

An Unusual Case of Cutaneous Vasculitis

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Abstract

Introduction: We report an unusual case of a patient with clinical and histological features of cutaneous vasculitis. **Case Picture:** A middle-aged Chinese male presented with livedo reticularis and digital gangrene without visceral involvement. Skin biopsy showed features suggestive of cutaneous vasculitis. Repeated testing for anticardiolipin antibody was negative. **Treatment:** He was treated with two courses of intravenous prostacyclin and pulsed with one course of intravenous methylprednisolone. He was also put on oral prednisolone, pentoxifylline, aspirin, nifedipine and colchicine in addition to symptomatic therapy. **Outcome:** There was gradual improvement of his toe discolouration and relief of pain. **Conclusions:** This is an interesting case of cutaneous vasculitis, which has features of polyarteritis nodosa and the antiphospholipid syndrome, who responded well to intravenous prostacyclin, steroids, pentoxifylline, aspirin, nifedipine and colchicine.

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Key words: Antiphospholipid syndrome, Digital gangrene, Livedo reticularis, Polyarteritis nodosa

Case Report

A 49-year-old Chinese man presented at the Tan Tock Seng Hospital with painful gangrene of the right second and left third and fourth toes for 6 weeks, purple discolouration of the toes for 3 months and arthritis of the left knee for 3 months.

He also had a past history of bilateral ankle arthritis 1½ years before, which resolved with traditional Chinese medication. There was no history of Raynaud's phenomenon, oral ulcers, malar rash, photosensitivity, weight loss or fever. He neither smokes nor consumes alcohol.

Physical examination revealed a livedo reticularis over both lower limbs up to the mid-thighs. The right second toe and left third and fourth toes were dry and gangrenous over the middle and distal phalanges (Fig. 1). The nails were intact. The skin of his toes was cold but there was no xerosis. There were scars from healed ulcers on his shins. The distal pulses of both lower limbs were strongly palpable and there was no neurological deficit. The upper limbs were both normal.

There was no abnormality of the left knee joint or other joints on physical examination. He was afebrile. His blood pressure was normal at 130/70 mmHg, and his pulse rate was regular at 72 bpm. Fundoscopic examination was unremarkable. Examination of the cardiovascular, respiratory, alimentary and nervous systems was also unremarkable.

Clinically, the main diagnosis was anticardiolipin syndrome, either primary or secondary to underlying collagen vascular disease. The differential diagnoses were polyarteritis nodosa, livedo vasculopathy and cholesterol embolisation.

The results of investigations were as follow: haemoglobin 13.3 g/dL, total white count $14.1 \times 10^9/L$ and platelets $434 \times 10^9/L$. Prothrombin time 13.6 s (12 to 15), partial thromboplastin time 30.8 s (26 to 42) and erythrocyte sedimentation rate (ESR) 45 mm/h. Sodium 140 mmol/L, potassium 3.7 mmol/L, chloride 105 mmol/L, bicarbonate 24.9 mmol/L, urea 5.7 mmol/L, creatinine 55 µmol/L, creatinine clearance 122 mL/min (70 to 150) and total urinary protein 90 mg/24h (N <150). Urine microscopy

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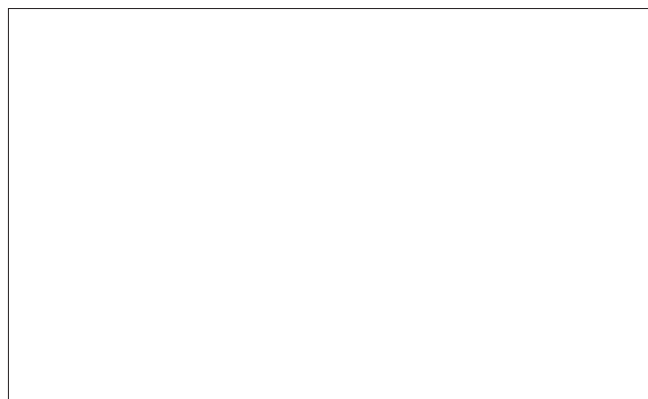


Fig. 1. Painful gangrene involving the left third and fourth, and the right second toes.

was normal. Total protein 71 g/L, albumin 37 g/L, alanine aminotransferase 31 U/L, aspartate aminotransferase 15 U/L, alkaline phosphatase 74 U/L and gamma glutamyl transferase 51 U/L. Total cholesterol 5.37 mmol/L (4.4 to 7.5), triglycerides 0.88 mmol/L (0.85 to 1.92), high-density lipoprotein (HDL) cholesterol 1.25 mmol/L (desirable >0.9) and low-density lipoprotein (LDL) cholesterol 3.72 mmol/L (0 to 5.17). Random blood glucose 7.7 mmol/L and HbA1c 6.1% (4.6 to 6.4). Uric acid 178 μ mol/L $\downarrow$ (232 to 494). Stool occult blood was not detected.

Antinuclear antibody (ANA), anti-dsDNA, lupus anticoagulant, rheumatoid factor, anti-neutrophil cytoplasm antibody (ANCA) and anticardiolipin antibody (ACA) were all not detectable. Cryoglobulins were not detected. Protein electrophoresis: α 1 globulin 2 g/L (1-3), α 2 globulin 5 g/L (4 to 8), β globulin 9 g/L (6 to 12) and γ globulin 9 g/L (10 to 19). Serum immunoglobulins: IgG 13.3 g/L (7.3 to 15.4), IgM 0.6 g/L (0.29 to 1.52) and IgA 5.47 g/L $\uparrow$ (0.7 to 3.76). C3 1.59 g/L $\uparrow$ (0.49 to 1.28) and C4 0.36 g/L (0.20 to 0.72). Electrocardiogram was normal. Venereal disease research laboratory (VDRL) was non-reactive. HBsAg and anti-HCV IgG were negative.

X-rays of knees and ankle joints showed osteoarthritis. There were no bone erosions. Arterial scan of both legs showed no sign of atherosclerosis. The aorta had no ultrasonographic signs of vasculitis. Angiogram of both lower limbs were normal. Echocardiography showed a normal left ventricular ejection fraction of 57% and normal valves. There was mild to moderate pulmonary hypertension of 44/15 mmHg (N <35/10).

Skin biopsy of the right calf showed features suggestive of cutaneous vasculitis. There was evidence of chronic occlusion of the mid-dermal blood vessels but no thrombosis was seen. Direct immunofluorescence of the skin showed fibrinogen deposits in the walls of the blood vessels, which was consistent with vasculitis. There were also faint C1q deposits in the walls of a few upper dermal blood vessels.

The results of the investigations suggested the diagnosis of a cutaneous vasculitis.

The patient was managed in the Department of Rheumatology, Tan Tock Seng Hospital. He was put on prednisolone 10 mg tds, pentoxifylline 400 mg tds, tramadol [a relatively new non-NSAID (non-steroidal anti-inflammatory drug), non-narcotic analgesic] 50 mg tds and nifedipine 10 mg tds. He was infused with prostacycline for 10 days and intravenous methylprednisolone 500 mg/day for three days.

There was improvement with slight decrease in area of gangrene of the affected toes. He was discharged from Tan Tock Seng Hospital with prednisolone 20 mg tds, cloxacillin 500 mg 6H for 10 days, nifedipine 10 mg tds, pentoxifylline 400 mg tds, aspirin 100 mg om, paracetamol 1g qds and sublingual buprenorphine (Temgesic) 0.2 mg prn.

After discharge, there was worsening of his toe gangrene requiring readmission and a further 5-day course of prostacycline infusion was given with slight improvement of his discolouration and relief of pain.

He was discharged with: prednisolone 20 mg tds, nifedipine 10 mg tds, pentoxifylline 400 mg tds, aspirin 100 mg om, paracetamol 1g qds, sublingual buprenorphine (Temgesic) 0.2 mg prn with metoclopramide 10 mg and colchicine 0.5 mg tds.

Discussion

A middle-aged male first presented with painful digital gangrene of 6 weeks' duration. Important differential diagnoses include the antiphospholipid syndrome, polyarteritis nodosa and cholesterol embolisation (Table I).

Anticardiolipin Syndrome

A group of patients with diffuse widespread progressive livedo vascularis, which precedes cerebrovascular lesions by several years, was first described by Sneddon in 1965. Evidence of peripheral ischaemia may also occur. The patients described had no evidence of systemic lupus erythematosus (SLE)¹ but since then, many patients with Sneddon's syndrome have been found to have elevated anticardiolipin antibodies (ACA), and some have also had SLE.²

Patients with anticardiolipin syndrome are mostly young females. They have elevated ACA and/or lupus anticoagulant, false positive VDRL, and an increased frequency of both arterial and venous thrombotic episodes, especially involving the central nervous system. Other signs include livedo reticularis, a history of repeated foetal loss, labile hypertension, thrombocytopenia, leg ulcers and gangrene. Many of these patients have SLE, some develop SLE, or have other underlying disorders. ACA has also been associated with drug-induced LE, other connective

TABLE I: DIFFERENTIAL DIAGNOSES CONSIDERED

Diagnosis	For	Against
Antiphospholipid syndrome	Livedo reticularis Leg ulcers Gangrene Pulmonary hypertension	No cerebrovascular thrombosis No ACA/Lupus anticoagulant— more sensitive tests may be required
Polyarteritis nodosa	Myalgia/arthralgia Livedo reticularis Ulcers Biopsy findings suggestive of cutaneous vasculitis Negative markers for connective tissue disease Gangrene	No constitutional symptoms No renal insufficiency No peripheral neuropathy No aneurysms on angiogram of lower limbs, (renal and mesenteric angiogram not done) No cutaneous/subcutaneous nodules No nail fold and digital pulp infarcts
Livedo vasculopathy	Livedo reticularis Healed ulcers	No atrophie blanche No telangiectasia Digital gangrene not reported No thrombosis on histology
Cholesterol embolisation	Livedo reticularis Leg ulcers Digital gangrene	No lower body pain No renal insufficiency No atherosclerosis of abdominal aorta Normal lipid profile

ACA: anti-cardiolipin antibody

tissue disorders e.g. rheumatoid arthritis, polymyalgia rheumatica/giant cell arteritis and carcinoma.

Patients with livedo vasculitis may have elevated ACA and may fall within the anticardiolipin syndrome. However, serum ACA in our patient has been repeatedly negative, making this diagnosis less likely. There is still one subset of ACA which cannot be assayed at our lab currently, i.e. anti-GP I, and this may be positive when the test is available. The pulmonary hypertension also needs to be further evaluated as it may be due to pulmonary embolism, making anticardiolipin syndrome more likely.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a disease of small- and medium-sized arteries, with a predilection for sites of vessel bifurcation, with resultant weakening and the formation of aneurysms and thrombosis. The vessels heal with proliferation and fibrosis.

PAN typically affects patients in the middle age, with a male predominance. Constitutional symptoms are malaise, weakness, fever and weight loss. Renal complications occur in about 70% of patients and peripheral neuropathy in 60%. Myalgias and arthralgias are common. Visceral arteriography of the hepatic, renal, coeliac and mesenteric arteries shows characteristic small saccular aneurysms, which are typical of PAN.

Skin involvement approaches 50% of cases.³ Cutaneous and subcutaneous nodules occur over affected vessels, most commonly in the lower extremities. They tend to appear in crops, are sometimes painful, and persist for days

to months. Other cutaneous manifestations include ulcers, livedo reticularis,⁴ nail fold and digital pulp infarcts, and a nonspecific erythematous rash.

Cutaneous polyarteritis nodosa⁵ is a distinct clinical entity with a benign prognosis. The most common presentation is painful cutaneous nodules on the lower legs, livedo reticularis and ulceration. Skin biopsy reveals a necrotising vasculitis of small- and medium-sized arteries, and direct immunofluorescence is positive for immunoglobulin and/or complement in a majority of cases.

Our patient has normal renal and liver function tests and normal lower limb angiogram findings, making this diagnosis less likely. However, renal and mesenteric angiograms have not been done, and these may reveal the characteristic aneurysms. The patient has no systemic features now but may develop these features later.

Livedo Vasculopathy

Livedo vasculopathy is an uncommon clinicopathologic condition clinically characterised by early, focal, painful purpuric lesions of the lower extremities that frequently ulcerate and slowly heal, leaving white, stellate, atrophic scars (atrophie blanche), telangiectasias, livedo-like hyperpigmentation, and livedo reticularis. The histological finding of leukocytoclasia is usually absent. So far, there have been no reports of digital gangrene in patients with this condition. Histologically, it shows segmental hyalinisation, endothelial swelling, and thromboses of dermal vessels. A variable number of perivascular lymphocytes are usually observed.

The most likely pathogenetic mechanism is mediated by platelet activation and/or a hypercoagulable state (primary) or is secondary to chronic venous insufficiency, peripheral arterial occlusion, cryoglobulinaemia, hypercoagulable disease, anticardiolipin antibody syndrome (e.g. in lupus erythematosus, rheumatoid arthritis, or scleroderma), and protein C deficiency.

The disease is chronic and can remain cutaneous without systemic involvement. There is a natural history of exacerbations and remissions. Pregnancy may worsen the condition. The prevalence is usually estimated around 1:100,000 per year and is more frequent in young women (1:3).⁶

This diagnosis was clinically thought to be less likely as there was no atrophie blanche and digital gangrene has not been reported in this condition before. Furthermore, no thrombosis was seen in the dermal vessels on histology.

Cholesterol Embolisation

In patients with advanced atherosclerosis of the abdominal aorta, cholesterol crystals may microembolise to the lower extremities, particularly after invasive vascular procedures or surgery. The pulses may remain normal.⁷ The patient may present with pain in the legs, buttocks and lower back, myalgia, restless legs, abdominal symptoms, renal insufficiency and various skin lesions.⁸

Livedo reticularis may affect the lower abdomen, back, buttocks, legs and feet. Lower limb ulcers, cyanosis and digital gangrene may occur.⁹

This diagnosis is unlikely in view of the normal arterial scan and angiogram, as well as the normal lipid profile.

The final diagnosis was that of cutaneous vasculitis, either due to antiphospholipid syndrome or PAN, based on the presence of livedo reticularis, healed ulcers on legs and biopsy findings. Arteriography of the renal vasculature may be performed to look for microaneurysms in order to confirm if the diagnosis is polyarteritis nodosa.

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