Digital ulcers and gangrene are common skin manifestations of connective tissue diseases, especially systemic sclerosis, although they are relatively rare in systemic lupus erythematosus. We describe here three patients with digital gangrene and systemic lupus erythematosus. None of the patients showed high disease activity of systemic lupus erythematosus at the time the digital gangrene developed. Two patients were positive for anti-RNP antibodies; however, no symptoms of other collagen diseases were present. One patient had anti-phosphatidylserine/prothrombin complex antibodies, and the other had anti-phosphatidylserine/prothrombin complex antibodies and lupus anticoagulant at low titre. All patients showed narrowing or occlusion of radial and/or ulnar arteries in addition to digital arteries. Although a complication of anti-phospholipid syndrome is considered to be a possible cause, there may be unidentified causes other than thrombosis, atherosclerosis, overlap syndrome and vasculitis. Key words: digital gangrene; systemic lupus erythematosus; antiphospholipid syndrome.

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Digital Gangrene in Systemic Lupus Erythematosus

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CASE REPORT

Case 1

A 35-year-old woman was diagnosed with SLE at the age of 20 years in 1993. She was reported by us in 2008 (1). She had two healthy children and had had no miscarriages. She had been treated with prednisolone and the dose had been increased due to the worsening of a skin rash and laboratory findings. Since 1997, multiple indurated plaques had developed on her back and extremities and gradually increased in number. The plaques were diagnosed histologically as lupus erythematosus profundus. In 2005, a digital ulcer with severe pain and Raynaud’s phenomenon developed on her right fourth fingertip even though her disease activity had been stable.

Abnormal laboratory findings included positive anti-dsDNA antibodies at a titre of 25 U/ml (normal < 7 U/ml), positive anti-nuclear antibodies (ANA 1:320) and highly elevated levels of anti-phosphatidylserine/prothrombin complex (PS/PT) antibodies over 200 U/ml (normal < 12 U/ml). Lupus anticoagulant (LAC), anti-cardiolipin β2 glycoprotein I (anti-β2GPI) antibodies and anti-cardiolipin IgG/M antibodies were negative. Arteriography of the upper limbs revealed narrowing of the right ulnar and radial arteries. The digital arteries of both hands were almost completely occluded.

Oral preparations of beraprost sodium, aspirin, sarpogrelate hydrochloride and warfarin were not effective in preventing the development of new ulcers. Alprostadil intravenous infusion, hyperbaric oxygenation and sympathetic ganglia block also failed to improve the ulcers. Finally, the patient was administered bosentan, which, along with debridement and topical therapy with silver sulfadiazine, successfully alleviated the pain and stopped the emergence of new lesions. Only one ulcer, on the dorsal aspect of the left third finger, remained one year later.

Case 2

A 50-year-old woman had been diagnosed with SLE at the age of 32 years in 1992. She presented with malar rash, positive anti-dsDNA antibodies, pancytopaenia and positive ANA. She had two healthy children and had not had any miscarriages. Central nervous system (CNS) lupus developed in 1993, and was treated successfully with methylprednisolone (mPSL) pulse therapy. Since then, she had been given oral PSL 10–20 mg/day.

In February 2008, digital gangrene developed on her right fourth finger with severe pain (Fig. 1a). She presented with Raynaud’s phenomenon. Abnormal
laboratory findings included positive ANA (1:320), as well as positive ribonucleoprotein (RNP), Sm, and SS-A antibodies. LAC, anti-β2GPI, anti-cardiolipin IgG/M and PS/PT antibodies were all negative. Arteriography of the upper limbs revealed occlusion of the digital arteries in the right third and fourth fingers. Narrowing of the left radial artery was also noted.

The same dose of PSL, 10 mg/day, was continued, because her disease activity was moderate. In addition to oral preparations of beraprost sodium and aspirin, intravenous infusion of alprostadil was effective in alleviating the pain. After the necrotic area was demarcated, debridement was performed. The digital ulcer has gradually improved (Fig. 1b) and no new lesions have developed.

Case 3

A 28-year-old woman was diagnosed with SLE at the age of 20 years in 1999. She had malar rash, increased levels of anti-dsDNA antibodies, leucopaenia, and positive ANA. She had been treated with PSL and later, cyclosporin A was added in 2005. In 2006, she had a caesarean section at week 24 of gestation because of severe pregnancy-induced hypertension. Her disease activity had been stable with PSL 20 mg/day and cyclosporin A 150 mg/day.

In December 2007, digital ulcers developed on her right second and fourth fingers with severe pain and acrocyanosis (Fig. 2a). She presented with Raynaud’s phenomenon. Abnormal laboratory findings included positive ANA, as well as positive RNP and SS-A antibodies. Anti-dsDNA antibodies were within normal limits. Anti-β2GPI antibodies were slightly elevated at a titre of 4.3 U/ml (normal < 3.5 U/ml); however, LAC, anti-cardiolipin IgG/M antibodies and anti-PS/PT antibodies were negative. Arteriography of the upper limbs revealed an occluded right radial artery, and narrowing of the left radial and digital arteries (Fig. 3).

In addition to the oral preparations of beraprost sodium, aspirin and salpoglate hydrochloride, intravenous infusion of alprostadil and hyperbaric oxygenation were administered; however, they failed to improve her pain. After the sympathetic ganglia block was performed, her pain improved significantly. Her gangrene gradually improved with debridement and topical therapy with silver sulfadiazine (Fig. 2b).

DISCUSSION

The most likely cause of digital gangrene in SLE may be APS, as SLE is the most common underlying disease of secondary APS. LAC and aCL antibodies, both IgG and IgM, are included as laboratory APS criteria, and anti-β2GPI assays were added in the revised version (2). Prothrombin is another antigen of APS. Nojima et al. (3) reported that the presence of anti-PS/PT antibodies may be the most significant risk factor for both arterial and venous thrombosis. In patients with SLE, the relationship between positive anti-PS/PT antibodies
and neuropsychiatric symptoms has been suggested (4). Furthermore, high correlation between positive PS/PT antibodies and cutaneous polyarteritis nodosa was demonstrated, indicating that the thrombotic process can trigger cutaneous vasculitis (5).

Cutaneous manifestations of APS are diverse, such as livedo reticularis, livedoid vasculitis, thrombophlebitis, cutaneous ulceration and necrosis, erythematous macules, purpura, ecchymoses, painful skin nodules, and subungal splinter haemorrhages (6). Frances et al. (7) reported that skin manifestations were present in 49% of patients. In the series reported by Alegre et al. (8), the cutaneous lesion developed as the first manifestation of anti-phospholipid syndrome in 41% of LAC-positive patients. Livedo reticularis is the most common skin manifestation that is significantly associated with anti-phospholipid antibodies (6). Skin ulcers are also common, and are often seen on the pre-tibial and ankles. Cutaneous gangrene was found in 19% of APS patients and cutaneous necrosis in 3% (8). Some patients with APS develop digital ischaemic symptoms resulting in gangrene of digits. The prevalence is reported to be 3.3–7.5% of APS patients (9).

Another contributing factor to digital gangrene in SLE could be atherosclerotic changes in the arteries. Increasing attention has been drawn to late complications of lupus-like atherosclerotic vascular disease (10, 11). Emerging evidence supports the concept of vasculopathy in APS that may cause arterial stenosis, possibly contributing to vascular occlusions and pregnancy morbidity (12). In autopsy cases of APS, occlusive vascular or thrombotic microangiopathy-related changes and arterial intimal fibrotic hyperplasia have frequently been found (13). These findings suggest that there may be two pathogenic mechanisms associated with the presence of aCL, an abnormal coagulation-related mechanism and an endothelial cell injury-related mechanism.

In the three cases described in this paper, anti-PS/PT antibodies were positive in case 1, and anti-β2GPI antibodies in case 3 (Table I). Case 2 was previously diagnosed with CNS lupus and case 3 had experienced premature birth. Collectively, we considered that APS was the most likely cause of gangrene in our patients, although no patient fulfilled the criteria for definite APS (2). In arteriographic examinations, all our patients showed occlusion or narrowing of the radial and/or ulnar arteries in addition to digital arteries. No atherosclerotic
changes were noted in the large proximal arteries. These findings were similar to those found in systemic sclerosis, in which macrovascular involvement is due to the thickening of the intimal wall (14).

In general, anticoagulant therapies as well as anti-platelet therapies and low-dose aspirin are required to treat skin manifestations of APS (9). In our cases, combined therapies were given to improve the symptoms. In addition to the oral medications, alprostadil infusion was effective in case 2, and sympathetic ganglia block in case 3. In case 1, severe skin symptoms were refractory to conventional therapies including warfarin. Since new digital ulcers developed repeatedly, we finally chose bosentan, which is usually used for pulmonary hypertension. Its efficacy for digital ulcers in SSc has been well recognized (15–17). It might be an alternative treatment for refractory digital ulcers in SLE.

Two of the cases described here presented positive anti-RNP antibodies. An association between anti-RNP antibodies and Raynaud’s phenomenon has been reported (18, 19), thus they might have had an effect on the development of digital gangrene.

The aetiology of digital gangrene in SLE is complex. Several factors, such as the presence of APS, overlap syndrome, atherosclerosis or vasculitis, are potential causes. The most likely cause may be a complication of APS; however, there may be unidentified causes in addition to these conditions.

REFERENCES