peripheral vascular disease, systemic vasculitis, cryoglobulinemia, cholesterol embolization, pyoderma gangrenosum, bullous pemphigoid, leukocytoclastic vasculitis, Wegener granulomatosis, lupus erythematosus, oxalosis and benign nodular calcification (a common condition in patients with CKD).

### Treatment

**General measures:** The promoters (use of Vitamin D analogs, parenteral iron therapy, calcium supplementation and warfarin) of calcification should be avoided while vitamin K supplementation will be necessary in coumarin-induced CUA.

**Medical treatment:** However, the medical management has been effective with the use of chelating agent like sodium thiosulphate or use of biphosphonates (e.g. pamidronate and ibandronate; and orally available etidronate).<sup>23-27</sup> The use of these agents with intensified dialysis adopting low calcium dialysate has been found to be successful. Sodium thiosulfate, an inorganic salt, reduces metastatic tissue

calcifications by chelating calcium from soft tissues. Sodium thiosulfate also acts as an antioxidant and induces endothelial nitric oxide synthesis, which improves blood flow and tissue oxygenation. Intravenous sodium thiosulfate at a dosage of 5–25 g during dialysis seems to be a successful treatment for CUA in combination with the above-mentioned therapies (i.e. avoidance of risk factors, and care of the wound).<sup>23,24</sup> This approach should be combined with measures aimed at restoring the patient's calcium and phosphate balance with the use of non-calcium based phosphate binders (e.g. sevelamer and lanthanum carbonate). Some reports have found calcimimetics (e.g. cinacalcet) to be effective for the rapid control of secondary hyperparathyroidism with complete healing of skin ulcers.<sup>28</sup> These agents increase the sensitivity of calcium receptors to available calcium thus reducing the serum PTH considerably.

**Surgical treatment:** Treatment has been mainly surgical with debridement of the ulcer, care of ulcer including use of hyperbaric oxygen and control of pain with opioid analgesia<sup>(3,21,22)</sup>. Parathyroidectomy would lead to correction of hyperparathyroidism which would consequently lead to normalization of calcium phosphate product.

### Conclusion

CUA remains a rare complication of ESRD with devastating consequences. Early presentation to the nephrologist, aggressive management of hyperphosphataemia, adequate renal replacement therapy and chelation with sodium thiosulphate could reduce the morbidity associated with the disease.

### REFERENCES

1. Janigan DT, Hirsch DJ, Klassen GA, MacDonald AS. (2000) Calcified subcutaneous arterioles with infarcts of the subcutis and skin ('calciphylaxis') in chronic renal failure. *Am J Kidney Dis* **35**: 588–597.
2. Wilmer W and Magro CM. (2002) Calciphylaxis: emerging concepts in prevention, diagnosis, and treatment. *Semin Dial* **15**: 172–186.
3. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. (2007)

- Calciophylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* **56**: 569–579.
4. Mazhar AR, Johnson RJ, Gillen D, Stivelman JC, Ryan MJ, Davis CL, Stehman-Breen CO. (2001) Risk factors and mortality associated with calciophylaxis in end-stage renal disease. *Kidney Int* **60**: 324–332.
  5. Gipstein RM, Coburn JW, Adams DA, Lee DB, Parsa KP, Sellers A. (1976) Calciophylaxis in man. A syndrome of tissue necrosis and vascular calcification in 11 patients with chronic renal failure. *Arch Intern Med* **136**: 1273–1280.
  6. Seyle H. (1962) Calciophylaxis. Chicago, 111: University of Chicago Press.
  7. Shroff RC and Shanahan CM. (2007) The vascular biology of calcification. *Semin Dial* **20**: 103–109.
  8. Weenig RH (2008) Pathogenesis of calciophylaxis: Hans Selye to nuclear factor  $\kappa$ B. *J Am Acad Dermatol* **58**: 458–471.
  9. Moe SM and Chen NX. (2003) Calciophylaxis and vascular calcification: a continuum of extra-skeletal osteogenesis. *Pediatr Nephrol* **18**: 969–975
  10. Griethe W, Schmitt R, Jurgenssen JS, Bachmann S, Eckardt KU Schindler R. (2003) Bone morphogenic protein-4 expression in vascular lesions of calciophylaxis. *J Nephrol* **16**: 728–732.
  11. Ahmed S, O'Neill KD, Hood AF, Evan AP, Moe SM. (2001) Calciophylaxis is associated with hyperphosphatemia and increased osteopontin expression by vascular smooth muscle cells. *Am J Kidney Dis* **37**: 1267–1276.
  12. Vattikuti R and Towler R. (2004) Osteogenic regulation of vascular calcification: an early perspective. *Am J Physiol Endocrinol Metab* **286**: E686–E696.
  13. Schafer C, Heiss A, Schwarz A, Westenfeld R, Ketteler M, Floege J. (2003) The serum protein  $\alpha$ 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. *J Clin Invest* **112**: 357–366.
  14. Cranenburg EC Vermeer C, Koos R, Boumanns ML, Hackeng TM, Bouwman FG. (2008) The circulating inactive form of Matrix Gla Protein (ucMGP) as a biomarker for cardiovascular calcification. *J Vasc Res* **45**: 427–436.
  15. Chen NX and Moe SM. (2006) Uremic vascular calcifications. *J Invest Med* **54**: 380–384.
  16. Seyle H, Gabbiani G, Strebel R. (1962) Sensitization to calciophylaxis by endogenous parathyroid hormone. *Endocrinology* **71**: 554–558.
  17. Soni S and Leslie WD. (2008) Bone scan findings in metastatic calcification from calciophylaxis. *Clin Nucl Med* **33**: 502–504.
  18. Bleibel W, Hazar B, Herman R. (2006) A case report comparing various radiological tests in the diagnosis of calcific uremic arteriopathy. *Am J Kidney Dis* **48**: 659–661.
  19. Wilmer WA, Voroshilova O, Singh I, Middendorf DF, Cosio FG. (2001) Transcutaneous oxygen tension in patients with calciophylaxis. *Am J Kidney Dis* **37**: 797–806.
  20. Essary LR and Wick MR. (2000) Cutaneous calciophylaxis: an under-recognized clinicopathologic entity. *Am J Clin Pathol* **113**: 280–287.
  21. Rogers NM, Teubner DJ, Coates PT. (2007) Calcific uremic arteriopathy: advances in pathogenesis and treatment. *Semin Dial* **20**: 150–157.
  22. Vassa N, Twardowski ZJ, Campbell J. (1994) Hyperbaric oxygen therapy in calciophylaxis induced skin necrosis in a peritoneal dialysis patient. *Am J Kidney Dis* **23**: 878–881.
  23. Guerra G, Shah RC, Ross EA. (2005) Rapid resolution of calciophylaxis with intravenous sodium thiosulfate and continuous venovenous haemofiltration using low calcium replacement fluid: case report. *Nephrol Dial Transplant* **20**: 1260–1262.
  24. Meissner M, Kaufmann R, Gille J. (2007) Sodium thiosulfate: a new way of treatment for calciophylaxis? *Dermatology* **214**: 278–282.
  25. Shiraishi N, Kitamura K, Miyoshi T, Adachi M, Kohda Y, Monaguchi H, Misumi S. (2006) Successful treatment of a patient with severe calcific uremic arteriopathy (calciophylaxis) by etidronate disodium. *Am J Kidney Dis* **48**: 151–154.
  26. da Costa JB, da Costa AG, Gomes MM. (2007) Pamidronate as a treatment option in calciophylaxis. *J Eur Acad Dermatol Venereol* [doi:10.1111/j.1468-3083.2007.02532.x]
  27. Hanafusa T, Yamaguchi Y, Tani M, Umegaki N, Nishimura Y, Katayama I. (2007) Intractable wounds caused by calcific uremic arteriopathy treated with bisphosphonates. *J Am Acad Dermatol* **57**: 1021–1025.
  28. Velasco N, MacGregor MS, Innes A, Mackay IG. (2006) Successful treatment of calciophylaxis with cinacalcet—an alternative to parathyroidectomy? *Nephrol Dial Transplant* **21**: 1999–2004