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Fulminant and Relentless Cutaneous Necrosis with Excruciating Pain Caused by Calciphylaxis Developing in a Patient Undergoing Peritoneal Dialysis

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Abstract

A 50-year-old Japanese female with chronic renal failure who had been on continuous ambulatory peritoneal dialysis developed fulminant systemic cutaneous necrosis that began as painful livedo reticularis-like skin lesions on her thighs. Because of disseminated vascular calcification within the muscular layer of her lower limbs, we eventually diagnosed her with calciphylaxis. The skin necrosis progressed rapidly, and she died of sepsis and pneumonia on the 53rd hospital day. In addition to her long-lasting severe hyperparathyroidism and extremely elevated serum phosphorus and calcium levels, mechanical, frictional stimulation inflicted on the local skin and administration of corticosteroids were suspected to have precipitated the calciphylaxis. Our lack of awareness of this disease in its early stages resulted in our missing the chance to do a parathyroidectomy that might have changed the course. It is important to know the clinical features of this rare disease in order to make a diagnosis as early as possible.

Key words: calciphylaxis; CAPD; chronic renal failure; cutaneous necrosis; secondary hyperparathyroidism

Introduction

The term "calciphylaxis" refers to a generally fatal, necrotizing cutaneous syndrome secondary to vascular calcification. It is usually observed in patients having end-stage renal disease (ESRD) with secondary hyperparathyroidism (1–10). The characteristic skin lesions appear initially as painful and violaceous mottling resembling livedo reticularis and rapidly progress to ulceration and gangrene (1–3). Secondary infection and sepsis constitute a major cause of death (1–10). Calciphylaxis is estimated to occur in 1% of patients with ESRD each year (4). However, reports have been rare in Japan (10–12).

We present here a patient with continuous ambulatory peritoneal dialysis (CAPD) who died of painful fulminant skin necrosis along with secondary hyperparathyroidism.

Case Report

A 50-year-old female with a 5-year history of CAPD due to chronic renal failure following chronic nephritis was admitted to the renal disease ward of our hospital to undergo a parathyroidectomy (PTX) on October 31, 1997. She had suffered from severe secondary hyperparathyroidism with elevated levels of serum phosphorus (P) and calcium (Ca) that were unresponsive to oral vitamin D for two years. On November 25, while she was waiting for the PTX, which had been postponed because of her arrhythmia, painful erythema appeared symmetrically on her thighs one day after the skin was mechanically rubbed with an alcohol gauze. Be-

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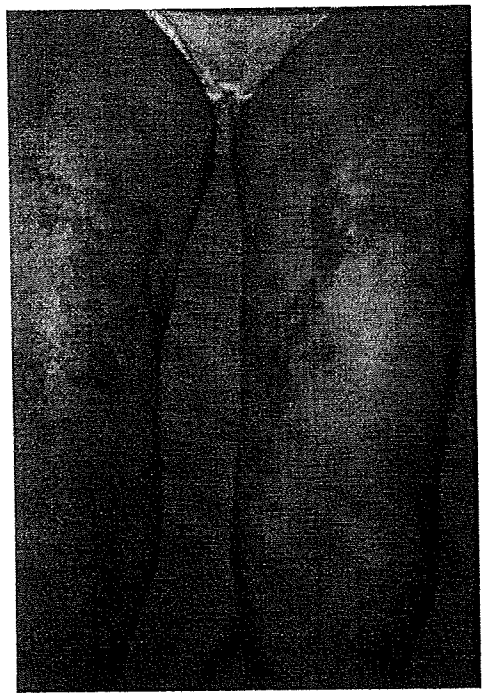

Fig. 1. An irregular early stage livedo-type reddish skin rash, symmetrically covering the anterior and medial surfaces of the thighs

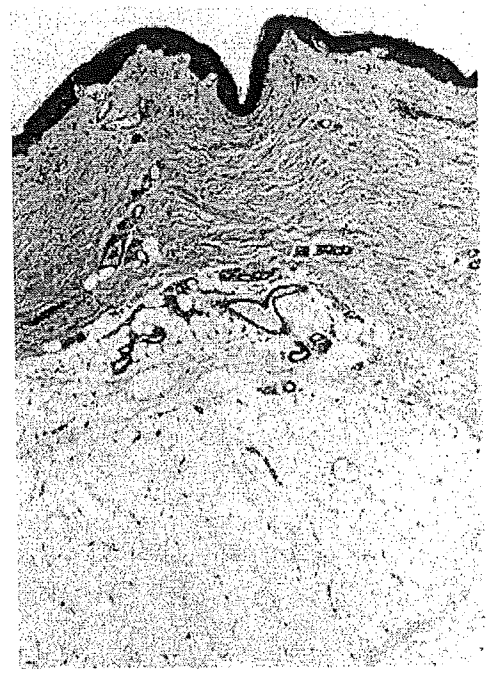

Fig. 2. Skin biopsies taken from an area of erythematous change; only mild lymphedema and vasodilatation in the dermis are seen without any sign of Ca deposition, thrombosis, vasculitis or panniculitis. (H & E, ×100)

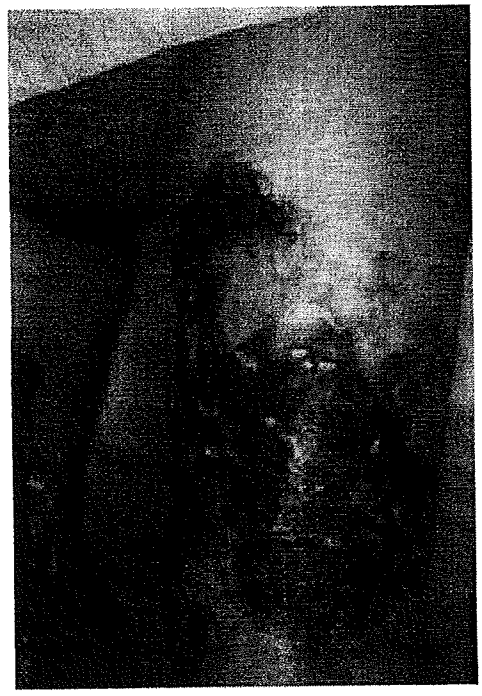

Fig. 3. Rapidly extending late stage necrotic ulcers around the thigh

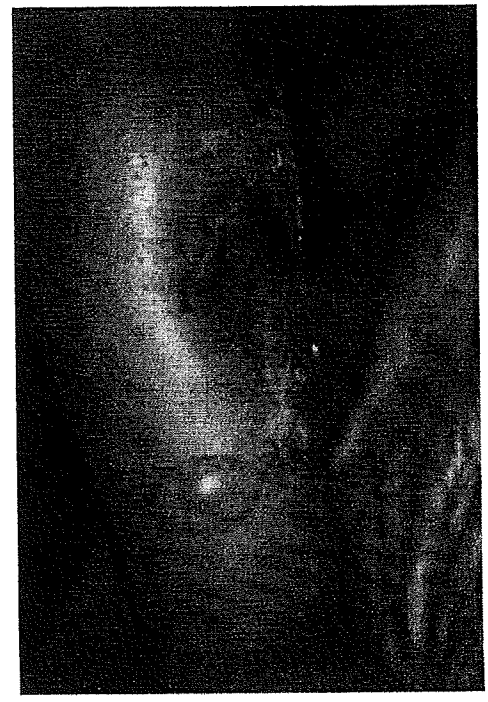

Fig. 4. Bulla-formation on the markedly swollen leg

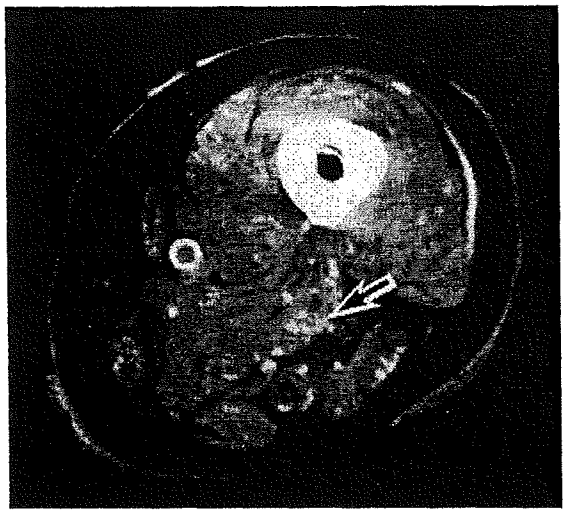

Fig. 5. Numerous calcified vessels (arrow) were revealed by computed tomogram within the muscle of the thigh.

cause the exanthema soon became painful and began to show a reticulate pattern, she was referred to our dermatology department on December 2.

She was 153 centimeters in height and 42.5 kilograms in weight (obesity score −17%). Physical examination revealed irregular reticular reddish skin lesions, symmetrically spreading over the extensor and medial surfaces of the thighs (Fig. 1). Purpura was scattered over these erythematous areas, and induration was palpable beneath them. The patient complained of pain and tenderness. Similar erythema and purpura were also found on the medial sides of the lower legs.

Complete blood cell count performed at the onset of the skin eruption revealed mild leukocytosis with WBC 10,200/mm^3 and mild anemia. Platelet count was normal. Biochemical data relating to renal function were as follows: blood urea nitrogen 63.8 mg/dl and serum creatinine 12.0 mg/dl. Her serum Ca and inorganic P concentrations were elevated at 11.4 mg/dl (normal: 8.0~10.0) and 9.9 mg/dl (normal: 2.3~4.1), respectively. Serum concentrations of high-sensitive parathyroid hormone (HS-PTH) and intact PTH were extremely high at 140,000 pg/ml (normal: <800) and 940 pg/ml (normal: 15~50), respectively. Myogenic enzymes in the serum were slightly elevated. Serum total protein and albumin levels were within normal limits. C-reactive protein level was 3.7 mg/dl.

Because of her clinical presentation of ischemic mottling resembling livedo reticularis, we suspected the possibility of the following conditions: livedo vasculitis, periarteritis nodosa, and systemic lupus erythematosus. Thus, we immediately started a trial of oral prednisone 20 mg/day and carried out serum immunological tests as well as a skin biopsy. However, despite slightly prolonged lupus anticoagulant, serum immunoglobulins, cryoglobulin, autoantibodies including antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) as well as serum complement levels were all negative or within normal ranges. Only mild lymphedema and vasodilatation were found in the dermis in a skin biopsy specimen, but no apparent abnormal change was seen in the vascular walls in the dermis and subcutis. There was no evidence for Ca deposition, thrombosis, or vasculitis (Fig. 2).

The skin eruption and pain temporarily improved after the start of prednisone administration, but rapidly worsened after a reduction of its dosage, resulting in the development of skin necrosis, for which even minipulse therapy using methylprednisone (200 mg/day for 3 days) was of no avail. Her leukocytosis progressed to 17,100/mm^3, and her serum myogenic enzyme levels increased to GOT 185 IU/L, LDH 1,109 IU/L, and CPK 2,439 IU/L. Three weeks later, a MRSA infection was identified in the necrotic lesion. Because of the rapidity of progression and spreading of the skin necrosis, we suspected that her skin lesions represented a severely infectious problem such as toxic shock syndrome or necrotizing fasciitis. Therefore, we vainly started intensive antibiotic applications to the necrotic areas, but her thighs developed extensively necrotized areas around almost all of their circumference and were covered with thick crusts. Erythema, purpura, and subdermal induration appeared one after another on the edges of the necrotic areas (Fig. 3). Her entire lower legs became swollen and developed necrosis, bullae, and exudating ulcers (Fig. 4). Similar lesions extended to the abdomen

and upper extremities.

Computer tomography (CT) performed at this point revealed remarkable calcification in numerous small blood vessels in the muscles of both the thighs and the lower legs (Fig. 5). Based on these CT findings and her extremely high serum PTH, P and Ca levels, we finally diagnosed her disease as calciphylaxis.

Her pain was so severe and intolerable that she underwent epidural nerve block and was given morphine injections. However, even these analgesic measures could not control her excruciating pain; she often fainted because of it. We failed to conduct her PTX because of the rapidly progressive hypoproteinemia, anemia, and somnolence followed by sepsis. She died of pneumonia on the 53rd hospital day. No autopsy was performed.

Discussion

Generally, the diagnosis of calciphylaxis can be based upon the characteristic skin lesions, hyperparathyroidism with high CaxP product, and vascular calcification observed in skin biopsy specimens and/or by radiographic studies (1–7). Our patient presented the dramatic clinical manifestations of calciphylaxis. However, despite the demonstration of disseminated calcification of blood vessels within the muscular layer of the thighs on the CT scan, we did not observe any vascular calcification in the skin biopsy specimen. This absence of calcified vessels in the skin might have been due to insufficient or inappropriate sampling as to location and size. Serial sections are necessary in such cases because the vascular calcification in calciphylaxis may not be easily detected in the cutaneous tissue (1).

Initially suspecting that she had systemic vasculitis, specifically polyarteritis nodosa (2, 4), we started corticosteroid therapy without waiting for the results of serological and pathological examinations, because of the rapid progression of the extremely painful skin lesions. The corticosteroid administration was initially effective, but soon failed. Later, we learned that, in general, corticosteroids should not be used for such cases because they can trigger calciphylaxis and precipitate it (1, 2, 4, 10). On the other hand, there has been a report that corticosteroid administration for a short period was effective in inducing remission of the inflammation of calciphylaxis (9). Our patient's general condition deteriorated rapidly, so we missed our chance to conduct an early PTX, which has been proven to be effective for some patients with calciphylaxis (1–4, 10).

The diagnosis of calciphylaxis can not always be clearly made, because histological examinations do not necessarily reveal any specific findings; some cases with calciphylaxis even show normal serum CaxP and PTH levels (1, 3, 4, 10). Therefore, it is important to consider the possibility of calciphylaxis in differential diagnosis whenever we encounter a condition or disease that is associated with painful ischemic skin changes in ESRD patients including vasculitis, panniculitis, and abnormalities of coagulation (1, 3).

The pathogenesis of calciphylaxis remains unknown, but it seems to be multifactorial (1–10). Patients wih ESRD commonly have metabolic abnormalities of serum Ca, P, and PTH, and they frequently develop vascular calcification (1, 3–8). However, even in cases of vascular calcification, it is unusual for tissue necrosis to develop (1, 3, 8). Although the tissue ischemia and necrosis observed in calciphylaxis are closely associated with vascular calcification, they do not seem to be caused only by mechanical obstruction secondary to vascular calcification (4, 5, 8). Other mechanisms proposed for the development of calciphylaxis include vasospasm related to elevated Ca or PTH levels and thrombosis secondary to coagulopathy, especially to functional protein C deficiency (1–10). Several experimental and clinical studies have reported that some triggering factors produce or precipitate tissue calcification and calciphylaxis in individuals who have already been sensitized by calcifying agents such as high levels of vitamin D, phosphate, PTH or calcium salts (1, 3–9,

13). These factors include blood products, metallic salts, corticosteroids, immunosuppressive drugs, and even trivial local trauma (1, 4, 5, 7, 13).

In our case, mechanical friction caused by wiping with an alcohol gauze might have acted as a triggering factor for the sudden onset of calciphylaxis in the skin when she had extremely high serum Ca, P, or PTH levels. The inappropriate corticosteroid therapy might also have had an effect on precipitating calciphylaxis.

In conclusion, because calciphylaxis is a rare condition, it is seldom recognized by dermatologists and it is, therefore, important for us to know its clinical features in order to make a diagnosis as early as possible.

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症例報告

Proximal calciphylaxisによる皮膚病変を伴った血液透析2症例

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key words：calciphylaxis, calcifying panniculitis, calcific uremic arteriolopathy, 二次性副甲状腺機能亢進症, 慢性腎不全

〈要旨〉
症例1は49歳男性．透析歴20年．2回目の副甲状腺摘出術(PTX)目的に入院．入院時両大腿内側に境界明瞭な暗赤色の色素沈着を認め，生検により血管壁のCa沈着がみられた．PTX後皮疹は軽快した．症例2は75歳女性．透析歴7年．左大腿内側の有痛性の紫斑が出現し，数週間の経過で急速に潰瘍化した．生検では脂肪組織と血管壁にCa沈着を認めcalcifying panniculitisと診断された．潰瘍部に対し保存的治療を行うも効なく，PTXを予定していたが，突然の心肺停止をきたし死亡した．近年calciphylaxisは皮下脂肪の豊富な部位での報告が多く，二次性副甲状腺機能亢進症を伴わず発症する例も少なからず存在する．Proximal calciphylaxis合併例の予後は極めて不良であり，発症因子の解明が待たれる．

Two cases of proximal calciphylaxis in chronic hemodialysis patients

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The first case was a 49-year-old man with end-stage renal failure maintained on hemodialysis for 20 years, who was admitted to our hospital for parathyroidectomy. He had dark-red asymptomatic hyperpigmentations on his thighs. A skin biopsy revealed small vessel calcification in the dermis and subcutaneous adipose tissues, leading to a diagnosis of calciphylaxis. The hyperpigmentations attenuated after parathyroidectomy. The second case was a 75-year-old woman who had been on hemodialysis for 7 years and had severe hyperparathyroidism. She was admitted for painful purpura on her left thigh. She developed ulceration in a few weeks and a skin biopsy revealed numerous calcifications in small vessels and necrotic fat tissues, leading to a diagnosis of calcifying panniculitis. She underwent repeated debriedement of ulcers and skin autografting but responded poorly. The patient refused parathyroidectomy and she died of sudden cardio-pulmonary arrest. The family refused autopsy.

Recently calciphylaxis has been reported to predominantly involve the thighs and abdomen (proximal calciphylaxis), and has also been noted in patients with normal PTH levels and minimal Ca and P abnormalities. To establish specific therapeutic regimens for this life-threatening syndrome, a clear understanding of the pathogenesis is indispensable.

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緒　言

慢性腎不全患者の腎性骨異栄養症は，種々の治療法の開発にもかかわらず依然克服困難な合併症の一つである．二次性副甲状腺機能亢進症を基盤とした異所性石灰化としては，関節周囲の軟部組織に腫瘤を形成する tumoral calcinosis が代表的であるが，比較的稀な合併症として血管の石灰沈着により指趾の壊死をきたす calciphylaxis[1,2]が知られている．今回我々は，皮下血管の石灰化による大腿部の皮膚病変を 2 例経験した．近年 calciphylaxis は，大腿部や腹部など皮下脂肪の豊富な部位での報告[3,4]が多く（proximal calciphylaxis），病因論的にも単なる二次性副甲状腺機能亢進症の終末像ではなく種々の病態が関与すると考えられている[5,6]．これら文献的知見をふまえ自験例を報告する．

I．症　例

症例 1：49 歳，男性．

主訴：関節痛，皮膚瘙痒感．

家族歴・既往歴：特記すべきことなし．

現病歴：1979 年慢性糸球体腎炎による慢性腎不全のため血液透析に導入となり，以後週 3 回の外来維持透析を受けていた．1990 年二次性副甲状腺機能亢進症のため副甲状腺摘出術（PTX，亜全摘）を受けた．1998 年頃より両膝関節痛，皮膚瘙痒感が強くなり，同時に intact PTH（iPTH）の上昇を認めたため再 PTX 目的にて 1999 年 6 月当院紹介入院となった．

現症：身長 165 cm，体重 48 kg，血圧 130/68 mmHg，脈拍 70/分，整，体温 36.6°C．両大腿内側に境界明瞭な無症状の暗赤色の色素沈着を認めた（図 1）．

検査成績（表 1）：血液検査では一般的な透析症例にみられる異常に加え，高 P 血症，高 ALP が著明で iPTH，オステオカルシンの高値，salt and pepper skull および指節骨骨膜下吸収の存在より二次性副甲状腺機能亢進症と診断した．副甲状腺シンチグラフィーでは 2 腺，頸部超音波検査では 1 腺の腫大を認め，手術適応と判断した．なお単純 X 線上血管壁，軟部組織の石灰化は明らかではなかった．

経過：第 10 病日に PTX および大腿部の皮膚生検を行った．甲状腺下極より左右それぞれ 1288 mg と 940 mg の副甲状腺を摘出した．組織学的には過形成で，正常組織に近い右下極の副甲状腺を 80 mg 右前腕に自家移植した．皮膚生検では，表皮は菲薄化し，表皮突起の減少と平坦化を認め，真皮下層から脂肪組織内の血管内壁に von Kossa 染色陽性の沈着物（図 2）

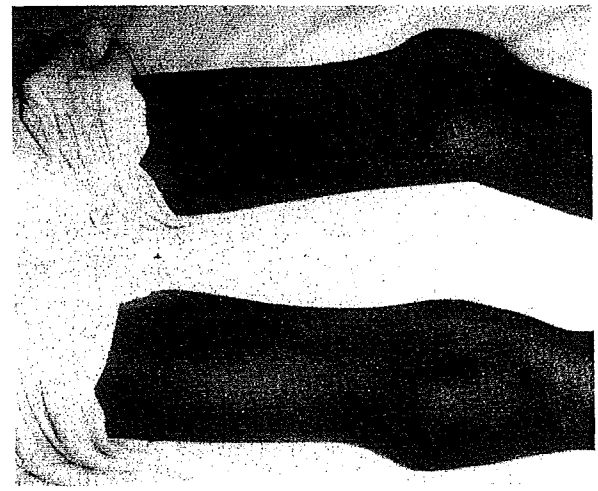

図 1　Thighs of case 1 showing dark-red hyperpigmentation.

表 1　Clinical and laboratory findings of case 1

生化学的検査				心電図：左室肥大
TP	6.2 g/d*l*	Mg	2.0 mg/d*l*	
ALB	3.8 g/d*l*	Al	1.5 μg/d*l*	胸部 X 線：心胸比 50%
T-Bil	0.2 mg/d*l*	空腹時血糖	97 mg/d*l*	
GOT	6 U/*l*	CRP	0.3 mg/d*l* 以下	全身骨 X 線：
GPT	4 U/*l*	iPTH	1310.8 pg/d*l*	右第 2，3 指中節骨に骨吸収像
ALP	1583 U/*l*	オステオカルシン	695 ng/d*l*	salt and pepper skull
LDH	106 U/*l*			
BUN	51 mg/d*l*			副甲状腺シンチ：両下極 2 腺の腫大
Cr	8.89 mg/d*l*	血液学的検査		
Na	137 mEq/*l*	WBC	5800 /μ*l*	頸部超音波：
K	5.5 mEq/*l*	RBC	319 万/μ*l*	左葉下極に 16.3×11.9×6.2 mm
Cl	101 mEq/*l*	Hb	9.9 g/d*l*	の副甲状腺を認める
Ca	8.9 mg/d*l*	Ht	30.6 %	
P	5.8 mg/d*l*	Plt	21.6 万/μ*l*	

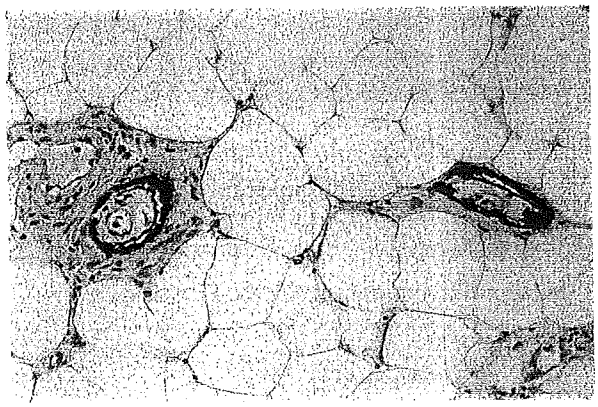

図 2　A skin biopsy from case 1 showing vascular calcification (von Kossa stain, × 200).

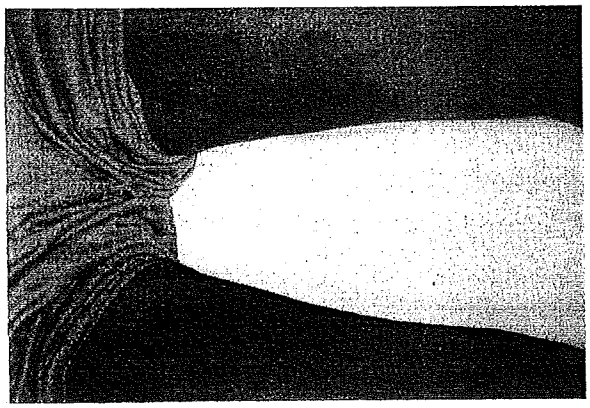

図 3　Skin lesions of case 1 three months after PTX.

を認めた．関節痛や皮膚瘙痒感は術直後より劇的に軽快した．第 28 病日に退院，このとき iPTH は 19.6 pg/m*l* と低下，ALP は 3185 U/L と上昇していた．術後 4 か月 iPTH 106.0 pg/m*l*，Ca 11.2 mg/d*l*，P 6.3 mg/d*l*，ALP 182 U/L，と正常化した時点において，大腿部の皮疹は入院時に比べ色調が淡くなっており軽快傾向にあると考えられた（図 3）．

症例 2：75 歳，女性．

主訴：左大腿内側部痛．

家族歴：母に子宮癌．

既往歴：特記すべきことなし．

現病歴：1990 年慢性糸球体腎炎による慢性腎不全のため血液透析に導入，以後週 3 回の外来維持透析を受けていた．1997 年 4 月，特に誘因なく左大腿部内側に皮下出血様の皮疹が出現，次第に疼痛を伴うようになった．ゲンタマイシン軟膏，アズレン軟膏などの外用剤に反応せず皮疹は拡大傾向となったため当院紹介入院となった．

図 4　(A) Skin lesions on the left thigh of case 2 showing dark-red mottling with ulcerations. (B) Early skin lesions on the right thigh showing dark-red maculae.

入院時現症：身長 148 cm，体重 64 kg，血圧 150/88 mmHg，脈拍 50/分，不整，体温 37.2°C．下腹部皮下に直径 1～2 cm の硬結を数個触知した．左大腿内側に 15×15 cm の紫斑を認めた．紫斑は一部淡血性の水疱と糜爛面を形成しており（図 4 A），下床に腹部と同様の硬結を触知した．右大腿内側にも網状の赤紫色斑を認め，同様に下床に硬結を触知した（図 4 B）．

検査成績（表 2）：末梢血では，白球血増多はなく腎性貧血を認めた．生化学的検査では，一般的な透析症例に見られる異常に加え CRP 高値，高 P 血症，高 ALP 血症が著明で，iPTH，オステオカルシン高値より二次性副甲状腺機能亢進症と診断した．副甲状腺シンチグラフィーでは，3 腺の腫大が確認された．X 線検査では，心胸比 57%，胸腹部大動脈，両大腿動脈の石灰沈着著明，rugger jersey spine および salt and pepper skull を認めた．心電図，心臓超音波検査にて下壁の陳旧性心筋梗塞と大動脈弁，僧帽弁の石灰化，収縮能および拡張能の障害を認めた．

経過：左大腿部の紫斑部に対しステロイド軟膏の外用を行ったが効果はなく数週間の経過で潰瘍化した．原因検索のため両大腿部の硬結の部位より皮膚生検を施行した．表皮の菲薄化，真皮の萎縮に加え真皮下層

表 2　Clinical and laboratory findings of case 2

生化学的検査				心電図：左室肥大，心筋障害
TP	6.2 g/dl	Mg	2.2 mg/dl	心エコー：
ALB	3.3 g/dl	Al	1.7 μg/dl	下壁の hypokinesis
T-Bil	0.4 mg/dl	空腹時血糖	130 mg/dl	大動脈弁・僧帽弁に石灰化
GOT	10 U/l	CRP	4.7 mg/dl	EF 50%，%FS 28%
GPT	7 U/l	iPTH	1880 pg/dl	胸部 X 線：心胸比 57%
ALP	710 U/l	オステオカルシン	1080 ng/dl	全身 X 線：
LDH	125 U/l			大動脈，大腿動脈に石灰化著明
BUN	74 mg/dl			両大腿部皮疹に一致して淡い石灰化影
Cr	7.90 mg/dl	血液学的検査		salt and pepper skull
Na	139 mEq/l	WBC	6000 /μl	rugger jersey spine
K	5.4 mEq/l	RBC	302 万/μl	
Cl	104 mEq/l	Hb	9.4 g/dl	
Ca	10.5 mg/dl	Ht	29.4 %	副甲状腺シンチ：
P	8.7 mg/dl	Plt	17.7 万/μl	左葉下極，右葉上極に 2 腺腫大

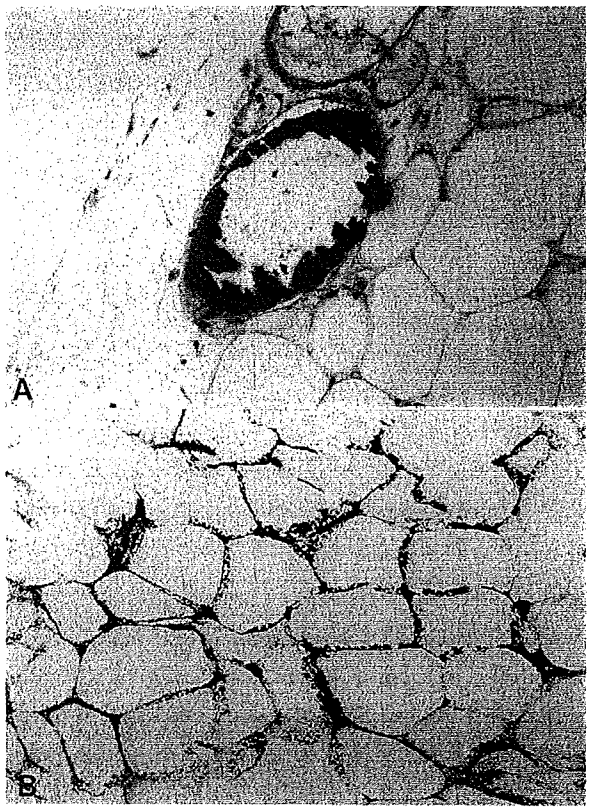

図 5　A skin biopsy from case 2 showing extensive calcification in a small blood vessel (A) and in the necrotic fat tissues (B). von Kossa stain, ×200.

から脂肪組織内の血管壁（図 5 A）や脂肪組織自体（図 5 B）に石灰沈着を認め，皮膚科的には calcifying panniculitis と診断された．ストレプトキナーゼ軟膏の外用と壊死物質のデブリドマンを繰り返し，潰瘍部の状態が安定した後に培養同種皮膚移植を行った．生着は良好であった．疼痛に対しては局所冷却とアミノ安息香酸エチル軟膏の外用を行ったが次第に無効となったため硬膜外ブロックを行った．二次性副甲状腺機能亢進症に対しては入院当初より PTX の適応であったが，患者の同意が得られずまた心機能障害，CRP 強陽性のため手術のリスクも高いと考えられたため，まず皮膚潰瘍の治療を優先し同時に経口ビタミン D パルス療法を施行した．しかし高 Ca 血症により継続不可能となり再度 PTX を考慮し術前検査中であったところ，突然の心肺停止をきたし死亡した．剖検は家族の同意が得られず，正確な死因は特定できなかったが，いわゆる突然死にあたると考えた．

II. 考　察

慢性腎不全にみられる異所性石灰化はその沈着する組織により，① 関節周囲の軟部組織の石灰化（tumoral calcinosis），② 心弁膜・肺・腎臓・眼球結膜（red eye）にみられる内臓石灰化，③ 血管石灰化に分類される．血管の石灰化は主に中動脈の中膜にみられるが，稀に皮膚や皮下組織の細動脈の石灰化による閉塞とその栄養領域の壊死を特徴とする calciphylaxis が発症する．症例 1 は生検で真皮下層の細動脈に von Kossa 染色陽性の沈着物を認めた．症例 2 の皮膚病変は壊死，潰瘍化していたが，生検では同じく細動脈に石灰沈着を認めたため症例 1 と同様の皮膚病変がさらに進行した状態と考えられた．症例 2 には症例 1 には認められなかった脂肪組織自体の石灰沈着や皮下脂肪層炎を伴っており皮膚組織学的には calcifying panniculitis と診断された．Calcifying panniculitis は，早期においては皮下の小血管中膜の石灰沈着を主とし，進行重症化すると脂肪組織にまで石灰沈着をきたし皮膚および皮下組織の壊死を伴う組織像と定義されている[7]．一方 Janigan ら[6]は，calciphylaxis の病理組織像を一次性病変と二次性病変に分け，前者は細小動脈中膜への

石灰沈着とその結果としての内腔の狭小化，後者は血流の途絶による皮膚および皮下組織の梗塞であり，壊死組織に石灰沈着を生じた場合しばしばcalcifying panniculitisと称されてきたと述べている．したがって両者は全く同一の概念と考えることができる．すなわち症例1がもう少し放置され，また以下に述べる誘因が加わった場合，症例2のような病態へ発展していくものと思われる．彼らはさらに動物モデルより名づけられたcalciphylaxisという言葉は適当ではなく，より正確に病態を表すcalcific uremic arteriolopathy of skin[4,5]といった名称が望ましいとしている[6]．

異所性石灰化は，二次性副甲状腺機能亢進症を中心としたCa，Pの代謝異常に活性型ビタミンDや炭酸Caの過剰投与，体液の過剰なアルカリ化などが増悪因子として加わって発症する[8]．しかしこれらの因子を持つ症例の多くに発生するのは古典的なtumoral calcinosisや中動脈の石灰化であってなぜ限られた症例だけがcalciphylaxisへと進行するのかは明らかでない．文献的にはcalciphylaxisの誘因としてワーファリン[4]，protein C[9]やprotein S[10]，cryofibrinogen[11]といった凝固系に影響する因子の関与が報告されているが，すべての症例にこれらが認められるわけではない．自験例はいずれもワーファリンの服用はなく一般的な凝固検査にも異常はなかったが，残念ながらprotein C，protein S，cryofibrinogenは測定していない．近年calciphylaxisは，指趾よりもむしろ腹部や大腿など脂肪組織の豊富な部位での報告（proximal calciphylaxis）が目立ち，患者背景として白人女性，肥満，2型糖尿病，低アルブミン血症を有する症例が多いとされる[3,6]．症例2は白人ではないが耐糖能異常も存在し，これらによく符合する．興味深いことに，報告された症例は必ずしも著明な二次性副甲状腺機能亢進症，Ca×P積の高値を呈しているものばかりではなく，透析患者として妥当なiPTH，Ca，Pレベルである症例も少なからず存在する[3,12]．Ca×P積の高値を必要条件として何らかの局所因子が加わって急速に壊死が進行するという従来のcalciphylaxisの概念ではこのような症例の発症機序は説明できない．

異所性石灰化の対策は，十分な透析と適正なビタミンDやP吸着薬の使用による血清Ca，Pのコントロールおよびの抑制が基本となる．calciphylaxisに対してもCa×P積の上昇が少なくとも増悪因子となることに疑いの余地はなく，同様の対策が重要である．PTXについては，二次性副甲状腺機能亢進症が存在する場合積極的に行われるが，生命予後の改善にはつながらないとの報告もある[12,13]．さらにPTHの低い症例にPTXを施行しても皮膚病変は改善しないことも知られている[13]．したがってPTXには，Ca，Pの代謝異常を改善する以上にcalciphylaxisに対して直接の治療効果はないと考えられる．症例1では，PTX後皮疹に改善傾向がみられた．症例2はPTXを受けることなく死亡した．もしPTXが施行できていたらどのような経過をたどったか興味が持たれる．

Calciphylaxis以外の異所性石灰化は，機能障害をきたすものの生命予後はさほど悪くはない．一方calciphylaxisの生命予後は不良で，特にproximal calciphylaxisは創部からの敗血症や心筋梗塞，虚血性腸炎などの虚血性疾患合併のため予後が極めて悪い[3~5]．正確な発症機序が不明であるため予防法を確立することは困難であるが，肥満，低アルブミン血症，女性，糖尿病など危険因子を有する症例では，積極的なCa，P代謝異常の是正とともに好発部位への皮下注射，ワーファリン，ステロイド，血液製剤の投与など皮膚潰瘍の誘因となりうる治療の際には十分な注意が必要である．

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症 例

Reactive Perforating Collagenosis を併発した Calciphylaxis の1例

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要 約 61歳，女性。糖尿病性腎症患者に生じ reactive perforating collagenosis を併発した calciphylaxis の1例を報告する。両下肢の有痛性紫斑で初発，まもなく潰瘍となり，約4カ月後に両手・両下肢に潰瘍・壊死が多発してきた。同時に腹部・両大腿に角化性丘疹が多数出現。検査上，二次性副甲状腺機能亢進症，下肢のX線で著明な血管の石灰化を認めた。病理組織学的に潰瘍部では広汎な壊死のほか皮下組織には血管の中膜の石灰化があり，角化性丘疹では膠原線維の経表皮排泄像を認めた。カルシトリオール投与後，血中PTH，CaおよびP値の改善を認めたが皮膚壊死は進行し，初診の約7カ月後，敗血症のため死亡した。

I はじめに

calciphylaxis（以下CPX）は，1962年Selyeら[1]によって提唱された概念で，感作された生体に，ある腫の因子が加わるとさまざまな臓器に急速な石灰化がひきおこされる過敏状態と定義される。しかし，感作の意味は必ずしも明確ではなく，報告例をみると主に末期腎不全患者に生じる汎発性石灰沈着として認められ，典型的には指趾の壊疽を伴い，四肢の皮膚壊死あるいは潰瘍を生じるまれな疾患としてとらえられている。今回われわれは，糖尿病性腎症患者に生じたCPXを経験したので報告する。自験例は reactive perforating collagenosis（以下RPC）を併発していたが，このような報告はわれわれが調べえた限り認めない。

II 症 例

患 者 61歳，女性
初 診 1999年5月12日
主 訴 両下腿の有痛性紫斑，びらん
家族歴 母と同胞2人に糖尿病
既往歴 1985年から糖尿病。1993年糖尿病性網膜症。1995年狭心症のためバイパス術施行
現病歴 1999年4月から糖尿病性腎症のため透析目的で当院泌尿器科に入院中，両下腿に疼痛を伴う紫斑，びらんが出現し当科を紹介された。皮疹はまもなく潰瘍となり，保存的治療に抵抗性であった。同年8月9日，右下腿の潰瘍を治療をかねて生検縫

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〔キーワード〕 糖尿病性腎症，Calciphylaxis, Reactive Perforating Collagenosis

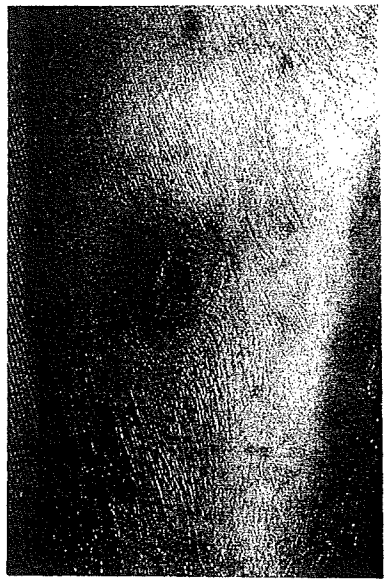

図1　右下腿の潰瘍

縮術施行。同月下旬からは右中指爪囲の壊死も出現してきたため当科に入院した。なお泌尿器科では内シャント術を行うも血管が閉塞し透析は施行できなかった。

現　症　両下腿に鶏卵大までの周囲に紫紅色斑を伴う黄色から淡褐色の痂皮を付着した潰瘍を認める(図1)。網状皮斑は認めない。

病理組織学的所見　右下腿の潰瘍：表皮は欠損し真皮は壊死におちいっている。真皮下層から皮下脂肪織の血管壁にカルシウムの沈着を認める。血管の中膜に輪状のカルシウム沈着があり，組織球様細胞と線維芽細胞の浸潤，毛細血管の増生を認める（図2)。

入院時検査成績　白血球18600/mm³，赤血球381万/mm³，Hb 9.3 g/dl，Plt 28.1万/mm³，Na 145 mEq/dl，K 4.7 mEq/dl，Cl 109 mEq/dl，Ca 7.3 mg/dl，P 5.4 mg/dl，BUN 97.1 mg/dl，Cr 4.9 mg/dl，CRP 2.9 mg/dl，PTH 4835 pg/ml(正常値100～500)，FBS 90 mg/dl，HbA_{1c} 6.0%。ANA，RF，抗CL抗体は陰性。下肢のX線では血管の著明な石灰化あり。胸・腹部CT上臓器への石灰の沈着なし。PTHの上昇は原発性ではなく，慢性腎不全に伴う二次性副甲状腺機能亢進症と考えられた。

経　過　リポプロスタグランジンE1投与と抗潰瘍剤外用による治療は無効で，9月中旬ころから両手・両下肢に疼痛を伴う潰瘍，壊死が多発し，また腹部・両大腿には角化性丘疹が出現してきた（図3)。カルシトリオール投与により血中PTH，CaおよびPが正常化した後も皮膚壊死の進行は続いた。10月23日には下血し，肛門鏡にて直腸下部に潰瘍を認めた。その後，徐々に全身状態が悪化し，敗血症により12月5日永眠。剖検は施行できなかった。

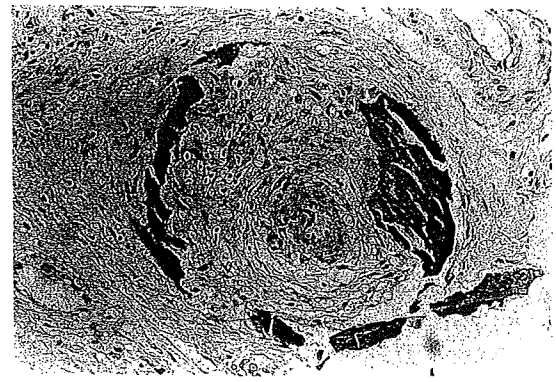

図2　血管壁の中膜の石灰化像（HE染色）

病理組織学的所見　左大腿部角化性丘疹：表皮は中央部で欠損し厚い壊死組織で被われ，この中に好酸性に染まる膠原線維が縦方向に排出されている像が認められた。真皮上層においては好中球の浸潤と変性した膠原線維が認められた（図4）。エラスチカワンギーソン染色では好酸性に染まる膠原線維の排出を認めた。

III　考　案

CPXの報告例は本邦皮膚科領域では現在まで2例[2)3)]のみであるが，欧米では多数報告されている。通常，疾患名として用いられるが，病態をあらわす言葉として用いられる場合もある。また，uremic small artery disease, calcifying panniculitisなどと同義として報告されることも多い。近年Dennisら[4)]は本症の特徴をまとめている。それによると臨床的には，主に四肢に生じ，多くは指趾の壊疽を伴い，有痛性の紫斑あるいは紫斑様局面から始まり急速に壊死あるいは潰瘍となる。病理組織学的には血管の中膜の石灰化が重要で他に血管内膜の増殖性変化やseptal panniculitisを伴うとしている。しかし，組織像は必ずしも特異的でなく，転移性石灰沈着症の特殊型との意見もある[5)]。自験例においては皮膚壊死が多発した時の組織学的検索を行っていないが初期の潰瘍で病理組織学的に血管の中膜の石灰化

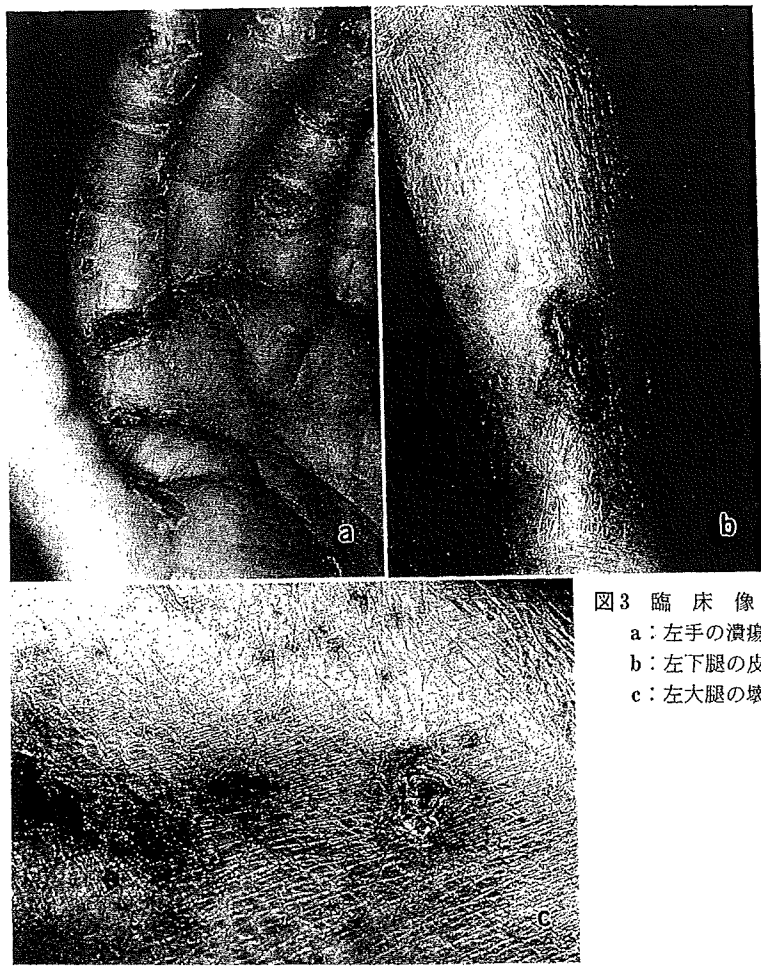

図3 臨 床 像
a：左手の潰瘍
b：左下腿の皮膚壊死
c：左大腿の壊死と角化性丘疹

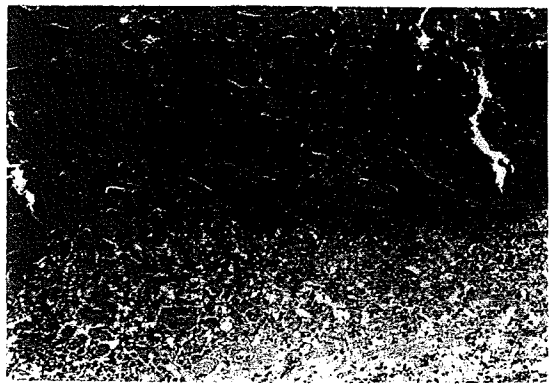

図4 膠原線維の経表皮排出像（HE 染色）

を認めたことと特徴的な臨床経過から本症と診断した。

皮膚以外の病変はまれで，眼症状[6]や消化管潰瘍[7]を呈した報告があるが，組織学的検討が十分行われておらず，皮膚と同様の機序によるものか，必ずしも明確ではない。皮膚は圧迫，温度変化，外傷など物理的刺激をうけやすいため好発するのかもしれない。

検査上，約80%に PTH の上昇を認め，Ca あるいは P の高値，両者が高値のことがあるが一定しない。また X 線上，著明な石灰化を認めることが多いが，これらは慢性腎不全に伴う二次性副甲状腺機能亢進症の所見と考えられている。

自験例は RPC を合併していたが，われわれが調べえた限りではこのような報告はみられない。RPC は糖尿病や腎不全あるいは透析患者に生じやすいことが知られ，perforating folliculitis など他の経表皮排泄をきたす疾患と合併しやすいこ

とから，一括してacquired perforating dermatosisと呼ばれている[8]。発症機序として微小循環異常などの内的要因に激しい掻破などの外的要因が加わり真皮上層の変性した膠原線維が経表皮的に排出されるとする説が有力である。自験例においては，強い瘙痒があり，皮膚壊死が多発した際に角化性丘疹が出現したことから，瘙痒に伴う掻破のほか血管の石灰化により膠原線維の変性が起きやすい状態にあったものと推測した。

CPXの予後因子として発生部位があげられ[9]，大腿・臀部・軀幹の近位に生じた場合，致死率は約63%，下腿・前腕・指趾・陰茎の遠位に生じた場合は約23%といわれている。死因は，敗血症，心停止，消化管出血が多く[10]，自験例も敗血症で死亡した。

治療としては，創処置とともにまず副甲状腺機能亢進症に対し保存的治療が試みられる。副甲状腺摘出は著効例も散見されるがその評価は難しく，保存的治療の無効例，皮疹が急速進行性の時に行われるべきと考えられている。

自験例においてはカルシトリオール投与後にPTH，CaおよびPが正常化しているにもかかわらず皮膚壊死の進行は続いた。全身状態が不良であったこともあり副甲状腺摘出は行わなかったが，皮膚壊死は四肢の近位にも生じており予後不良であったと考えられる。

本症はまれではあるが特徴的な病像を呈し，時に致死的である。末期腎不全，特に透析患者に，四肢の有痛性の紫斑あるいは壊死・潰瘍を生じた場合，念頭におくべき疾患と考えられる。

(2000年9月29日受理)

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□ CASE REPORT □

Calciphylaxis in a Patient with End-Stage Renal Disease Secondary to Systemic Lupus Erythematosus Associated with Acral Gangrene and Mesenteric Ischemia

Naoya IGAKI, Rintarou MORIGUCHI, Yusi HIROTA, Makoto SAKAI, Hiroyuki AKIYAMA, Fumihiko TAMADA, Munetada OIMOMI and Takeo GOTO

Abstract

A patient with end stage renal disease secondary to systemic lupus erythematosus (SLE) ultimately required amputation of the four extremities and developed mesenteric ischemia. The patient presented with widespread medial calcification involving various small to medium sized arteries, although no noticeable secondary hyperparathyroidism was observed. We speculated that SLE associated with systemic vasculitis and uremic milieu over a number of years may represent the perfect preexisting condition for calcific arteriolopathy to occur following which several factors including chronic administration of corticosteroids, photosensitivity in lupus, and significant weight loss may have contributed to acral gangrene and mesenteric ischemia. (Internal Medicine 40: 1232–1237, 2001)

Key words: calcific arteriolopathy, corticosteroid, photosensitivity, secondary hyperparathyroidism

Introduction

Calciphylaxis is a rare life-threatening condition typically affecting chronic renal failure patients, that involves vascular calcium deposition with subsequent progressive cutaneous ischemia and necrosis (1–11). The term "calciphylaxis" was introduced by Selye (12) in 1962 after work on experimental animals. He found that injection of a sensitizer such as parathyroid hormone (PTH) or vitamin D, followed after a period of time by exposure to a challenger such as albumin, metal salt or trauma, resulted in calcium deposition and necrosis of skin and subcutaneous tissue. The similarity in macroscopic appearance between the animal lesions and those in renal failure-associated calcific arteriolopathy producing ischemic tissue necrosis led to the term "calciphylaxis" being applied to the latter. In the reports (2, 9–11), dysregulation of the calcium-phosphorus-parathyroid axis is the sine qua non of calciphylaxis. However, while all dialysis patients suffer from disordered calcium metabolism, relatively few develop calciphylaxis. The original concept of calciphylaxis has markedly changed over the past few years as more cases have been reported (13). Recently, Coates et al (14) reported that the classic divalent ion abnormalities and high PTH associated with calciphylaxis are not common. We describe here a patient with end-stage renal disease secondary to SLE who received administration of corticosteroids, and in whom acral gangrene and mesenteric ischemia developed without noticeable secondary hyperparathyroidism (HPT) or elevation of serum calcium-phosphorus product.

For editorial comment, see p 1174.

Case Report

The patient was a 54-year-old woman who was admitted to our hospital for evaluation of painful bluish discoloration and ulceration of the left heel in March 2000.

In 1975, at the age of 29, she presented with fever, and polyarthralgia; positive anti-DNA antibody was diagnosed as SLE. Thereafter, lupus activity was controlled with corticosteroids. In 1990, at the age of 44, she developed proteinuria and hypertension. In December 1995, at the age of 49, she developed chronic renal failure secondary to lupus nephritis and was placed on hemodialysis (HD). The patient was dialyzed 3 times a week with bicarbonate dialysate containing 3.0 mEq/*l* of calcium. Drug therapy included betamethasone, nicardipine, doxazosin, furosemide and epoetin beta. In October 1998, precipitated calcium carbonate was prescribed as a phosphate binder. She had a history of corticosteroid-induced hyperglycemia requiring treatment with an oral hypoglycemic agent (glibenclamide, 2.5 mg) from 1995 to 1996.

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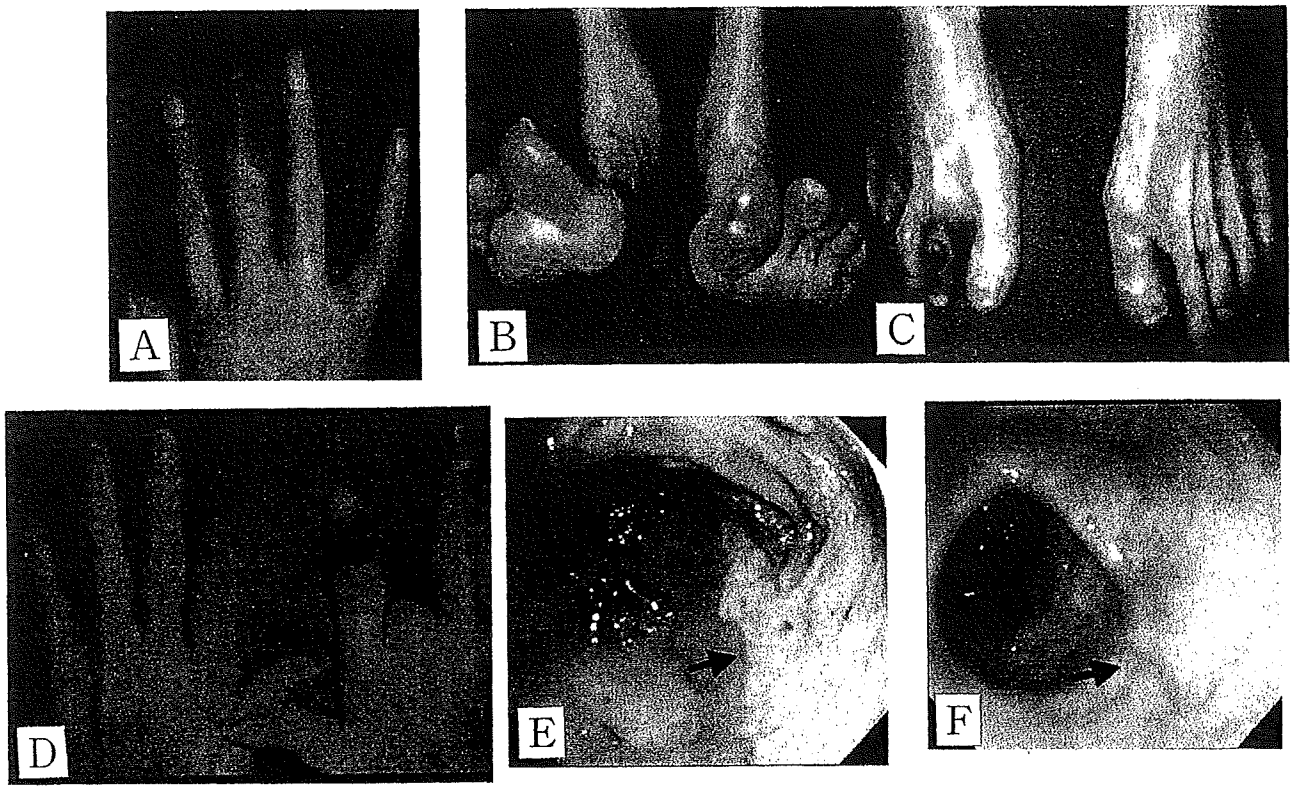

Figure 1. Dry gangrene in the right third finger, bilateral toes, right second toe, and left second and right second fingers. Blackened eschar formation progressed to the feet (A–D). Colonoscopy revealed a longitudinal and irregularly shaped ulcer (E, arrow) which was characteristic of ischemic change. This finding was markedly improved and scarred (F, arrow).

In August 1998, at the age of 52, she suddenly developed pain and blackened eschar formation in the right third finger (Fig. 1A) and right first toe and left first toe (Fig. 1B) with preserved pulses of radial, ulnar, femoral, popliteal, and dorsal pedal arteries. No bruits were present in the upper or lower extremities. Despite treatment with prostaglandin E1 (PGE1) and broad-spectrum antibiotics, the finger lesion progressed to gangrene of the involved phalange over a period of a few weeks and the gangrenous finger phalange was amputated. In January 1999, the resulting ischemic and gangrenous change involving the right toe and second digit deteriorated to the foot and heel (Fig. 1C) and the right leg below the knee joint was amputated. In October 1999, she developed massive hematochezia. Colonoscopy revealed extensive longitudinal ulcerations of the rectosigmoid, descending, transverse (Fig. 1E), and ascending colon. Biopsies of ulcerated lesions did not reveal vasculitis or amyloid deposits. These ulcers healed spontaneously without PGE1 (Fig. 1F). Thereafter, gangrenous eschar formation in the left second finger was noted in December 1999, and in the right second finger in January 2000 (Fig. 1D) and these phalanges were amputated. She was finally admitted to our hospital for evaluation of painful bluish discoloration and ulceration of the left heel in March 2000. Despite intensive conservative therapy including PGE1 and antibiotics, these wounds worsened, and the left leg was amputated below the knee joint. Histopathological study of the amputated segments was not performed. We suspected systemic calciphylaxis associated with acral gangrene and mesenteric ischemia, and we evaluated the patient accordingly.

Calcium-phosphorus-parathyroid axis

At the initiation of hemodialysis, her height was 157 cm, dry body weight, 49 kg; calcium, 9.1 mg/dl; phosphorus, 4.5 mg/dl; calcium-phosphorus product, 41 mg/dl^2; albumin, 3.9 g/dl; alkaline phosphatase, 80 IU/ml; intact-PTH, 100 pg/ml. The trends for dry weight, calcium-phosphorus product, intact-PTH, alkaline phosphatase and albumin values are shown in Fig. 2. A marked loss of body weight was noted (26.5% of body weight) over 2 years which may have been induced by the correction of edematous states. Although the intact-PTH level increased to 540 pg/ml temporarily in January 1997, levels of calcium-phosphorus product and intact-PTH remained within acceptable limits. In August 2000, bone specific alkaline phosphatase (BAP) was 14 IU/*l* (normal 15–35 IU/*l*); 1,25 $(OH)_2$-D_3, 9 pg/ml (normal 20–60 pg/ml); osteocalcin (bone Gla protein, BGP) 51 ng/ml (normal 2.5–13 ng/ml, immunoradiometric assay (IRMA)); serum aluminum 0.4 μg/*l* (normal<10 μg/*l*).

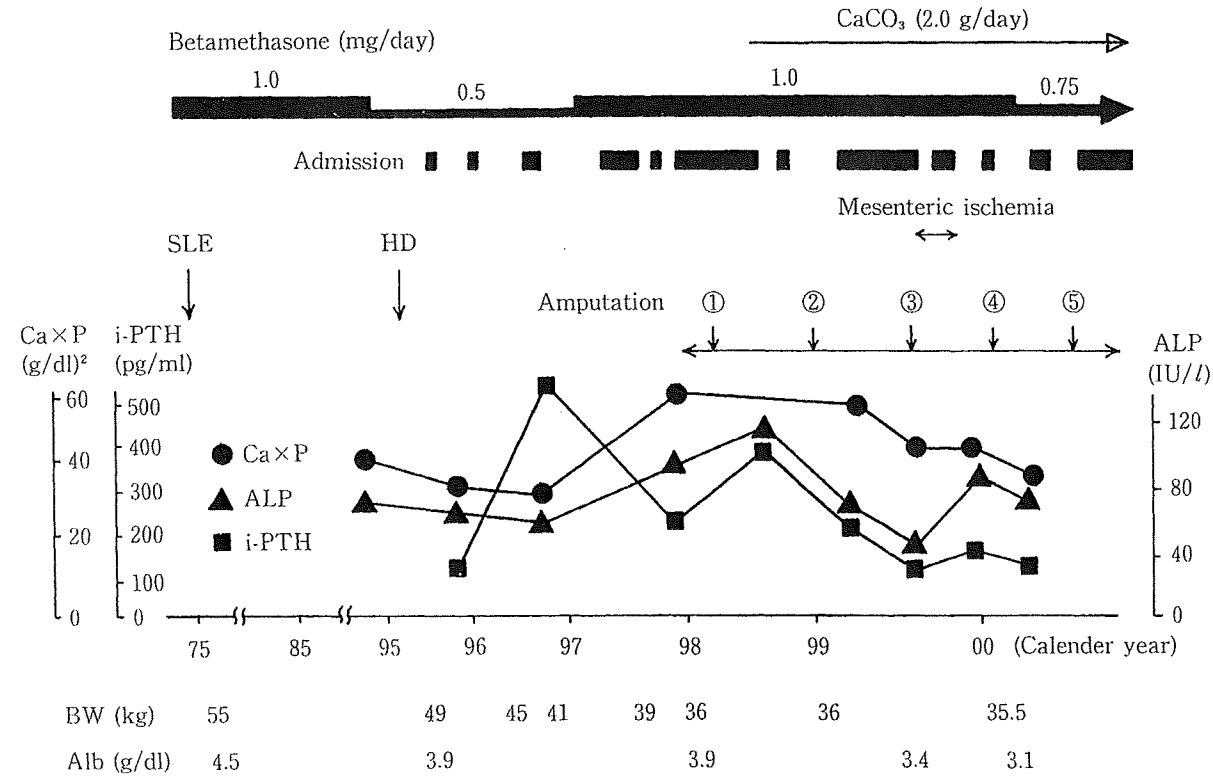

Figure 2. The clinical course of the patient. Amputation of the right third phalanx (①), right leg below the knee joint (②), left second finger (③), right second finger (④), and left leg below the knee joint (⑤). Although intact-PTH level increased to 540 pg/ml temporarily in January 1997, levels of calcium-phosphorus product remained within 60 mg/dl².

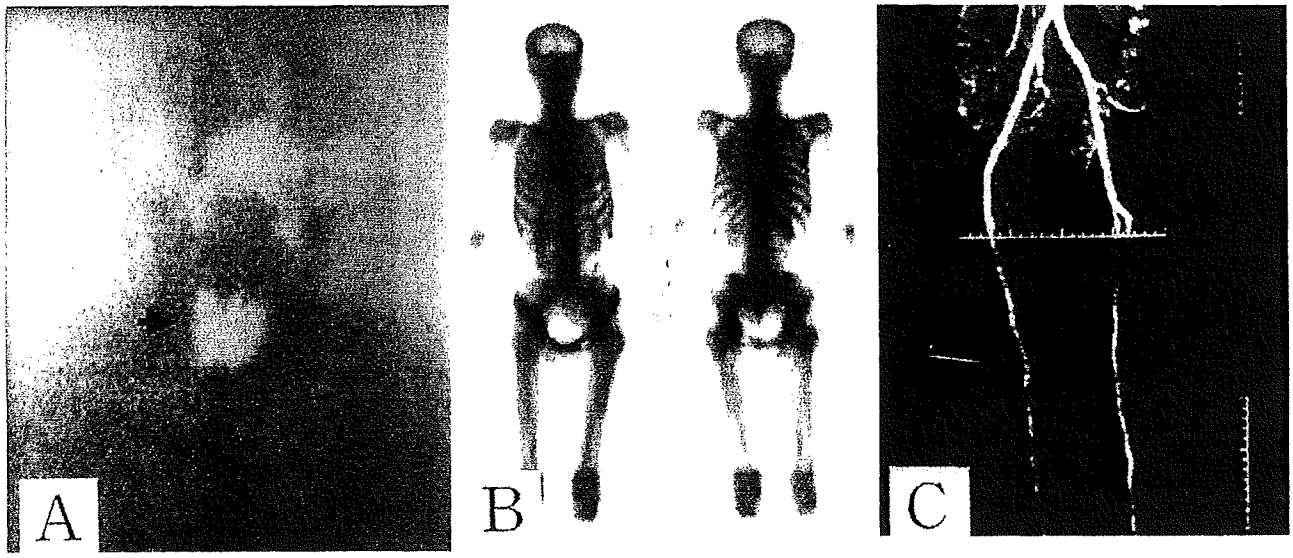

Figure 3. Parathyroid scintigraphy using ^{201}Tl-chloride and ^{99m}Tc-pertechnetate (Tl/Tc) subtraction image revealed no accumulation in parathroid glands (A, arrow). Bone scintigraphy using ^{99m}Tc-pertechnetate did not reveal abnormal accumulation nor an abnormal ratio of bone to soft tissue (B). Gadolinium-enhanced magnetic resonance angiography revealed no significant stenosis of the aortoiliac, femoral, popliteal, and peroneal arteries (C).

Several modalities such as ultrasonography (US), computed tomography (CT), and parathyroid scintigraphy using ^{201}Tl-chloride and ^{99m}Tc-pertechnetate (Tl/Tc) subtraction image (Fig. 3A) did not detect parathyroid abnormalities. Bone scintigraphy using ^{99m}Tc-pertechnetate did not reveal abnormal accumulation or an abnormal ratio of bone to soft tissue (Fig. 3B).

Lupus and coagulability

Immunologic evaluation performed in July 2000 included an antinuclear antibody (ANA) 1:320 titer in a diffuse pattern, and normal complements (C_3 level, 86 mg/dl; C_4 level, 30 mg/dl); anti-double strand DNA, 1.0 IU/ml (normal<12.0 IU/ml). Coagulability included prothrombin time (PT)-international ratio (INR) 1.06 (normal 0.85–1.15); activated partial thromboplastin time (APTT) 30.3 seconds (normal<45 seconds); antithrombin (AT)-III 24.7 mg/ml (normal>25 mg/ml); D-dimer 0.68 μg/ml (normal<0.72 μg/ml); protein C of 114% (normal 70–150%); protein S of 127% (normal 60–150%). Cryofibrinogen, lupus anticoagulant and anticardiolipin antibody was negative. Lupus activity was erradicated and no hypercoagulability was observed.

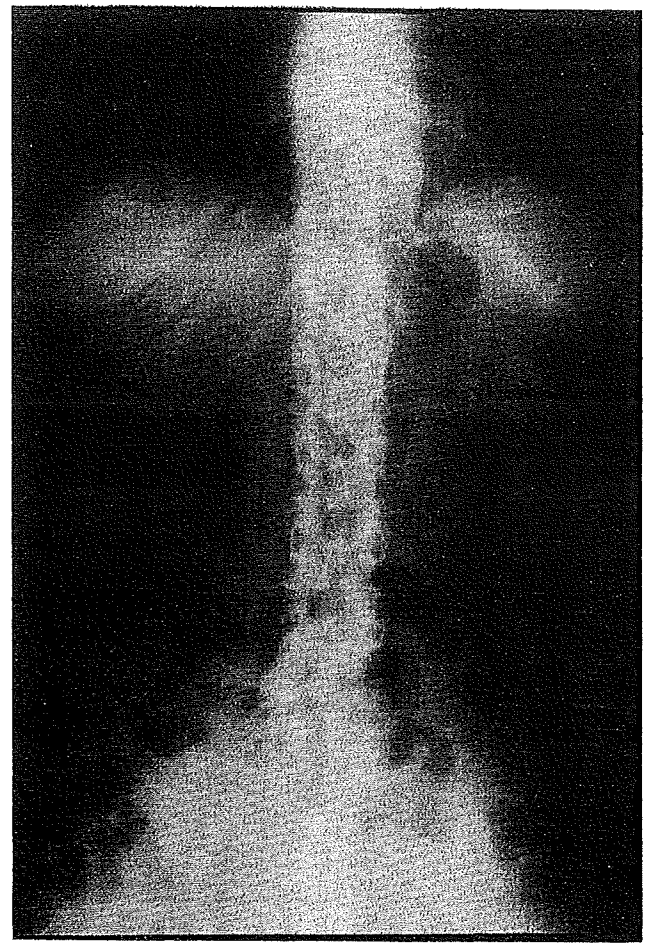

Figure 4. X-ray of abdomen revealed diffuse ring-shaped calcification of caeliac, common hepatic, proper hepatic, gastroduodenal, and splenic arteries. However, there was no calcification in the descending aorta or aortoiliac arteries.

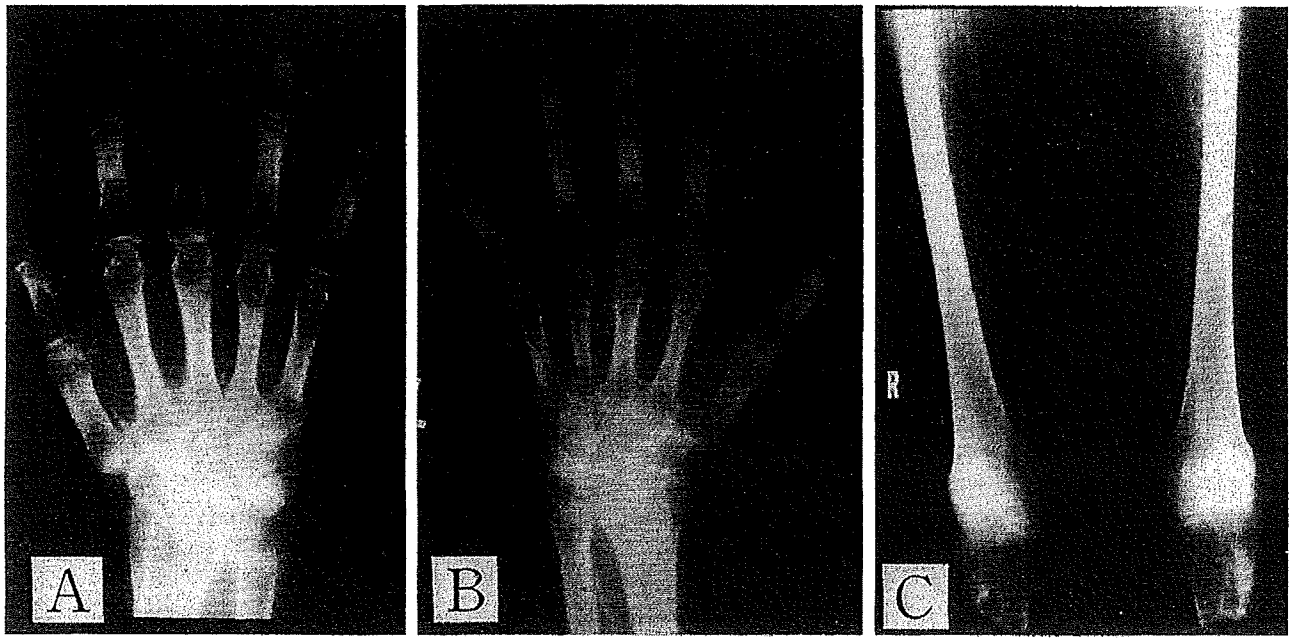

Figure 5. Right (A) and left (B) palmar arteries were markely calcified, and femoral and popliteal arteries (C) were also calcified like a spontaneous arteriogram.

General X-ray examinations and MRA

X-ray examination was performed in July 2000. Widespread ring-type medial calcification involving various small to medium sized arteries (caeliac, hepatic, gastroduodenal, splenic, forearms, femoral, and digital arteries as shown in Fig. 4 and Fig. 5A, B, C) were observed. Palmar arches produced a spontaneous arteriogram. However, calcification of the aortic arch and main arteries was not observed. Magnetic resonance angiography (MRA) revealed no marked obstruction of the main artery and its tributaries (Fig. 3C). These findings were characteristic of calciphylaxis, along with persistence of palpable pulses distal to the necrosis in this case.

Discussion

Selye's animal model (12) was characterized by metastatic systemic calcifications developing after significant invasive manipulations of the animal model, though no vascular calcifications were present. Retrospectively, it appears that uremic soft tissue calcifications in the syndrome are most analogous to differences between Selye's model and uremic calciphylaxis (13–15). The term "calciphylaxis" had been used most often, and had pathogenetic implications that were not substantiated in all clinical cases. Recently, descriptive terms for the vascular lesions have become increasingly more common such as calcific uremic arteriolopathy (14), uremic small artery disease (16), subcutaneous calcific arteriolopathy with infarcts of the subcutis and skin (17). Janigan et al (17) emphasized that calcific arteriolopathy develops slowly, sometimes over years, and silently, whereas the infarctions are acute and clinically dramatic. In the present case, we considered that it was unlikely that atherosclerosis affecting large vessels played a role in causing compromised blood flow to the upper and lower extremities; thus, the onset of skin discoloration and painful lesions on the fingers and toes and mesenteric ischemia was suggestive of calciphylaxis. Together with some recently developed mouse models, vascular calcification and atherosclerosis are different genetically (18). The generation of two mutant mouse strains, mice lacking matrix GLA protein or osteoprotegrin, has had the biggest impact on the understanding of vascular calcifications since both strains show isolated medial calcification of arteries. The histopathological diagnosis of calciphylaxis on the amputated segments was not confirmed in this case. The pathology of calciphylaxis was characterized by small vessel calcification, endovascular fibrosis, and panniculitis with vascular calcification (19). General X-ray examinations revealed extensive calcification of small to medium sized arteries like a spontaneous arteriogram, but not the large vessels in this case. Medial calcification of peripheral arteries is common in the setting of chronic renal failure (20), but it typically does not result in vascular compromise or lead to tissue ischemia as is also the case in nonuremic patients with Mönckeberg sclerosis. Not only does this case present the features typical of systemic calciphylaxis, namely acral gangrene from arboreal palmar and pedal vascular calcification, but it also demonstrates mesenteric ischemia from intestinal vascular calcification.

The pathogenesis of calciphylaxis remains unclear, but several factors have been implicated including HPT, persistent or transient hyperphosphataemia, vitamin D treatment, calcium salt administration, steroid therapy, obesity, and protein C and S deficiencies.

A link between calciphylaxis and HPT was further supported by the observation that parathyroidectomy (PTx) markedly improves the syndrome (2, 9–11). PTx with subsequent improvement in calcium phosphate control has been advocated as treatment for calciphylaxis; however, this aggravated the condition further in other patients, leading to high morbidity and mortality (1). In this case, calcium phosphorus product was less than 60 $(mg/dl)^2$ and no marked secondary HPT was observed. Vitamin D supplements and precipitated calcium carbonate were never loaded prior to the occurrence of calciphylaxis. Thus, we considered that HPT, persistent or transient hyperphosphataemia, vitamin D treatment, and calcium salt administration were not markedly involved in triggering calciphylaxis in this case.

It has been reported that calciphylaxis often appears in patients with renal transplantation, rheumatoid arthritis, and chronic renal failure while receiving corticosteroids (21, 22). Tamura et al (23) reported a case of diffuse calcification of the arteries and progressive gangrene after the initiation of hemodialysis and the administration of corticosteroids without marked secondary HPT and atherosclerotic lesion of the arteries at autopsy. The present patient received corticosteroid throughout the clinical course because of the suppression of lupus activity. Thus, retrospectively in this case we hypothesized that chronic administration may be implicated in the development of calciphylaxis.

Other possible contributors to the development of calciphylaxis in this case include photosensitivity in lupus and significant weight loss. There was no evidence of an exacerabation of lupus activity, but photosensitivity may occur in up to 45% of patients with SLE. James et al (24) reported a case of calciphylaxis precipitated by ultraviolet light in a patient with end-stage renal disease secondary to SLE. Since our patient also had a history of sensitivity to sunlight, photosensitivity may have contributed to calciphylaxis. The patient also experienced significant body weight loss (26.5% of body weight) over the 2 years preceding the development of ischemic tissue necrosis due to calciphylaxis. Coates et al (14) speculated that rapid weight loss may be associated with relative intravascular volume depletion and as a result reduction in tissue perfusion may occur. Previously, it was considered that heavily calcified vessels may be unable to reactively vasodilate to increase skin blood flow; thus, ischemic areas may develop.

Perez-Mijares et al (25) reported a case of calciphylaxis in a hemodialysis patient with severe secondary HPT, severe diffuse calcification of arteries of several sizes, and functional protein S deficiency with a favorable response to treatment with low molecular weight heparin. Functional protein S deficiency can occur secondary to severe HPT and extensive vascular calcifications. However, Goldsmith (26) clearly pointed out that