

CUTANEOUS CALCIPHYLAXIS CASE REPORT

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ABSTRACT :

In this report we describe a 45 years old female who had end stage renal failure and had been on hemodialysis for 13 years. She developed systemic calciphylaxis five years before she showed cutaneous and subcutaneous calciphylaxis.

INTRODUCTION

Calciphylaxis is a wide spread systemic calcification affecting the media of small to medium size arteries with intimal proliferation leading to ischemic tissue necrosis^(1, 2).

It is seen mostly in patients with chronic renal failure, particularly those undergoing long term hemodialysis and peritoneal dialysis^(3, 4, 5, 6). Calciphylaxis may occur after 6 months or even after 15 years of hemodialysis^(7, 8). One hundred and four cases of calciphylaxis have been reported world wide up to December 1995⁽³⁾. Calciphylaxis may rarely occur in patients with parathyroid adenoma or carcinoma⁽²⁾.

Systemic calciphylaxis has been reported to cause acral gangrene which ultimately required amputation of four limbs⁽⁹⁾. Calciphylaxis may cause cere-

bral, myocardial, splenic and intestinal infarction. Intra-and-extra cellular myocardial calcification was reported in a systemic lupus erythematosus patient who had renal failure⁽¹⁰⁾. Ocular and penile calciphylaxis were also reported^(11, 12).

Calciphylaxis commonly affects the skin and is a poor prognostic sign⁽²⁾. Cutaneous and subcutaneous necrosis are the most serious complications with a mortality rate that is almost 60%. The usual cause of death is septicemia⁽¹³⁾.

Clinically, calciphylaxis cutis may appear as large painful livedo reticularis like involvement of the skin on trunk and/or limbs which rapidly becomes gangrenous and ulcerates.

CASE REPORT

Z.Z.A. a female from Pakistan 45 years old had end stage renal failure secondary to chronic glomerulonephritis for the past 14 years (since 1982) and was on regular renal dialysis 4 hours 3 times per week for the past 13 years complicated with multiple vascular access problems. She was hypertensive (170/100). In July 1983 she had right kidney transplant which failed and was rejected in 1985. She had cataract extraction 9 years back.

In June 1991 she began to get recurrent painful swelling of her left forearm diagnosed as recurrent cellulitis. In 1994 the recurrent painful swelling of her left upper limb showed violaceous discoloration. She also had illdefined mass of both breasts with the overlying skin congested and necrotic and mammography done in April 1994 was normal. In January 1995 X-ray left upper arm showed soft tissue swelling in the posterior aspect of the left elbow. Joint and vascular calcification were demonstrated. In addition there was illdefined calcific opacity in the subcutaneous tissue in the distal third of her left arm.

Her blood calcium estimated repeatedly ranged from 2.38 to 2.56 with an average of 2.5 m.mol/l (normal 2.1 - 2.6 m.mol/l). Blood phosphorus was

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1.07 (normal 0.8 - 1.61 m.mol/l). Her parathyroid hormone was 960 picogram per liter in April 1995 and 1320 picogram per liter in December 1995. CBC : WBC : 12.2 , RBCS :2.52 Hgb :6.9. During the last 12 years she was complicated with renal osteodystrophy and hyperparathyroidism manifested by bony pains, osteopenia of pelvis, osteoporosis and fracture of the intertrochanteric region of right femer in August 1995.

In September 1995 X-ray abdomen showed calcification of abdominal aorta, splenic, adrenal and pelvic vessels. Medical treatment of one Alpha calcidol and calcium carbonate as phosphate binder failed to control the renal osteodystrophy.

In June 1996 the patient was admitted because she developed since 3 months blackish skin lesions on right side of lower abdomen (Fig.1), both breasts,

back of right buttock, lateral side of left buttock (Fig. 2) and lateral side of right buttock (Fig. 3), lateral side of left thigh (Fig. 4). The lesions were sore and extremely tender. Culture from ulcer grew Klebsiella pneumonia. X-ray pelvis showed extensive atheromatous calcification in pelvic vessels with osteopenia of bones. A dermatologist was called and diagnosed the case as calciphylaxis.

Three biopsies were taken (from the right thigh, left breast lump and areolar skin). Biopsy of the right thigh included skin and underlying adipose tissue, with surface ulceration (Fig 5) due to necrosis of the epidermis and upper dermis. Necrotic debris and fibrinopurulent exudates were seen in the ulcer crater. Dermis at the ulcer base also showed ischaemic changes. Vessels in the ulcer base and in the adjacent dermis contained fibrinous emboli (Fig 6). Extensive fat necrosis and abscess formation were seen

Fig 1 : Calciphylaxis lower abdomen (right)



Fig 3 : Calciphylaxis lateral side right buttock



Fig 2 : Calciphylaxis lateral side of left buttock



Fig 4 : Lateral side left thigh



Fig 5: Ulcer of the right thigh : necrosis and acute inflammatory infiltrates involving full thickness of epidermis and dermis ; hyalinised scar tissue in the adjacent dermis

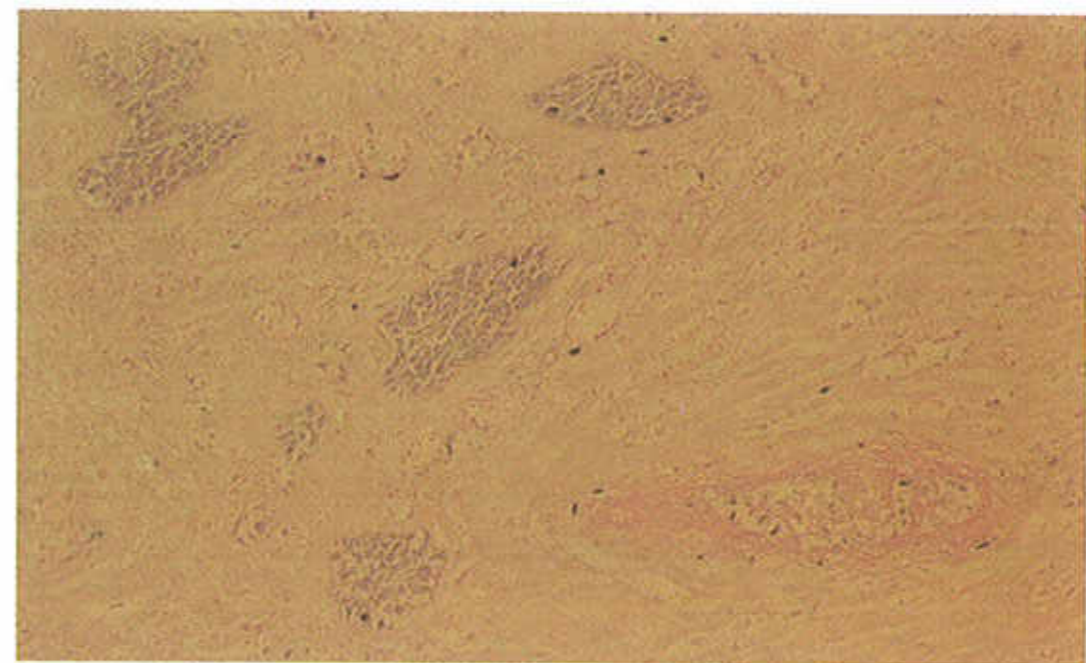


Fig 9: Ghosts of infarcted ductulo-lobular units in the breast. Only a few myoepithelial cells are visible in the periphery.



Fig 6 : Fibrinous emboli in vessels in the ulcer base and adjacent dermis

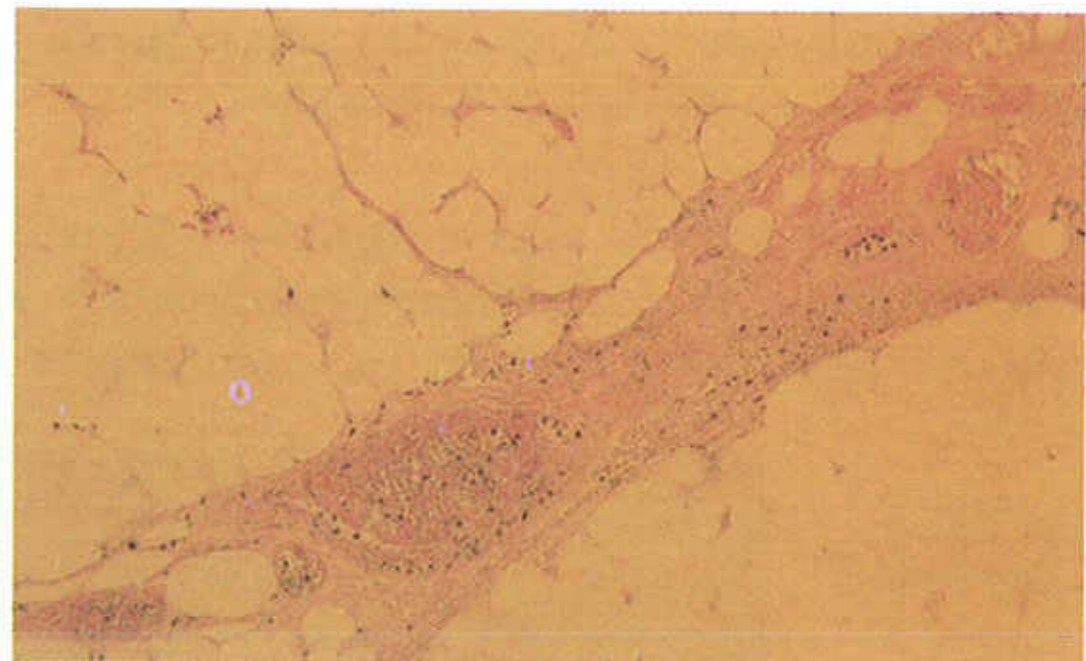


Fig 10: Fibrinous emboli in the vessels in fibrous septum of the breast adipose tissue.

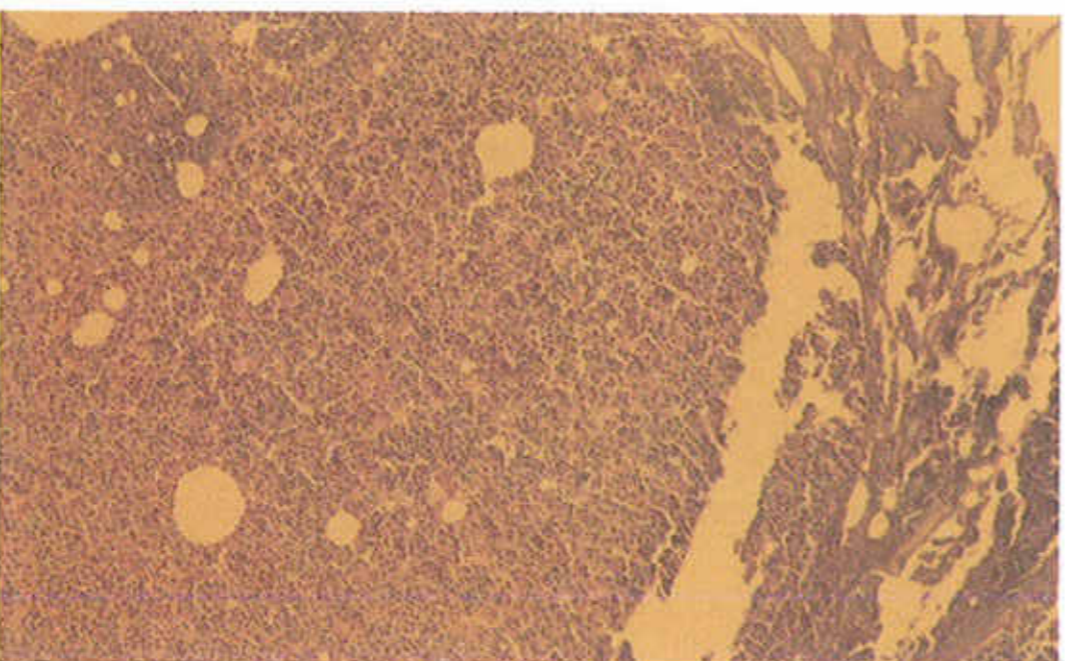


Fig 7 : Fat necrosis in the subcutaneous tissue with abscess formation consisting of polymorphonuclear leukocytes



Fig 11: Nodules of calcification in the fibrous stroma of the breast. Also note infarcted ductulo-lobular units on the left.

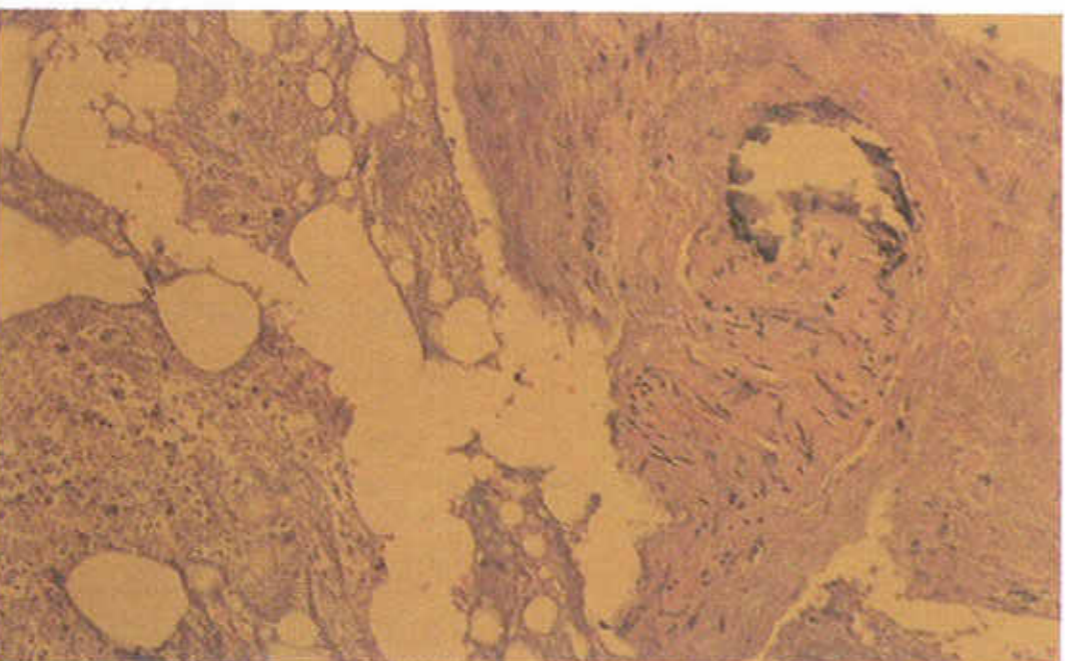


Fig 8 : A calcified nodule (right upper corner) in the fibrous septum of subcutaneous adipose tissue



Fig 12: Fibrinous emboli in the vessels at the base of the ulcer of the areola.

in the subcutaneous adipose tissue (Fig 7). A nodule of calcification (Fig 8) was found in one of the fibrous septa separating fatty lobules.

The specimen taken from the left breast consisted mostly of adipose tissue containing occasional ductulo-lobular units in a hyalinised connective tissue stroma. The epithelial elements in these units were completely infarcted with only a few surviving myoepithelial cells visible in the periphery (Fig 9). Vessels in the fibrous septa showed fibrinoid necrosis of the walls and obliteration of the lumens with fibrinous emboli (Fig 10). Nodules of calcification were present in the fibrous stroma of the infarcted ductulo-lobular units (Fig 11).

Sections of the biopsy from areola showed ulceration with necrosis and purulent exudate extending deep into the granulation tissue of the ulcer base. Fibrinous emboli and fibrinoid necrosis of the walls were seen in multiple vessels in underlying and adjacent dermis (Fig 12).

Patient was put on daily haemodialysis because her condition was deteriorating. She was on metoprolol 100 mg once daily, zantac 150 mg daily and calcium carbonate tablets 500 mg three times daily.

Parathyroidectomy was recommended but the patient condition deteriorated rapidly and developed respiratory and cardiac arrest and expired on 27/7/1996.

DISCUSSION

This patient had kidney transplant rejection ; end stage renal failure for 14 years, regular hemodialysis for the past 13 years. She had been showing signs of early calciphylaxis since 1991 when she developed, recurrent swelling of the left forearm diagnosed as recurrent cellulitis.

In 1995 more evidence of systemic calciphylaxis was shown by calcification of aorta, splenic, adrenal and pelvic vessels. In April 1996 she developed gangrene of skin and subcutaneous tissue in both breasts, lower abdomen, buttocks and thighs and was diagnosed as calciphylaxis. The histopathologic examinations confirmed the diagnosis.

The main underlying conditions in chronic renal failure are an increased calcium phosphate product, secondary hyperparathyroidism, vascular calcifications and cutaneous gangrene. It has been proposed to term these associations "uraemic gangrene syndrome"⁽¹⁴⁾ or "uremic small artery disease with medial calcification and intimal hyperplasia"⁽³⁾. Some cases reported had no noticeable hyperparathyroidism or elevation of serum calcium phosphate product⁽⁹⁾. The disease shows female preponderance⁽³⁾.

The combination of hyperparathyroidism and chronic renal failure seems to produce a particular biochemical environment leading to systemic calciphylaxis⁽¹⁵⁾ which is poorly understood and may be a hypersensitivity reaction where the sensitizer is the parathyroid hormone.

The laboratory data in a patient under, long-term hemodialysis (11.5 years) showed hypocalcemia, hyperphosphatemia, elevated serum calcium phosphate product, advanced metabolic acidosis, hyperalkaliphosphatemia and elevated parathyroid hormone⁽¹⁶⁾.

Administration of corticosteroid in chronic renal failure while undergoing dialysis⁽⁹⁾, albumin infusion, immunosuppressants, trauma, infection (especially HIV⁽⁴⁾, low protein S functional level⁽⁸⁾, metallic salts, intramuscular non-dextran complex, calcium heparinate, intramuscular tobramycin injections⁽⁷⁾ are factors that may help to create a microenvironment in the tissues that leads to a precipitation of calcium.

Calciphylaxis is characterized by ischemic necrosis. The endovascular calcification with a superimposed fibrosis and giant cell reaction simulates an endovascular form of calcium crystal induced inflammatory disease⁽¹⁷⁾. Electron microscopic tomographic studies of varieties of calcified tissues revealed different crystal structure and arrangements in the organs. In calciphylaxis, hydroxyapatite crystals of various size and shapes are aligned to collagen in a manner different from that found in normal calcified tissue⁽¹⁸⁾. X-ray films of calciphylaxis showed soft tissue and arterial calcification and histopathology revealed calcium phosphate in the main blood vessels⁽¹⁹⁾. Some investigators suggest that protein C functional deficiency is a risk factor

for calciphylaxis⁽²⁰⁾. Whether this is a factor in pathogenesis of calciphylaxis or is a marker for a coagulation defect that predisposes some of these patients to calciphylaxis is unknown⁽²¹⁾.

Calciphylaxis has to be differentiated from vascular oxalate deposit. Renal failure in adults may be a complication of primary hyperoxaluria type - 1 (P.H - 1) which presents in childhood with recurrent urolithiasis. These patients may develop vascular oxalate deposits resulting in livedo reticularis and distal acral vascular insufficiency with cutaneous necrosis that may suggest or be confused with calciphylaxis⁽²²⁾. The differential diagnosis of calciphylaxis includes localized calcinosis which may be seen in scleroderma or dermatomyositis; dystrophic calcification when calcium is deposited in cutaneous and subcutaneous tissue affected by connective tissue disease.

The cause of calciphylaxis in chronic renal failure is still not clear. Some believe that intimal hyperplasia in calcified small arteries (0.4 - 0.5 mm in diameter) is the primary cause of ischemia and arterial thrombosis may occur in some of the narrowed vessel lumina but does not necessarily play a key role⁽²³⁾. Some authors⁽²¹⁾ believe that patients with renal failure and calciphylaxis might have an underlying small-vessel disease perhaps related to their renal failure that in conjunction with hyperparathyroidism predisposes the patients to

small and medium size artery medial calcification and soft tissue necrosis. The same authors⁽²¹⁾ pointed out that seven out of series of nine patients with calciphylaxis had diabetes mellitus and hence raised the question if diabetic angiopathy may promote small vessel disease and thereby in conjunction with hyperparathyroidism lead to small artery calcification^(21, 23).

Surgical treatment of calciphylaxis includes total parathyroidectomy. In a retrospective study of 104 cases of calciphylaxis parathyroidectomy was significantly related to survival⁽³⁾. Autotransplant of one gland into the forearm may be done and this can be removed if the condition does not improve⁽⁴⁾. Pharmacological treatment of calciphylaxis with phosphate binding agents such as calcium acetate together with cautious substitution with 1,25-(OH)₂ vitamin D₃ have been tried⁽³⁾. It has been also recommended to avoid precipitating factors such as trauma and to provide good skin care to prevent sepsis and systemic antibiotics may be given when needed. Hyperbaric oxygen may be useful⁽²⁴⁾.

The patient currently reported developed respiratory and cardiac arrest and died 4 months after the occurrence of the cutaneous calciphylaxis. So it can be concluded that cutaneous calciphylaxis is a grave prognostic sign. It is also noted that blood calcium and phosphorus levels were normal and parathyroid hormone level was elevated.

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