Colchicine myoneuropathy and renal dysfunction*

Sir: Colchicine has been used in the treatment of gout and other diseases for over 200 years. Unusually high dosing regimens have resulted in multiorgan toxicity affecting the haemopoietic, renal, nervous, dermatological, and musculoskeletal systems. 1 2 Recently, a myoneuropathy has been noted in elderly patients taking low doses of colchicine over months to years. 3 All patients had underlying chronic renal insufficiency, which is considered an important component of the syndrome. We report the development of colchicine myoneuropathy in a woman with a transient prerenal illness.

A 75 year old woman presented with a three week history of progressive proximal muscle weakness. The onset of her symptoms followed a 10 day diarrhoeal illness that spontaneously resolved. Her medical history included longstanding hypertension, degenerative joint disease, and calcium pyrophosphate deposition disease, for which she had been treated with oral colchicine, 0·6 mg twice daily, over the preceding 16 months. Other drugs included a thiazide diuretic taken three times daily. Physical examination showed an elderly woman weighing 61·4 kg who appeared well. Motor testing disclosed weakness of the shoulder and pelvic girdle muscles with normal distal strength, and results of a neurological examination were normal. Laboratory studies showed a creatine kinase of 646 IU/l (normal range 0–170 IU/l), and a Westergren sedimentation rate of 10 mm/hr. Blood urea was 13·2 mmol/l and serum creatinine 132·6 mmol/l. Renal function studies six months earlier had been within normal limits: blood urea 6·4 mmol/l and serum creatinine 106·1 mmol/l. Electrocardiography showed myopathic changes characterised by resting membrane instability, positive sharp waves, fibrillations, and decreased amplitude and duration of potentials in proximal muscles. Nerve conduction studies were consistent with a mild polyneuropathy of the legs. A muscle biopsy showed vacuolation of 30% of myofibres without necrosis, inflammatory infiltrates, atrophy, or inclusion bodies (figure). Treatment with colchicine and diuretic was discontinued. Ten days later her motor strength had returned to normal and the serum creatine kinase was 5 IU/l. Blood urea was 6·1 mmol/l and serum creatinine 114·9 mmol/l.

In the nervous system colchicine interferes with neutrotubule assembly causing a disruption of axonal transport. 4 This probably accounts for the mild polyneuropathy seen in affected patients; however, the mechanism of injury in muscle, is less clear. In rat skeletal muscle an accumulation of ‘large sarcoplasmic membranous bodies’—with presumed autophagic activity—appears two to three days after the intraperitoneal injection of colchicine and is coincident with clinical weakness. 5 In the arterial smooth muscle cells of rats colchicine causes structural and functional changes, including the increased appearance of autophagic vacuoles and lysosomes. 6 In humans electron microscopy of proximal skeletal muscle from patients with colchicine myopathy shows abnormal accumulation of lysosomes and autophagic vacuoles. 7 An anatomical linkage between lysosomes and microtubules has been demonstrated in cultured fibroblast studies. 8 It seems likely that colchicine disrupts the microtubular-lysosomal network that directs the movement and function of intracellular organelles including lysosomes and autophagic vacuoles. Ironically, however, microtubules have not been clearly shown in human adult skeletal muscle. Whether colchicine exerts its myotoxic effects through intracellular microtubular disruption or by a yet undisclosed mechanism remains to be shown.

This case of colchicine myoneuropathy was thought to arise in a patient with normal renal function who had transient prerenal azotaemia resulting from diuretic abuse superimposed on a diarrhoeal illness. A more careful analysis of her renal function by the Cockcroft-Gault equation, 9 however, showed an underlying creatinine clearance of only 46 ml/min, which decreased to 16 ml/min during her prerenal state. It is unclear whether a transient decrease in the renal clearance of colchicine precipitated the development of symptomatic colchicine toxicity. It does suggest, however, that the risk of colchicine myoneuropathy may extend beyond the patient with obvious renal insufficiency to include any elderly patient with normal or near normal serum creatinine concentrations who may be prone to episodes of decreased renal perfusion. Because of partial dependence on hepatic metabolism, underlying liver disease may also predispose to colchicine toxicity. 10 Given the increasing application of oral colchicine in a variety of rheumatic and non-rheumatic diseases, increased awareness of its potential toxicities—even in the presence of a ‘normal’ serum creatinine—should not be overlooked.

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*The opinions contained herein are those of the authors and do not necessarily reflect the views of the Department of the Army, Department of Defense, or the United States Government.


Colchicine myopathy. Note the vacuoles and absence of inflammation. (Haematoxylin and cosin.)
Sir: Although about eight reports of patients with polyarteritis nodosa associated with interstitial pneumonia have been published,1-7 interstitial pneumonia has not been considered to be a complication of polyarteritis nodosa. Of the eight cases with this association, only two cases have been recorded in English publications.7 Thus we present one case of polyarteritis nodosa associated with acute interstitial pneumonia.

A 71 year old man was admitted to the hospital on 2 October 1990. He had complained of fatigue, weight loss, fever, and cough for two months before admission. His temperature was 39°C and oedema of the legs was noted. Abnormal laboratory data included a white blood cell count of 14.5 x 10^9/l (normal range 4-8 x 10^9/l) with neutrophilia, haemoglobin concentration 103 g/l (140-180 g/l), erythrocyte sedimentation rate 31 mm/h (1-7 mm/h), C reactive protein +5, and serum complemet (CH50) 18.8 U/ml (30-40 U/ml). Both rheumatoid factor and antinuclear antibody were positive. Hepatitis B surface antigen and antibodies were negative. Cryoglobulins were negative. A chest radiograph was normal. The patient was clinically diagnosed as possible polyarteritis nodosa and was treated with corticosteroids (prednisolone 60 mg/day). Two months later both rheumatoid factor and antinuclear antibody were negative, and CH50 had returned to normal.

On 4 January 1991 he complained of dyspnoea. Arterial blood gas analysis at room air showed a partial pressure of oxygen (Pao2) of 32 mmHg, partial pressure of carbon dioxide (Paco2) 32.7 mmHg, bicarbonate 23.4 mmol/l, and pH 7.5. The chest radiograph showed a diffuse reticular pattern in both lungs (fig 1). Although he was treated with a large dose of corticosteroids (1 g of prednisolone a day for six days) based on the clinical diagnosis of acute interstitial pneumonia, he died of respiratory failure on 15 January 1991.

Necropsy confirmed polyarteritis nodosa affecting multiple organs, including the lung, oesophagus, stomach, intestine, liver, spleen, kidney, pancreas, and testis. In the lung the bronchial and pulmonary arteries were affected. Most marked were the changes in the stomach. The arteries along the greater and lesser curvatures of the stomach contained numerous nodules, often arranged in chains like a string of pearls. Moreover, many nodules produced protuberances of the gastric mucosa so that the inner surface of the stomach appeared nodular. Histologically, the affected arteries represented the scar stage of necrotising arteritis according to our classification.8 Collapse of the alveolar sacs and dilatation of the alveolar ducts could be seen in all lobes of both lungs (fig 2). Hyaline membrane formation, fibroblast proliferation, and chronic inflammatory cell infiltrate were present in the alveolar septae. Moreover, cuboidalisation of the alveolar lining cells and thickened pulmonary arteries were noted. These findings correspond to acute interstitial pneumonia.9 There was no correlation between interstitial pneumonia and arteritis. Although interstitial pneumonia associated with collagen vascular diseases has been described, it was believed that polyarteritis nodosa is not complicated with interstitial pneumonia. Recently, Carratala and coworkers presented two cases of polyarteritis nodosa associated with interstitial pneumonia, and suggested that reports of new cases were needed to determine whether or not this association is real.7

Our case represents classic polyarteritis nodosa, indicated by nodule formation, with histological evidence of arteritis of polyarteritis nodosa type. Nodules were originally described, hence the term polyarteritis nodosa, but these nodules are frequently seen today, either clinically or pathologically. In the present case the arteritis represented the scar stage.8 On the other hand, the interstitial pneumonia corresponded to the acute stage.9 Thus we think that interstitial pneumonia overlapped the pre-existing polyarteritis nodosa in this case.

A nationwide research team was organised under the auspices of the Ministry of Health and Welfare of Japan in 1973 to investigate polyarteritis nodosa. The research team analysed 56 patients with polyarteritis nodosa, of whom 10 (18%) clinically had interstitial pneumonia.10 Moreover, our own experience of three patients with polyarteritis nodosa (the present one and two previously reported) showed that two had interstitial pneumonia. These findings indicate that polyarteritis nodosa associated with interstitial pneumonia is apparently more common than has previously been recognised. Thus during treatment of polyarteritis nodosa it may be necessary to treat overlapping interstitial pneumonia.

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Figure 1 Chest radiograph showing a diffuse reticular pattern in both lungs.

Figure 2 Acute interstitial pneumonia. Note collapse of the alveolar sacs and dilatation of the alveolar ducts. (Elastic van Gieson stain.)
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