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Calciphylaxis: case report and literature review

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Summary
Tissue calcification is a well-recognized common metabolic disease, but calciphylaxis still remains an enigmatic rarity. The latter may be induced experimentally and acquired naturally in human diseases. Although many chronic azotemic or end stage renal disease patients (ESRD) with hyperparathyroidism (HPT) are at risk of calciphylaxis not all of them do develop the disease, even non-renal, patients may also develop this disease. Out of a total of about 2000 hemodialysis, 15,000 dermatology and 26,000 medical patients seen over a three year period in a busy Saudi Arabian tertiary medical centre, we report a sentinel nephrology patient with sudden excruciatingly painful cutaneous calciphylaxis that necessitated acute dermatology emergency consultation, and present a review of the medical literature. In order to institute appropriate total quality management of this life-threatening, rare disease, it is advisable that a high index of suspicion should be entertained by dermatologists, general physicians, nephrologists, and pulmonologists in an appropriate clinical scenario.

Keywords; *Calciphylaxis, end stage renal disease, metastic calcification, hospital practice, Saudi Arabia*

Résumé
La calcification de tissu est une maladie métabolique très reconnue mais la « calciphilaxis » est encore une énigmatique de rareté. Le dernier peut être provoqué expérimentalement et obtenu naturellement dans les maladies humaines. Bien que beaucoup d'azotémique chroniques ou les malades d' hyperparathyroïde en phase terminale de maladie rénale subissent le risque de calciphilaxis, ils ne développent pas tous la maladie même les malades non-rénales, peuvent aussi développer la maladie. Dans un total d' à peu près 2000 haemodialyses, 15000 dermatologie et 26.000 des malades médicaux examinés pendant une durée de 3 ans dans un centre médical tertiaire d'Arabie Saoudite, nous signalons une sentinelle malade de néphrologie ayant le calciphylaxis cutané subit insoutenable ce qui a nécessité une intervention cutanée dermatologique d'urgence et une révision des documents médicaux. Afin d'établir une gestion de qualité totale adaptée à cette maladie rare et extrêmement grave, il est conseillé, que les dermatologues, les médecins généralistes, les néphrologues et les pulmonologues fassent des attention dans un contexte clinique approprié.

Introduction

Increased concentration of calcium in the extracellular compartment of the skin modulates epidermal proliferation and differentation [1]. This probably contributes to the thickened skin of calcinosis cutis. Heterotopic calcification in animals was demonstrated, in a pioneering feat by Selye who sensitized rats with a calcifying agent (e.g., Vitamin D, parathomone) and after an interval of few days challenged them with certain agents (egg albumin, ferric salt, etc) experimentally inducing a two-stage cutaneous metastatic calcification [2]. This phenomenon was called "calciphylaxis" by Selye. However, Bryant and White had earlier drawn attention to this phenomenon in a hydronephrotic child with tissue calcification [3]. Subsequently Dahl, Winkelman and Conolly published a vivid description of calcification of cutaneous arteries, livedo reticularis, and nodular skin in a hyperparathyroid patient [4]. The systemic involvement of calciphylaxis was recently attested to in the report of Androgue, Frazer and Seliff [5].

However, when the internal milieu of the skin is disturbed by an abnormal accumulation of endogenous divalent metabolites, the host may develop such an agonising local cutaneous pain that it may catch a physician unaware. This is illustrated by this case.

In view of the rarity of this disease we describe our first hemodialysis dependent patient with a short history of painful purpuric abdominal rash which initially bewildered us until after the skin biopsy. She was one of the outpatients attending North West Armed Forces Hospital, Tabuk, Saudi Arabia, a 250-bed medical institution, serving, among others, 22,313,14.494; 34,953, nephrology, dermatology and medical patients respectively from 1 August 1996 to 31 July 1999. This medical centre is one of the three government hospitals serving Tabuk City, populated by about 500,000 residents.

Case report

A 50-year old obese, hypertensive, dark brown Saudi female with end the stage renal disease (ESRD) on regular hemodialysis for past 3 months was seen on 30th June 1999 with acute complaint of sudden onset of acute, painful, abdominal paralaparotomy scar rash of five days duration. She remarked that the pain was like pins and needles or painful feeling of 'delusion of parasitosis'. Her drug therapy included: rocatrol, calcium carbonate, enalapril, ranitidine, iron tablets, erythropoetin, calcium carbonate and istradipine.

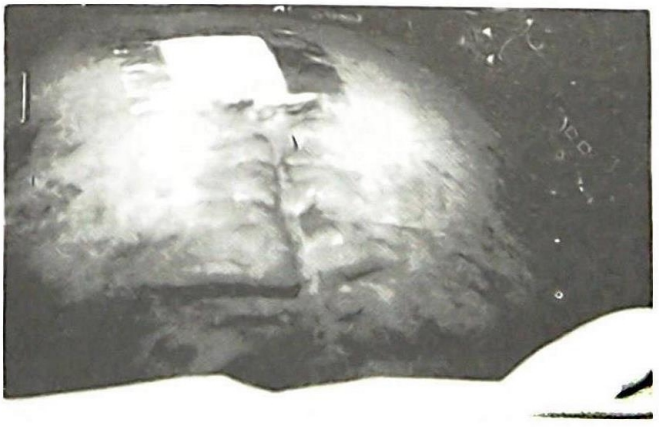

Fig. 1: Patient's abdominal photograph showing rash on both sides of the laparotomy scar, and hypochondrial areas.

Abstract was presented at the Sixth National Symposium of Saudi Society of Dermatology & Venereology, Tabuk, Saudi Arabia, October 31st - November 1st, 2001

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On examination, she was in distress with extremely tender, brownish-purple, firm para-umbilical infiltrative plaques with islands of agonizing tender creamy, corrugated nodules scattered over the right hypochondrium, bilateral inguinal areas, extending to the perineal area, and left calf (Figure 1). There was no lymphadenopathy or organomegaly. A clinical impression of infiltrative pathology was made while a differential diagnosis of acute sarcoidosis, cutaneous calcification (hyperparathyroidism) was entertained.

Table 1: Relevant investigations of the patient

Date	Urea mmol/l (n=1.7-6.4)	Creatinine umol/l (n=62-97)	Calcium mmol/l (n=2.08 2,54)	Phos phate mmol/l (n=0.6 - 1.2)	Parath omone ng/l (n=11-72)
08.2.99			1.62	2.14	397
15.2.99			1.54	1.88	568
12.4.99					791
09.5.99	30.6	881	1.44	2.23	328
04.7.99	14	790	2.88		

Investigations

Liver function tests, antinuclear antibody, Hepatitis B & C serology, serum iron, were all normal. Haemoglobin 8.7gm. Total iron binding capacity = 232 ug/dl (n = 274-494 ug/dl) iron saturation = 25% (n = 26-50%) Transferin = 180 mg/dl (n = 200-400).

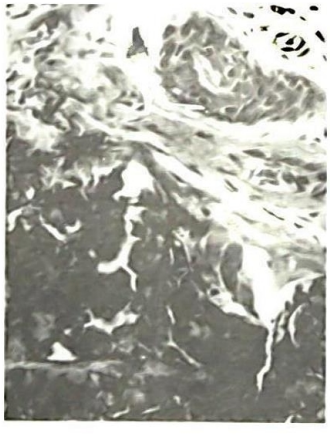

Fig. 2: Skin histology of abdominal rash showing dermal deposit of calcium.

Skin biopsy

Chalky, creamy white granular gritly texture of the skin while microscopy revealed, large subepidermal deposit of a calcific nodule, no foreign body type giant cell reaction, with minimal inflammation, and small blood vessels in the area show no calcification. No fat cells were seen; Calcinosis cutis.

Abdominal ultrasonography

Both kidneys were of small size measuring 7cm x 3cm each, and had marked parenchymal atrophy with partial loss of corticomedullary differentiation compatible with chronic bilateral renal failure. There was mild localized thickening of peri-umbilical and left groin skin.

Management:

She was treated with oral flucloxacillin 500mg 6 hourly, codeine/panadol injections. The biopsy site was treated with topical antibiotics. Her pain subsided but it was succeeded by pruritus, even though the patches improved slightly. She was being planned for further investigation for serum proteins S, C, and hyperparathyroidism and possible parathyroidectomy, but the patient was not seen again.

Discussion

The deposition of calcium in healthy or necrotic cutaneous tissues with or without abnormal calcium metabolism, constitutes calcinosis cutis and dystrophic calcification, respectively [6,7]. The widespread distribution of the latter in the diseased tissues is calcinosis universalis [8], but such calcification becomes metastatic when there is associated hypercalcaemia or hyperphosphatemia. However, such tissue calcifications in chronic ezotaemia are of two varieties: calcinosis cutis and calciphylaxis [8]. The latter is an acute disease characterized by painful mottled, purpuric cutaneous discoloration and arterial wall calcification [9].

Calciphylaxis occurs in 4.1% of outpatient hemodialysis, while it may be commoner in patients on long periods of such treatments [9]. This disease may involve various tissues including the lungs. Khafif, Delima, Silverberg, *et al*, reported that while tissue calcification is a well recognized complication of renal failure, systemic or pulmonary calciphylaxis is less common [10]. But Matsuo, Tsukamoto, Tamura, *et al* described pulmonary calciphylaxis in their haemodialysis patient [11]. However, Barri, Groves & Knockel, reported a non-renal cause of calciphylaxis in a patient with Crohn's disease and no obvious renal disease [12]. While subsequently Brown, Denney, Burns, described systemic calciphylaxis associated with massive gastrointestinal hemorrhage [13].

Calcification is a rare disease of unknown aetiology However, various aetiopathological factors have been incriminated. Calcific uremic arteriolopathy (calciphylaxis) 'ischaemic tissue necrosis' had been observed by nephrologists to be an evolving clinical entity [14,15]. However, because ectopic cutaneous calcification occurs in uremic hypercalcaemic tissues, it simulates Selye's model of metastatic calcification. But calciphylaxis differs from the latter because of its associated serological divalent abnormalities, cutaneous arterial calcification of small vessels wall with intimal hypertrophy, with or without thrombosis [16]. This was validated by recent studies showing association with hypercalcaemia, hyperphosphataemia, or a high calcium – phosphate product in azotaemic patient [17]. Others have mentioned the role of hyperparathyroidism (HPT) in the pathogenesis of this disease [18]. Other contributing factors include obesity, diabetes mellitus, skin trauma, hypertension and hypercoagulable state [19]. Our patient demonstrated some of these risk factors – obesity, gender, hypercalcaemia, hyperphosphataemia, and high calcium phosphate product, hyperparathyroidism. (see Table 1).

The clinical features manifested by our patient may be simulated by Crest syndrome, systemic lupus erythematosus, especially if it is associated with metastatic calcification. Other differential diagnoses include peripheral vascular disease, vasculitis, juvenile dermatomyositis, proteins C, S deficiency states, and cryofibrinogenaemia [19,22]. Dystrophic calcification seen in calcinosis cutis and tumoral calcinosis may also mimic calciphylaxis [8]. However, most of these conditions present with painless, chronic cutaneous lesions unlike in calciphylaxis.

While calciphylaxis is a clinical diagnosis with no definite laboratory test, its histology is very suggestive. It is characterized by soft tissue including vascular calcification, and skin necrosis. Our patient revealed clinical calciphylaxis even though the skin histology did not show arterial calcification. It is most likely that the skin biopsy was not deep enough to show such pathology, and fat necrosis [23]. But the development of sudden painful cutaneous nodules with discoloration in our ESRD patient suggests the diagnosis of calciphylaxis [24]. She showed certain supportive biochemical tests: hypercalcaemia, hyperphosphataemia, even though normocalcaemia or normophosphaemia may also occur. As shown by our patient secondary or tertiary hyperparathyroidism may be associated with calciphylaxis but it is not common with primary hyperparathyroidism.

Unfortunately our patient was lost to follow-up otherwise serum magnesium would also have been checked as hypomagnesaemia in ESRD may cause hyperparathyroidism leading to hypercalcaemia.

Management of calciphylaxis is mainly symptomatic and supportive. The aim of management is to create a normal calcium phosphate product in hyperparathyroid uraemic patients. Furthermore cautious administration of calcium, vitamin D drugs or use of low calcium phosphate diet or phosphate binders (aluminum hydroxide) among uremic patients may prevent onset of probable calciphylaxis.

Moreover, use of low calcium dialysate fluid may also be useful in some dialysis patients. Parathyroidectomy may be indicated in hyperparathyroid calciphylaxis patients though and it is claimed to improve the outlook in some patients [25]. Such surgery removes the sensitising agent causing the hypercalcaemia elevated calcium-phosphate product and HPT. But it can not be routinely recommended in all patients [26].

Local aggressive nursing, antibiotic care of skin ulcers and infections, analgesics and avoidance of giving injections at calcific cutaneous areas will contribute to improving the outlook of calciphylaxis patients.

Poor prognostic parameters of this disease include: female gender, obesity and those with proximal calciphylaxis unlike those with distal involvement, i.e., lower limbs, hands. Our patients had proximal (abdominal) calciphylaxis.

Even though the outcome of the disease is poor, by identifying the risk factors, early diagnosis, close monitoring of clinical and biochemical profiles of suspected patients the clinician may reduce the mortality of this disease. A concerted effort by medical and surgical nephrologists, dermatologists, pulmonologist, gastroenterologists and general physicians will help immensely in the control of this highly morbid disease.

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