Acute neuromyopathy after colchicine treatment

Sir: Colchicine is an effective drug to treat and prevent gout and is the best treatment for patients with concomitant conditions to non-steroidal anti-inflammatory drugs. Acute side effects are nausea and diarrhoea, which disappear upon dose reduction or discontinuation of the drug. Severe toxic effects, affecting mainly the nervous system, the liver, and bone marrow, may be caused either by one single toxic dose or by customary doses taken for years in patients with mild renal insufficiency. The development of colchicine induced neuromyopathy in a patient after one or two weeks of regular use of colchicine was unexpected. We are not aware of a similar reported case history.

A 64-year-old had progressive muscular weakness. Within two to three weeks he could not walk without support and noticed a numbness in fingers and toes. Nausea and vomiting appeared a few days before admission. Four years S S, a renal transplantation had been performed because of end stage renal failure due to chronic glomerulonephritis. Treatment consisted of prednisolone 10 mg on alternate days and cyclosporin A 3 mg/kg. Renal function was stable with a creatinine clearance of 40–50 ml/min. Four weeks before admission he experienced urate-crystal arthritis and received colchicine initially 0.5 mg orally thrice daily, after 12 days 0.5 mg twice daily. The drug was tapered off as creatinine was 115 mmol/l (normal <64 mmol/l).

A biopsy of the quadriceps muscle showed an increased variation in fibre diameter, scattered necrotic fibres, and only a single fibre with a cytoplasmic vacuole. In the acid phosphatase reaction strong focal activity was seen in subsarcolemmal regions of many fibres. Electron microscopy showed vacuoles with membranous debris (figs 1 and 2). A diagnosis of colchicine neuromyopathy was made and the drug was discontinued. The patient regained normal strength within three to four weeks. The creatine kinase level normalised within two weeks. Renal function and the hepatic enzymes returned to pre-admission values. The electromyogram, six months after discontinuation of colchicine, showed sporadically polyphasic potentials. Nerve motor conduction velocities in the arms had normalised. Although faster, the motor conduction velocity was still abnormal in the peroneal nerves. Sensory conduction velocity of the median nerve remained unchanged. Both the myopathy and neuropathy showed improvement, but recovery was still not complete at that time.

The findings strongly point to colchicine as the cause of this patient's neuromyopathy. The toxic effect was gradual and rapid improvement after its discontinuation form additional evidence. The toxic effects of colchicine have been extensively studied in animal models, in which it causes an ascending paralysis, mainly of the hind limbs. Markand was the first to describe the ultrastructural changes of colchicine in the skeletal muscle of rats. Similar abnormalities were described in a patient with colchicine abuse for several years. Subsequently, Kuncl showed that myopathy often occurs in patients with mild renal impairment after the use of regular doses of colchicine for several years. The mechanism of acute colchicine neuromyopathy is unknown. The myopathy is suspected to be an altered autophagic process, and the accompanying neuropathy is likely to be caused by defective axonal transport resulting from impaired microtubule assembly. Our patient had histopathological changes similar to those described by Kuncl: a lysosomal vacuolar myopathy without evidence of inflammation. Although we cannot exclude the possibility that the presence of mild uraemia or long term use of steroids and cyclosporin A might have facilitated the onset of the neuromyopathy, these factors are probably of minor significance. Renal function was stable at a creatinine clearance of 45 ml/min during the preceding year, and only temporally decreased, probably owing to dehydration caused by vomiting. Moreover, the creatine kinase is usually normal when there is muscle weakness caused by uraemia.

The muscle biopsy specimen also lacked selective type 2 fibre atrophy, which can be seen in uraemic myopathy. A steroid myopathy was unlikely in view of the low alternate day regimen. Cyclosporin A treatment puts patients at risk for secondary gout by raising serum uric acid concentrations. Other cyclosporin side effects are usually related to toxic levels and include encephalopathy, tremor, and, uncommonly, a neuropathy based upon demyelination. This case shows that in patients with diminished renal function severe colchicine neuromyopathy may occur within a few weeks of treatment despite the use of conventional dosage. Therefore, doses should be as low as possible, and patients with diminished renal function should be checked frequently to detect toxic effects at an early stage.

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Figures 1 and 2 Electron micrographs of a muscle biopsy specimen of the quadriceps muscle showing vacuoles with membranous debris.
Reactive arthritis and group G streptococcal pharyngitis

Sir: A previously healthy 29-year-old man presented to his general practitioner with a week long history of fever, sore throat, and polyarthralgia. A throat swab was taken and treatment was started with ampicillin 250 mg and ibuprofen 600 mg, both four times daily. He was seen two days later with more profound malaise, and a synovitic left wrist, and was referred to us. There was no history of rash, dysuria, bowel disturbance, or eye symptoms. He had a stable heterosexual relationship. On examination his temperature was 39°C, with generalised tender cervical lymphadenopathy and an inflamed throat. There was synovitis in the left wrist and restricted movement. Neck movement was globally restricted, with evidence of capsulitis of the right shoulder and supraspinatus tendinitis in the left. The results of the rest of the examination were entirely normal.

The throat swab (taken by the general practitioner before starting treatment with antibiotics) showed a heavy growth of Lancefield group G streptococci. A left wrist aspirate showed no organisms on Gram staining, and no subsequent growth even after enrichment culture. Five sets of blood cultures were sterile. Antistreptolysin O titre was >1000 international units (IU) per millilitre (normal <200). White cell count was 17·5 x 10⁹/l (neutrophils 14·9), haemoglobin 143 g/l, platelets 327 x 10⁹/l, erythrocyte sedimentation rate 75 mm/h, C reactive protein 375 mg/l (normal <100), normal biochemistry except for alkaline phosphatase 412 IU/l (normal 80–280), γ-glutamyltransferase 82 IU/l (normal 10–40), ferritin 839 μg/l (normal 10–385). Rheumatoid factor, antinuclear antibodies, and antineutrophil cytoplasmic antibodies were negative. The following were normal or negative: left wrist and chest radiographs; urine analysis and mid-stream urine culture; electrocardiogram; echocardiogram; viral antibody screen; hepatitis B serology; versinia, brucella, and borrelia antibodies. HLA class I typing was A1 B8 B15.

He was admitted to hospital. Treatment was continued with ampicillin and indomethacin 50 mg three times daily. Over the next 10 days he experienced prolonged morning stiffness and a swinging fever. The neck pain and capsulitis of the right shoulder rapidly settled. There was sequential painful involvement of the left wrist, both supraspinatus tendons, left then right hip, right wrist, and bilateral adductor enthesitis, with each episode lasting 24–72 hours. The erythrocyte sedimentation rate peaked at 128 mm/h four days after admission, and the platelets at 859 x 10⁹/l nine days later, returning gradually to normal thereafter. The C reactive protein slowly fell to normal. Indomethacin was discontinued when a mild hepatic picture developed on the liver function tests, and prednisolone 40 mg daily was introduced. Thereafter, no new joint or enthopathic symptoms developed, and results of liver function tests were normal. He was discharged 16 days after admission. Within two months all inflammation had subsided with a full return to normal function of all joints. The prednisolone has been tapered rapidly, and the patient has returned to full time employment.

Group G streptococci have been associated with previous reports of septic arthritis, but the low virulence confines most serious disease to patients with a predisposition to infection. There are case reports of sterile reactive arthritis in septicemic patients. In this patient there was no evidence of septicema, joint aspiration of the wrist showed no growth, and he had been previously well. His subsequent arthritis and enthesitis was flitting and short lasting, which is much more characteristic of reactive and rheumatic fever arthritis than of multifocal sepsis, though the distribution of joint and enthesis involvement was unusual. Furthermore, bacteraemia rarely complicates pharyngitis. Host antibody responses are poor in streptococcal group G pharyngitis, so that until now cases of poststreptococcal sequelae have been described in group G pharyngitis. As far as we are aware this represents the first reported case of reactive arthropathy complicating such an infection in the absence of septicema. It appears therefore that group G streptococcal infection may be yet another cause of reactive arthritis and enthesitis.

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