

cases were males and developed skin changes within 8 months after the chemotherapy. Raynaud's phenomenon and digital pitting scars were seen in two and one cases, respectively. The ANA was positive in three of the patients, although no case had scleroderma-specific autoantibodies. In seven patients, skin sclerosis was limited to the extremities, while only one showed skin sclerosis of the trunk as well as the extremities. The atypical distribution of skin involvement without sclerodactyly was specific for our case. Two cases showed morphea-like plaques. None of the patients had a visceral involvement. Eight of nine cases had minimal persistent scleroderma after withdrawal of the drugs and additional treatments, including oral corticosteroids. Thus, the small incidence of Raynaud's phenomenon, digital pitting scars and ANA, and the absence of visceral involvement are characteristics of bleomycin- or peplomycin-induced scleroderma.

Although the pathogenesis of bleomycin- or peplomycin-induced pulmonary and dermal fibrosis is still unknown, numerous examinations have disclosed several aspects of its mechanism. In normal human dermal fibroblasts, bleomycin enhances the synthesis of type I collagen.⁷ In rat lung fibroblasts, bleomycin stimulates pro- $\alpha 1$ (I) collagen promoter through the transforming growth factor (TGF)- β response element.⁸ Bleomycin or peplomycin enhances reactive oxygen intermediate (ROI) generation from macrophages and polymorphonuclear leucocytes, which provokes inflammation, resulting in tissue fibrosis.⁹ Bleomycin or peplomycin induces cytokines such as interleukin- 1β and TGF- β , which activate macrophages and polymorphonuclear leucocytes to produce ROI and stimulate dermal fibroblasts to generate collagen, respectively.⁹ In addition, cutaneous collagenolytic activity is decreased in animal models treated with bleomycin.¹⁰ Moreover, bleomycin is concentrated in the lung and skin in several species because of the very low activity of the bleomycin-inactivating enzyme, bleomycin hydrolase, in these tissues, which clearly explains the organ-specific adverse effects of bleomycin or peplomycin.¹¹

In summary, we report the first case of peplomycin-induced scleroderma. Considering the widespread use of bleomycin or peplomycin, it is possible that this type of bleomycin or peplomycin complication may occur more frequently than recognized. Therefore, the history of exposure to chemicals or drugs should be investigated in patients with scleroderma.

Department of Dermatology,
Faculty of Medicine, University of
Tokyo,
Tokyo, Japan

Correspondence: Hironobu Ihn.
E-mail: IN-DER@h.u-tokyo.ac.jp

Y. ASANO
H. IHN
J. SHIKADA
T. KADONO
K. KIKUCHI
K. TAMAKI

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Digital infarcts showing microangiopathy in adult dermatomyositis suggest severe pulmonary involvement and poor prognosis

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SIR, Adult dermatomyositis (DM) is often associated with malignancy and interstitial lung disease (ILD).¹ It is estimated that ILD occurs in 5–40% of DM patients.¹ Patients with a subgroup of ILD, called rapid progressive ILD, have a rapidly progressive clinical course and are mostly unresponsive to corticosteroid therapy.¹ Cutaneous signs predicting severe pulmonary involvement and poor prognosis are lacking. We report three cases of DM with rapid progressive ILD. All patients had multiple digital infarcts with histopathological evidence of pauci-inflammatory microangiopathy in the early course of their illness.

Patient 1 was a 36-year-old female who presented in December 1999 with a 2-month history of arthralgia and rash on the face and hands. Examination revealed erythematous papules on the dorsa of the interphalangeal joints, erythema with swelling over bilateral periorbital areas and symmetrical proximal muscle weakness. Electromyography (EMG) showed a myopathic pattern. Muscle biopsy revealed muscle atrophy. Muscle enzymes were normal except for lactate dehydrogenase (LDH) which was elevated (570 U L⁻¹; normal 230–460). A skin biopsy taken from a finger papule showed microangiopathy with fibrinoid deposition in the dermal vessels. The chest X-ray (CXR) disclosed bilateral interstitial infiltrations and decreased lung volume. Pulmonary function tests (PFT) showed a moderate restrictive ventilatory defect with total lung capacity (TLC) of 3.68 L (83.5% of predicted), vital capacity (VC) 1.66 L (52.7%), forced expiratory volume in 1 s

(FEV₁) 1.7 L (60.6%), forced vital capacity (FVC) 1.89 L (60%), FEV₁/FVC 89.7%. A diagnosis of DM with ILD was made. Digital infarcts with multiple skin ulcers and progressive dyspnoea occurred in the following months. Adult respiratory distress syndrome (ARDS) developed despite vigorous corticosteroid therapy. High-resolution computed tomography (HRCT) showed massive bilateral diffuse infiltration while an open lung biopsy revealed diffuse alveolar damage. She died of ARDS in September 2000.

Patient 2 was a 47-year-old male with a history of chronic hepatitis C who presented with several weeks' history of dyspnoea, dry cough, skin rash and symmetrical muscle weakness in August 2001. Examinations revealed erythema on the central area of the face and forehead, periungual telangiectasia, digital infarcts with ulcers (Fig. 1). EMG showed a myopathic pattern. Serum aspartate aminotransferase (AST) 177 IU L⁻¹ (normal 5–31), alanine aminotransferase (ALT) 142 IU L⁻¹ (normal 0–41), creatine kinase (CK) 1010 IU L⁻¹ (normal 10–190), LDH 680 IU L⁻¹ and positive anti-Jo-1 antibody (35 EU mL⁻¹, normal <25) were found. Antinuclear antibody (ANA) was detected at 1 : 640 dilution on human epithelial (Hep-2) cells with a finely speckled pattern. A skin biopsy taken from a digital infarct revealed an obliterative microangiopathy with fibrinoid deposition, red



Figure 1. Digital infarcts with shallow ulcers in patient 2.

blood cell extravasation and pauci-inflammatory cell infiltration (Fig. 2). HRCT revealed a honey-combed appearance of the lung. PFT showed a severe restrictive ventilatory defect with TLC 3.29 L (56.6%), VC 1.57 L (37.84%), FEV₁ 1.64 L (46.71%), FVC 1.69 L (40.73%), FEV₁/FVC 97.04%. The carbon monoxide diffusing capacity (D_LCO) was reduced by 55%. DM with ILD was diagnosed and he was treated with pulsed methylprednisolone and cyclophosphamide, but he died of ARDS 1½ months after admission. Autopsy revealed intravascular fibrin thrombi deposition in the pulmonary capillaries, venules and large vessels.

Patient 3 was a 50-year-old female who presented with a 6-month history of skin rashes and symmetrical muscle weakness in June 2001. Examinations showed erythema on bilateral periorbital areas, erythematous papules on the interphalangeal joints, digital infarcts with shallow ulcers. EMG showed a myopathic pattern. Laboratory tests showed AST 76 IU L⁻¹, ALT 67 IU L⁻¹, LDH 605 IU L⁻¹, a normal CK and negative lupus anticoagulant. Dyspnoea occurred 1 month later. CXR showed a bilateral interstitial pattern and HRCT revealed interstitial fibrosis with ground glass appearance. She was diagnosed as having DM with ILD. Despite aggressive high-dose corticosteroid therapy she died of ARDS 1 month after the onset of dyspnoea.

Cutaneous manifestations have been reported to predict the presence of ILD or malignancy in DM patients. Feldman *et al.* suggested cutaneous vasculitis as a marker of an underlying malignancy.² Hunger *et al.* also proposed that leucocytoclastic vasculitis was associated with malignancy in DM.³ Atypical skin lesions such as mechanic's hand and cuticular hyperplasia were seen more often in DM patients with ILD.⁴ It has been reported that DM patients with recurrent ulcers and vasculitis had a poor prognosis.⁵ We observe that digital infarcts showing microangiopathy but not vasculitis are associated with severe lung involvement and a poor prognosis.

Microvascular injury is a well known mechanism of skeletal muscle lesions in DM.⁶ In conventional histopathology, DM cutaneous lesions are indistinguishable from

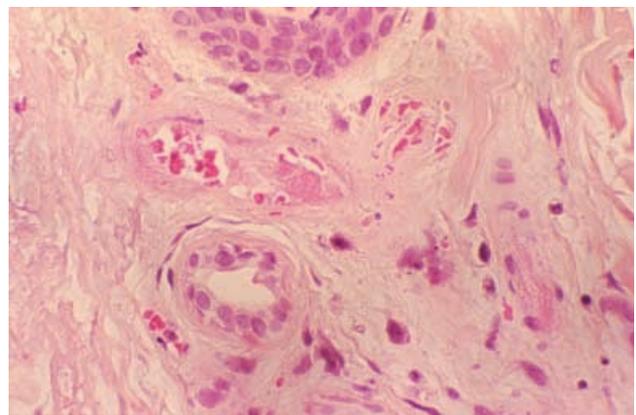


Figure 2. Pathological examinations revealed obliterative microangiopathy with fibrin deposition, red blood cell extravasation and pauci-inflammatory cell infiltrates (haematoxylin and eosin; original magnification ×400).

systemic lupus erythematosus and have no remarkable vascular change. But recent studies have provided evidence of microvascular injury in the pathogenesis of cutaneous lesions of DM by showing some degree of endothelial injury, ectasia, vascular fibrin and complement complex deposition.⁷ Digital infarctions represent severe cutaneous microvascular injuries and a high disease activity. A similar mechanism may involve the lung and cause severe pulmonary damage.

Rapid progressive ILD associated with DM usually is unresponsive to corticosteroid therapy and progresses to respiratory failure quickly.¹ Fever, arthralgia, a low serum CK or LDH level, and a higher serum AST level were reported to be associated with this ILD subgroup in DM patients.^{8,9} The prognosis is very poor unless aggressive immunosuppressive agents such as cyclophosphamide is started early enough to prevent irreversible pulmonary damage.¹⁰ Digital infarcts with microangiopathy might serve as a useful indicator for early intervention that might improve the outcome of DM patients with ILD.

Departments of Dermatology,
*Internal Medicine and †Pathology,
National Taiwan University Hospital,
and National Taiwan University
College of Medicine, 7 Chung-Shan
South Road, Taipei 100, Taiwan
Correspondence: Chia-Yu Chu, MD.
E-mail: chiayuju@seed.net.tw

J-W. TJIU
S-J. LIN
L-F. WANG
J-Y. SHIH*
C-J. YU*
C-W. LIANG†
C-Y. CHU

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Nodular prurigo responding to topical tacrolimus

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SIR, Nodular prurigo is characterized by the development of chronic, pruritic skin nodules. The aetiology is not fully understood and the disorder is typically resistant to treatment.

We report a case of an 83-year-old woman who responded to topical tacrolimus 0.1% and has remained in remission. She initially presented 10 years ago with widespread, pea-sized, brownish nodules principally affecting the extensor surfaces of her arms, legs and lower back (Fig. 1). Extensive investigations on two occasions, including recently, were noncontributory. A biopsy showed the classical signs of nodular prurigo; direct and indirect immunofluorescence were negative. Previous treatments that had failed included topical steroids twice daily, phototherapy, oral azathioprine and oral ciclosporin. Topical tacrolimus 0.1% was applied to a lesion on one arm. After 1 week the patient reported marked alleviation of her symptoms so topical tacrolimus was applied to all involved areas with good effect. One month later there was continued improvement in both her symptoms and

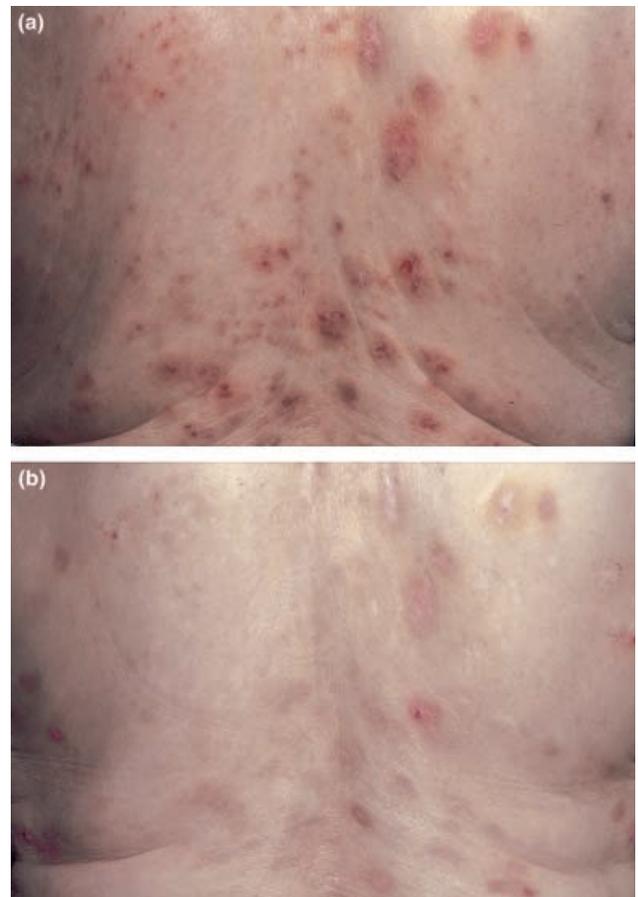


Figure 1. Nodular prurigo (a) before and (b) 1 month after administration of topical tacrolimus 0.1%.