CUTANEOUS GANGRENE SECONDARY TO METASTATIC CALCIFICATION IN END STAGE RENAL FAILURE - A CASE REPORT

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ABSTRACT

Metastatic calcification is a frequent association of chronic renal failure but skin involvement is accepted as a rare, albeit well recognised, complication accompanying the secondary hyperparathyroidism that results from renal impairment, although the aetiology remains unknown. Skin involvement can take the form of metastatic calcinosis cutis or cutaneous gangrene resulting from vascular calcification. There have been reported cases which describe the healing of gangrenous areas following parathyroidectomy as well as use of dietary restriction of phosphorus and phosphate binding antacids[1-6]. We report a case of a 35-year-old man with end stage renal failure who presented with cutaneous gangrene but who eventually succumbed despite a subtotal parathyroidectomy and review some of the literature concerning this subject.

Keywords: *secondary hyperparathyroidism, cutaneous gangrene, renal failure*

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INTRODUCTION

The process of metastatic calcification is a frequent complication of chronic renal failure and may occur when the solubility product of calcium phosphate ($CaPO_4$) is exceeded (normal < 3.84), although this need not always be so[7]. Despite this, cutaneous involvement is extremely rare. Kolton and Pederson reviewed the literature on metastatic skin calcification in chronic renal failure and found only 8 reported cases, to which they added one of their own[8]. P de Graaf et al could not demonstrate calcification of the skin in 60 skin biopsy specimens, selectively obtained from 30 chronic renal failure patients, although 21 or 70% of them had calcification at one or more sites other than the skin, including 11 or 33% who had arterial calcification. These patients also did not present with cutaneous gangrene despite arterial involvement[9]. Winkelmann and Keating reported 3 cases of cutaneous gangrene associated with hyperparathyroidism with differing responses to treatment (which included parathyroidectomy)[4] as did Lazorik et al, who reported 4 cases[10].

CASE REPORT

The patient was a 35-year-old Chinese male who first presented to the Department of Renal Medicine, Singapore General Hospital, in 1977, at the age of 19, for asymptomatic microscopic haematuria which was detected during a pre-enlistment medical examination. After a few visits, he defaulted from follow-up, only to be referred back to the unit in 1983 for a sudden episode of severe hypertension (BP 210/110 mm Hg) associated with acute renal insufficiency. A renal biopsy subsequently revealed a diffuse sclerosing glomerulonephritis diagnostic of IgA nephropathy. The intravenous urogram showed bilateral small kidneys with no evidence of obstructive uropathy, suggestive of chronic glomerulonephritis. The serum creatinine level then was 345 µmol/L (53-133), calcium was 2.2 mmol/L (2.2-2.7) and serum phosphate was 1.1 mmol/L (0.9-1.5). Within a year, he had developed end stage renal failure requiring haemodialysis which was started in March 1984.

He subsequently had 2 unsuccessful renal transplants; a living related renal transplant from his sister in November 1984 which was rejected and needed a transplant nephrectomy in March 1985, and a cadaveric transplant from the United States in August 1986 which was also rejected 2 months later. He thus remained on haemodialysis and remained relatively well, although serial biochemistry revealed a gradually increasing $CaPO_4$ product. In 1989, serum calcium was 2.4 mmol/L and phosphate was 2.3 mmol/L. He was already on dietary restriction of phosphates and phosphate binders but levels remained elevated. In 1990, serum calcium was 2.51 mmol/L and phosphate 2.09 mmol/L. A skeletal survey then showed extensive calcification of the radial and ulnar arterics, abdominal aorta and iliac vessels. There was osteomalacia of the hand bones and early sclerosis of vertebral end plates, all features consistent with renal osteodystrophy.

His first presentation for skin problems was in June 1993 when he complained of painful extensive irregular ulcerations on both flanks. The skin ulcerations were not preceded by vesicles (this was specifically asked for as the diagnosis of herpes zoster was initially thought of) but were quite sudden in onset and fairly rapidly extending. Many of the lesions were covered with crusts and appeared necrotic. (Fig 1) The lesions initially responded to daily dressings and local desloughing treatments but continued to recur and became even more extensive, eventually involving the chest wall and axillary regions. Secondary infections also complicated the healing and he was referred for a dermatological opinion. A skin biopsy of the necrotic ulcers was performed, and histological examination revealed extensive necrosis and haemorrhage of the entire dermis up to the subcutaneous fat. Calcification was seen within several large blood vessels in the lower dermis and the vessels within the necrotic areas showed fibrin within the vessel walls. (Fig 2) A diagnosis of cutaneous necrosis due to metastatic calcification of blood vessels was made.

A parathyroidectomy was recommended but the patient had other significant medical problems that required stabilisation first, including uraemic cardiomyopathy (ejection fraction of 24%) and *Pseudomonas aeruginosa* infection of the ulcers. He was treated with multiple courses of systemic antibiotics and local desloughing to contain the infection before he underwent a

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Fig 1 – Necrotic skin lesions on the posterior axillary fold

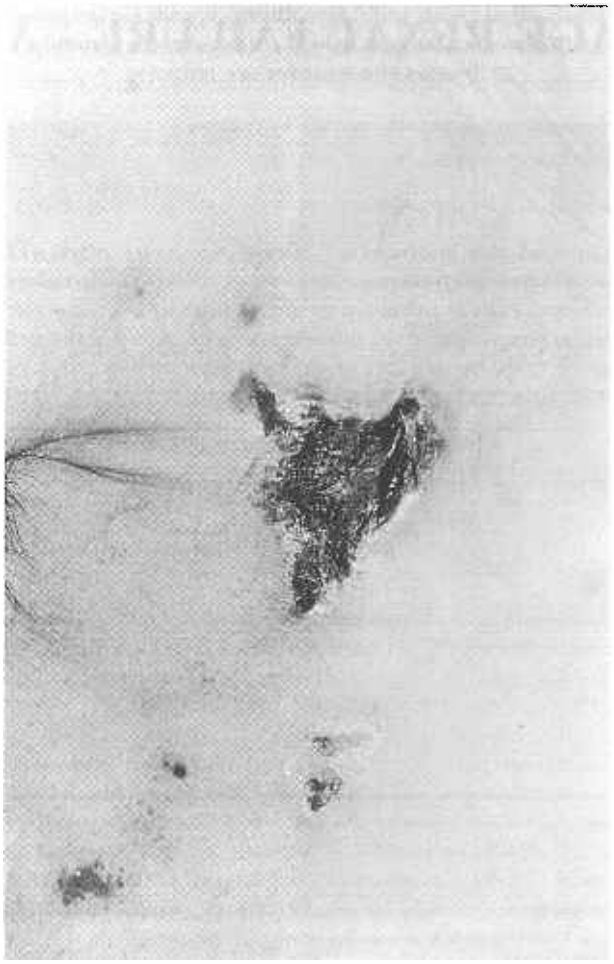
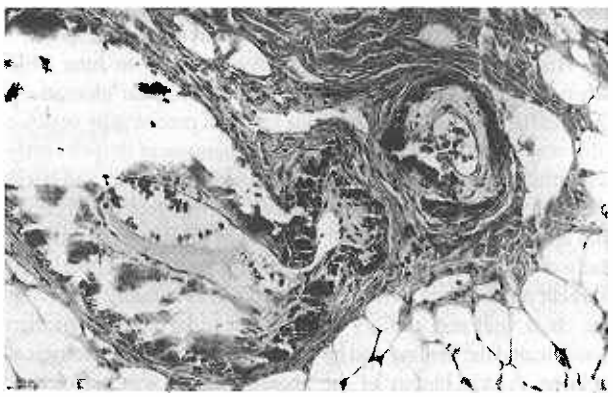


Fig 2 – Two thick-walled vessels with calcification in the lower dermis.



subtotal parathyroidectomy in August 1993. Preoperatively, serum calcium was 2.83 mmol/L, phosphate was 1.92 mmol/L giving a $CaPO_4$ product of 5.43. Post-operatively, the biochemistry levels normalised, with a serum calcium of 2.19 mmol/L and a serum phosphate level of 1.08 mmol/L, with a $CaPO_4$ product of 2.38.

Despite this, the patient continued to deteriorate and the cutaneous gangrene continued to extend, eventually affecting more than 60% of his body surface area. The biggest problem was that secondary infections of the ulcers continued unabated and this included the development of methicillin resistant *Staphylococcus aureus* infections as well. He eventually succumbed to septicaemia, two months post-operatively.

DISCUSSION

The occurrence of calcification in uraemia was first recorded in Guy's Hospital Report in 1898 by Bryant and White. Richardson et al were among the first to summarise a series of similar cases in 1969[12]. Metastatic calcification is a well-recognised complication of hyperparathyroidism. The advent of dialysis for renal failure has made calcification a more frequent problem in patient management. As renal disease progresses, nephron loss will lead to a progressive decline in glomerular filtration rate, leading to phosphate retention which causes a corresponding fall in calcium levels. Skeletal parathyroid hormone resistance in end stage renal failure and decreased 1,25 dihydroxy-cholecalciferol (1,25 DHCC) levels also contribute to hypocalcaemia and a state of secondary hyperparathyroidism then arises.

It has already been established that cutaneous involvement, whether in the form of metastatic calcinosis cutis or cutaneous gangrene, is rare. Our patient had disturbed calcium homeostasis secondary to renal osteodystrophy for three years before he developed this complication. Although the duration of hypercalcaemia would appear to have a role to play in the pathogenesis of this condition, it remains largely unresolved[11]. The sparing of other vessels and the lack of ischaemic symptoms in other organ systems in our patient also could not be explained. Winkelmann et al described three cases of vascular calcification, cutaneous gangrene and hyperparathyroidism in 1970[4]. All three cases presented with a picture of progressive cutaneous gangrene which started in the flanks associated with vascular calcification identified by roentgenogram and skin biopsy. The skin biopsies were remarkably uniform in demonstration of calcification in and about a muscular vessel in the deep dermis or panniculus. The media was replaced or compressed by the calcium masses. One of the three patients had a parathyroid adenoma that was treated by parathyroidectomy with complete resolution of the cutaneous ulcers, but the other two patients responded poorly to the same operation and progressed and succumbed to sepsis much like our patient. (One of them had a parathyroid carcinoma while the other had renal failure due to interstitial nephritis). Lazorik also described cutaneous gangrene in four patients who had chronic renal disease that resulted in secondary hyperparathyroidism and arterial calcification[10]. Three of them deteriorated in much the same fashion as our patient did despite similar attempts to reverse the disease process and the only survivor, a man who had polycystic kidney disease had complete resolution of the symptoms post-parathyroidectomy.

This case illustrates the fact that cutaneous gangrene in the context of renal failure is a very difficult management problem. Very often the patient is already in a poor state of health and not as likely to benefit from a parathyroidectomy, which might be life saving. They often die from sepsis as the ulcerations extend and become more difficult to manage, resulting in a rapid downward spiral. The initial recognition of this complication is also crucial, and sometimes the first signs of cutaneous gangrene secondary to vascular calcification can resemble vasculitic ulcers or ecthymas. The occurrence of such lesions in the correct clinical context should alert the attending physician to the possibility of this rare but often deadly complication. The local treatment to the skin should be equivalent to the treatment of burns, with meticulous charting of extent and location of ulcers and protection of the tissues from irritation. The limbs should not be treated with closed wet dressings, and cultures should be regularly taken to identify secondary infective agents, which are almost inevitable, so that appropriate antibiotics can be initiated. A definitive treatment of parathyroidectomy can then be carried out, along with ongoing supportive measures.

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