Systemic Calciphylaxis: Diffuse Cutaneous Involvement and Ischemic Optic Neuropathy – a case report.

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ABSTRACT

Calciphylaxis, or calcific uraemic arteriolopathy, is a rare disease that is difficult and challenging to treat and has a high mortality rate. Its pathogenesis remains to be fully elucidated. Cutaneous manifestations usually predominate although systemic calciphylaxis has been reported, whereby calcifications occur in other organs, including brain, eyes, lungs, intestines and the mesentery. Treatment option is limited. The most common disease-modifying treatment used is intravenous sodium thiosulphate. We report a case of systemic calciphylaxis in a dialysis-dependent patient who presented with cutaneous lesions and later developed bilateral ischemic optic atrophy. Our case had a poor clinical outcome despite optimal supportive care with multi-disciplinary approach and four weeks of intravenous sodium thiosulphate treatment.

Keywords: calciphylaxis, systemic calciphylaxis, diffuse calciphylaxis, calcific uraemic arteriolopathy, ischaemic optic neuropathy, sodium thiosulphate

INTRODUCTION

Calciphylaxis, or calcific uraemic arteriolopathy, is a rare disease that is difficult and challenging to treat. Its pathogenesis remains to be fully elucidated, despite its well-characterized features clinically and histologically. The disease was first described by Selye et al. in 1961 in a condition observed in rodents, defining it as 'a hypersensitivity in which, after sensitization by a systemic calcifying factor, exposure to certain challengers causes an acute, local calcification followed by inflammation and sclerosis'.[1] Calciphylaxis was then reported in uraemic patients presenting with cutaneous ulcerations.[2, 3] These investigators hypothesized that secondary hyperparathyroidism could be a 'sensitizing' agent, and iron therapy or local trauma could be the 'challengers' precipitating the formation of calciphylactic lesions. Cutaneous manifestations of calciphylaxis consist of excessively tender, firm cutaneous lesions that can ulcerate and produce a black eschar.[4] It usually has a proximal or distal distribution, less likely to be diffusely spread. Although cutaneous manifestations predominate, systemic calciphylaxis has been reported, whereby vascular calcifications occur in other organs, including brain, eyes, lungs, intestines and the mesentery.[4-7] Treatment option for calciphylaxis is limited. The most common off-label treatment is intravenous sodium thiosulphate.[1,4] We report a case of systemic calciphylaxis with biopsy-proven cutaneous skin

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lesions and an extra-cutaneous manifestation presented as bilateral optic nerve atrophy. This case illustrates systemic calciphylaxis with a poor clinical outcome despite optimal supportive care with multi-disciplinary approach and four weeks of intravenous sodium thiosulphate treatment.

CASE REPORT

A 42-year-old Malay woman presented to accident and emergency with a two-week history of severely painful lesions on her thighs. She suffered from end-stage renal disease secondary to chronic glomerulonephritis. She has been on regular haemodialysis through a left radiocephalic arteriovenous fistula for nine years. Her other co-morbid conditions included hypertension, morbid obesity (body mass index 43 kg/m^2) and atrial fibrillation. She was started on warfarin for atrial fibrillation eight months prior to presentation. She also had poorly controlled secondary hyperparathyroidism, for which she had declined parathyroidectomy. She was on calcium-based phosphate binders (calcium carbonate), calcitriol and cinacalcet.

On admission, she had a low blood pressure of 99/56mmHg. Physical examination revealed several tender subcutaneous, violaceous nodular lesions in both lower extremities predominantly on the thighs. Her pedal pulses were normal. Laboratory findings on admission included a corrected calcium of 2.43 mmol/L phosphate 2.41 mmol/L, blood urea nitrogen 22 mmol/L, creatinine 1061 µmol/L, intact parathyroid hormone level of 45.3 ng/L and albumin 34 g/L. Her inflammatory markers were also elevated and continued to increase in the initial days of hospitalization, with C-reactive protein peaking at 35.2 nmol/L, white cell count $19.5x10^3$/uL and a neutrophilia of $16.1x10^9$/L. Her previous parathyroid hormone levels were between the range of 31 and 42 ng/L. Clinical suspicion was high for calciphylaxis.

Skin biopsy was performed and pathology findings were suggestive of calciphylaxis with granular calcium deposits in the arteriolar wall, thrombosed thick-walled mid-dermis arterioles, septal inflammatory infiltrates with septal panniculitis (Figures 1a, 1b, 1c).

Calcium carbonate was stopped and sevelamer was started. Warfarin and calcitriol were discontinued. Cinacalcet was increased to its maximum dose of 180mg daily. The extensive cutaneous ulcerations could have a neuropathic component from injury to cutaneous nerves. Thus, her pain was managed with multimodal analgesia with intravenous fentanyl infusion, oral gabapentin and breakthrough fentanyl boluses as required. Despite these, she reported poor control of her pain.

Twenty-five grams of intravenous sodium thiosulphate was administered thirty minutes before the end of every haemodialysis session. A low dialysate calcium concentration of 1.25 mmol/L was used. Dialysis frequency was increased to four times a week. She did not experience any side effects from sodium thiosulphate, such as hypotension, nausea, emesis, fluid overload and metabolic acidosis.[1,4]

Two weeks into her admission, she developed an acute onset of bilateral blurry vision. There was no associated retro-orbital pain or headache. An ophthalmologist consult was made. Fundoscopy examination revealed bilateral optic nerve atrophy, consistent with bilateral optic nerve ischaemia. Computed tomography scans of the brain and orbits were unremarkable. Transthoracic echocardiography revealed no evidence of thrombus.

She was started on broad spectrum antibiotics for empirical treatment of sepsis as she developed febrile episodes, leukocytosis and high C-reactive protein levels. Blood cultures did not reveal any bacteraemia. Her skin

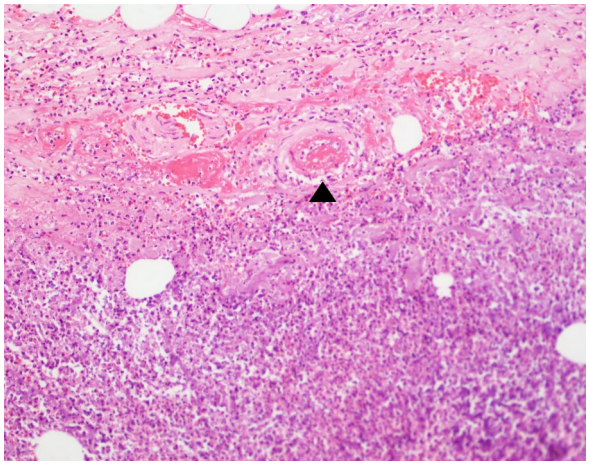

Figure 1a: Thrombosed arteriole in the dermis (shown by arrow head)

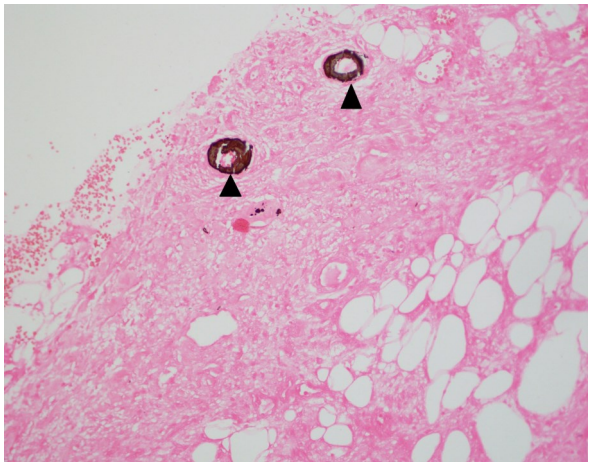

Figure 1b: Von-kossa stained slide showing calcified blood vessels (shown by arrow heads)

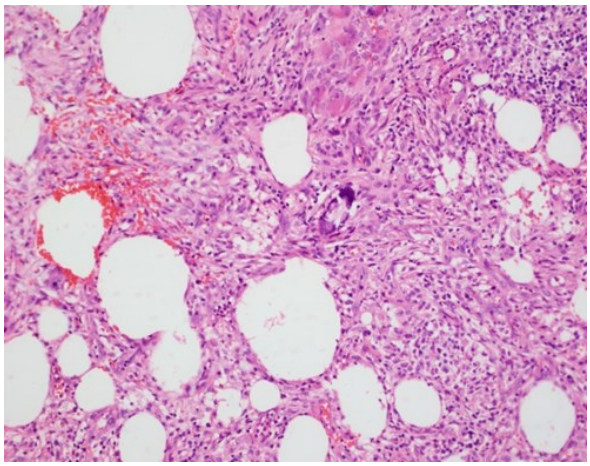

Figure 1c: Inflammatory infiltrates between adipocytes in septal panniculitis
(Histology slides courtesy of Histology Department, RIPAS Hospital, Brunei)

lesions were treated with regular dressings and wound care. These lesions unfortunately extended to her buttocks and lower back, forming ischaemic plaques and ulcerations (Figure 2a&b). Multidiscipline health care teams were involved in her care including nephrology, dermatology, ophthalmology, palliative medicine team, physiotherapy, and dietetics. She unfortunately continued to deteriorate and succumbed to her illness.

DISCUSSION

Our case illustrated systemic calciphylaxis in a morbidly obese patient on long term haemodialysis. This patient had a poor clinical outcome. Calciphylaxis is associated with a high mortality rate, ranging from 45% to as high as 80%.[1, 8-9] Similar to previously reported, the predisposing factors for our patient to develop calciphylaxis include female gender, obesity, poorly controlled secondary hyperparathyroidism and warfarin therapy.[1, 8] Warfarin is known to antagonize Vitamin K2, which is involved in the inhibition of calcium deposition in the vasculature. This is hypothesized to be the mechanism behind warfarin creating an unbalanced environment favouring vascular calcification in calciphylaxis.[10]

Our patient presented initially with proximal calciphylaxis with violaceous lesions on her thighs. Proximal calciphylaxis, which occurs predominantly on the thighs and abdomen, has been described in the literature, which suggested that morbid obesity (body mass index greater than 35 kg/m^2), white race and low serum albumin (decrement of at least 10 g/L) were associated with proximal calciphylaxis in dialysis-dependent patients.[4, 11] Our case was morbidly obese, one of the reported risk factors for the disease.[8, 11, 12]

She then developed bilateral optic nerve atrophy, with acute onset of painless bilateral blurry vision a few weeks after she presented with cutaneous calciphylaxis lesions. She also experienced intermittent hypotensive episodes during haemodialysis treatments. Hypotension together with calci-

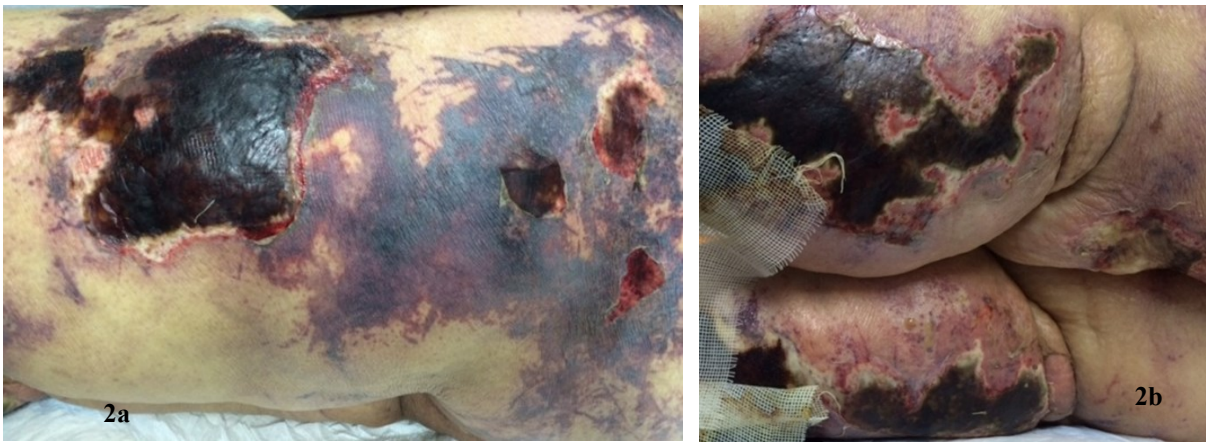

Figure 2a: Calciphylactic lesions on left thigh, 2b: Calciphylactic lesions on bilateral buttocks.

fied vessels in calciphylaxis restrict blood flow and create ischaemia. Hypoperfusion of the optic nerve leads to ischaemic optic neuropathy. Indeed ischaemic optic neuropathy was reported in two patients on long-term hemodialysis presenting with hypotensive episodes. Temporal artery biopsy in one of the patients showed extensive medial calcification without arteritis. The cause of the ischaemic neuropathy was thought to be due to both calcific uraemic arteriolopathy and hypotension. These two patients did not have cutaneous manifestations of calciphylaxis.[5]

Clinical data is limited on treatment for calciphylaxis and is mostly based on expert opinion and observational data. In general, supportive care with multidisciplinary approach is recommended. The specialties involved should include nephrology, dermatology, palliative care, nutrition, physiotherapy and wound care specialists. Pain is the main associating feature with calciphylaxis thus its management needs to be optimized. Combination of opioids and non-opioids including neuropathic agents is often used as pain in calciphylaxis may have a neuropathic component.[13] In our case, we used fentanyl infusion and gabapentin. Fentanyl dose was titrated up during haemodialysis as our patient experienced intense pain during dialysis. The involvement of palliative care team helped with symptom control.

In terms of disease-specific treatment, sodium thiosulphate was used successfully in small observational studies or case reports.[4, 14] A multicenter retrospective cohort study published in 2013 reported resolution in calciphylactic lesions in 26% and an improvement in 28% of the 57 patients treated with intravenous sodium thiosulphate in the last half hour of haemodialysis.[14] How the agent halts the progression of the disease is uncertain. There has been no studies on optimal treatment duration, however an improvement of pain within two weeks is thought to predict long-term response.[4] Recent literature reported successful treatment with intralesional sodium thiosulphate in four distinct cases of calciphylaxis. The skin lesions in their case series were active, violaceous and non-necrotic.[15] Intralesional sodium thiosulphate was not considered in our case as her lesions were extensive and progressed very quickly to ulcerated necrotic lesions.

In conclusion, this case illustrates systemic calciphylaxis in a middle-aged, morbidly obese, dialysis patient who eventually died despite multidisciplinary team approach and intravenous sodium thiosulphate treatment. She developed ischaemic optic neuropathy attributed by the repeated hypotensive insult. Prevention of this disease is therefore crucial

as it is difficult to treat. We recommend controlling the modifiable risk factors as preventative measures. Weight loss must be emphasized for obese dialysis patients. Secondary hyperparathyroidism should be managed through strict diet control and medications use. For those with uncontrolled secondary hyperparathyroidism and evidence of parathyroid adenoma, early treatment with surgical parathyroidectomy should be carried out. Blood pressure control must be optimum to prevent hypotension that could lead to optic neuropathy and blindness.

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