

Case Report

A rare extensive clinical presentation of calciphylaxis due to primary hyperparathyroidism

Mohamad Safwan A.*, K. N. Vijayan, Akash S., Ashwini T., Muhammed Irfan K. P. C.

Department of General Surgery, Kerala Institute of Medical Sciences, Thiruvananthapuram, Kerala, India

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*Correspondence:

Dr. Mohamad Safwan A.,

E-mail: mdsafwanmbbs@gmail.com

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ABSTRACT

Calciphylaxis is a dreadful condition predominantly seen in chronic kidney disease patients on haemodialysis or following renal transplant. Calciphylaxis occurring in patients with normal kidney function is extremely rare. Here we present 53-year-old women presented with painful, extensive eschar-like skin lesions involving bilateral lower limb of 3 months of duration. She had hypercalcemia, high serum parathyroid hormone (PTH) levels and elevated alkaline phosphatase. Ultrasound neck and sestamibi scan demonstrated left inferior parathyroid adenoma. Lower limb radiographic studies showed subcutaneous calcification. Cutaneous biopsy confirmed calciphylaxis. Cinacalcet to control hypercalcemia, antibiotics and pain control medications were started. Left inferior parathyroidectomy and debridement of gangrenous lesions of lower limbs were performed. Histopathology was consistent with parathyroid adenoma. Lower limb wound started granulating with Vacuum-assisted closure (VAC) dressing and skin graft was planned. Unfortunately, she succumbed 11 weeks from surgery due to proximal myopathy, aspiration pneumonitis, sepsis and multiorgan failure.

Keywords: Calciphylaxis, Vascular calcification, Primary hyperparathyroidism, Parathyroidectomy

INTRODUCTION

Calciphylaxis is also known as calcific arteriolopathy and characterized by extremely painful and progressive cutaneous necrosis due to calcification and thrombosis of arterioles and capillaries in the dermis and subcutaneous fat.^{1,2} Incidence of uremic calciphylaxis in end-stage renal disease patients on dialysis is 1% with a prevalence of 4%- and 1-year mortality of 45-80%.^{2,3} Non-uremic calciphylaxis (NUC) is rather unusual, with higher (52%) mortality. Death is mostly due to sepsis, which occurs between 2 weeks to 1 year after diagnosis.³

To the best of knowledge, an around 25 case of calciphylaxis due to primary hyperparathyroidism has been reported so far in world literature.^{4,5} This case had the most extensive presentation of calciphylaxis reported till date. Hence, report this case for its rarity as well as for

highlighting its unusual presentation to contribute in part to the better understanding and awareness of this condition.

CASE REPORT

54 years old women presented with extensive painful blackish lesions involving bilateral lower limbs up to mid-thigh; sparing the feet, of 3 months duration. Her comorbidities were type-II diabetic mellitus, hypertension and depressive disorder.

Clinical history revealed that she had been diagnosed and was being treated elsewhere conservatively as a case of bilateral lower limb cellulitis for the past 2 months. During her previous hospitalization, laboratory workup showed hypercalcemia (13.1 mg/dl), Computed tomography (CT) scan of lower limb revealed evidence

extensive calcific deposits in the subcutaneous plane of both lower limbs (Figure 1B).

As there was no relief of severe pain, inability to walk, worsening of skin patches and ulcers, she was referred to the institution.

In general examination she was well-oriented, obese and bed-ridden, vital signs were normal. She had pallor, pitting oedema over the dorsum of feet and weakness of limb muscles. Local examination showed multiple, circumferential, tender, necrotic leathery cutaneous plaques with irregular edges surrounded by violaceous brawny erythema over bilateral lower limb extending from mid-thigh up to ankle (Figure 1A). There was no local warmth and bilateral dorsalis pedis pulse were palpable



Figure 1: (A) Clinical picture of extensive necrotic leathery cutaneous plaques. (B) CT of lower limbs of extensive calcific deposits in subcutaneous plane of both lower limbs.

Table 1: Laboratory results.

| Laboratory parameters | Values | Inference |
|-------------------------------------|--------|-----------|
| Haemoglobin (g/dl) | 9 | Decreased |
| Total leukocyte count (cells/cu.mm) | 12600 | Increased |
| CRP (mg/dl) | 90 | Increased |
| Alkaline phosphatase (U/L) | 140 | Increased |
| Urea (mg/dl) | 40 | Normal |
| Creatinine (mg/dl) | 1.3 | Normal |
| Calcium (mg/dl) | 13.1 | Increased |
| Phosphorus (mg/dl) | 3.8 | Normal |
| Parathyroid hormone (pg/dl) | 614.4 | Increased |
| 24-hour Urinary creatinine (mg/dl) | 317 | Decreased |
| 24-hour Urinary calcium (mg/day) | 218 | Normal |

Ultra-sonography (USG) of neck suggested left inferior parathyroid adenoma. Technetium (^{99m}Tc) sestamibi localized adenoma involving left inferior parathyroid gland (Figure 2A). Thus, made a diagnosis of primary hyperparathyroidism due to left inferior parathyroid adenoma with suspected calciphylaxis. Had multi-disciplinary approach involving endocrinology, nephrology, infectious disease, cardiology, psychiatry and critical care medicine. She was started on broad spectrum intravenous antibiotics, intravenous normal saline, furosemide, oral cinacalcet 90 mg/day, daily colloid silver dressing and other supportive measures.

Under general anaesthesia, the neck was explored and left inferior parathyroid adenoma was excised (Figure 2B) along with intra-operative PTH assay followed by debridement of gangrenous patches of both lower limbs. Her pre-excision PTH level was 295 pg/nl which decreased to 95 pg/nl after 10 minutes post-excision, which satisfied Miami criteria. Her calcium declined to normal (9.1 mg/dl) post-operatively.

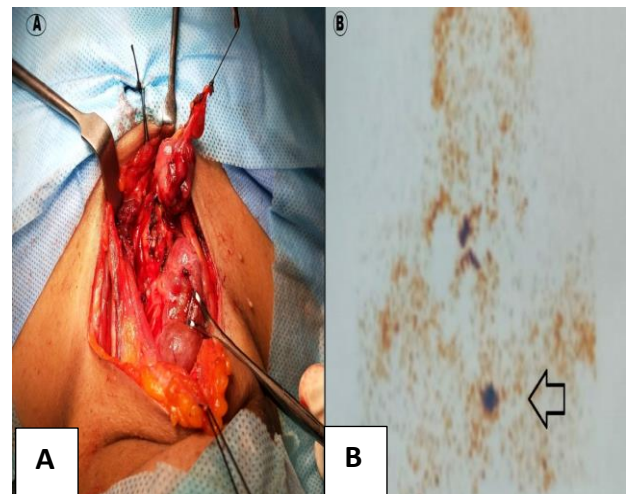


Figure 2: (A) Sestamibi scan of abnormal focal tracer uptake in left inferior parathyroid region. (B) Intra-operative image of left inferior parathyroid adenoma (Tied).

Dermo-cutaneous biopsy of lesion showed extensive fibrinoid necrosis of blood vessels with calcification and dermal vessel thrombosis which confirmed the diagnosis of calciphylaxis (Figure 3A, B, C). Histopathology examination of parathyroid gland was consistent with parathyroid adenoma weighing 2 gm. Her lower limb wounds improved and showed healthy granulation after treatment with vacuum-assisted closure dressing for 7 weeks (Figure 3D). She was planned for split skin graft.

Despite initial improvement with aggressive management, her general health deteriorated gradually. She developed difficulty in breathing and swallowing, hence was shifted to intensive care. Unfortunately, she had aspiration pneumonitis due to proximal muscle

weakness which led to sepsis, multi-organ dysfunction syndrome and death after 80 days of hospitalization.

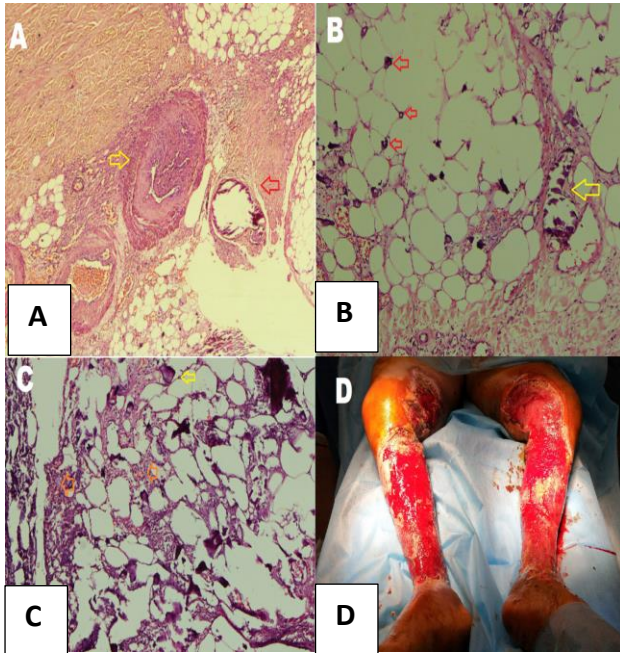


Figure 3: (A) Histopathology picture of gangrenous lesion showing dermo-cutaneous junction with intra-luminal thrombosis of blood vessel (yellow arrow) and intravascular calcification (red arrow). (B) Histopathology picture of subcutaneous medium sized (red arrow) and small size vessel calcification (yellow arrow). (C) Histopathology picture showing features of acute panniculitis with neutrophil debris (red arrow) and small size vessel calcification (yellow arrow).

DISCUSSION

Calciphylaxis or vascular calcification-cutaneous necrosis syndrome was first described by Selye et al in 1962 as hypersensitivity reaction, based on their experiments on nephrectomised rats.^{1,7} However first case in humans with histopathological diagnosis of non-uremic calciphylaxis was reported in 1956.⁸

Most common risk factor and co-morbidities associated with NUC are primary hyperparathyroidism, malignancy, alcoholic liver disease and connective tissue disorders. Others are obesity, female gender and rapid weight loss, diabetes, protein C and S deficiency, anti-phospholipid syndrome, vitamin D abnormalities and drugs like Warfarin and steroid.^{2,3}

The pathogenesis of NUC is not well understood. However, when serum calcium and phosphate levels are elevated, it leads to reduced solubility which results in calcium phosphate deposition in vessels, also known as metastatic calcification.⁹

Aetiology like primary hyperparathyroidism, steroids use and liver disease is recognized in stimulating the expression of RANK ligand and reducing the expression of osteoprotegerin, thus activating NF- κ B or breaking the inhibitory protein of NF- κ B and resulting in osseous mineral loss and extra-osseous mineral deposition.^{3,10}

As there is no specific diagnostic test for NUC, the diagnosis mainly depends on the clinician's suspicion from history and physical examination. Initially, skin changes begin as violaceous mottling of the skin and induration in a livedo reticularis pattern. When tissue thrombosis and infarction occur, it produces excruciating painful, black leathery lesions which often gets superinfected.^{2,11} Lesions are common in areas where fat tissue is the most abundant. Distal extremities lesions are considered to have a better prognosis when compared to truncal lesions. Proximal muscle weakness is an infrequent manifestation of calciphylaxis which can occur even without cutaneous necrosis, due to ischemic myopathy.¹²

A deep skin biopsy from the periphery of the lesion is necessary to confirm the diagnosis, especially in non-uremic patients. It shows calcium deposition within the arteriole-sized and small-sized vessel walls with endovascular fibrosis associated with fat necrosis, and neutrophil and macrophages infiltration.¹²

Although, there is no approved treatment for calciphylaxis, it should be approached with multifaceted and inter-disciplinary strategy. Treatment must aim at prohibition or reversal of the vascular calcification by regulating calcium-phosphate homeostasis and prevention of lethal local and systemic septic complication along with medical therapy for optimizing associated co-morbid condition.

Parathyroidectomy surgical or chemical debridement of eschar-like cutaneous lesions and underlying inflamed adipose tissue to facilitate wound healing.^{2,4} Opiates for pain control, Cinacalcet helps in suppressing PTH which interacts with Ca-sensing receptor on parathyroid cells.^{1,13}

Intravenous or intralesional sodium thiosulphate increases the solubility of the calcium deposits along with its antioxidant and vasodilatory property has been reported in uremic calciphylaxis. Adequate hydration and nutritional support are very essential.^{1,2,13}

Non-calcium containing phosphate binders like sevelamer carbonate or lanthanum carbonate, bisphosphonates, hyperbaric oxygen therapy (HBOT) are used for the treatment of resistant calciphylaxis.^{2,13,14}

In this case, couldn't use sodium thiosulphate, lanthanum carbonate and HBOT due to unavailability. However, VAC therapy helped in the rapid healing process.

CONCLUSION

Calciophylaxis is a terrible disease carrying high morbidity and mortality due to sepsis. A strong clinical suspicion must arise while managing patients with painful cutaneous ulcers with necrosis. Serum calcium screening and serum PTH should be done in such cases. Early identification and multi-faceted interdisciplinary treatment strategy with cinacalcet, parathyroidectomy, aggressive wound debridement followed by VAC therapy are required for a better outcome.

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