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BRIEF REPORT

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Colchicine myoneuropathy in a renal transplant patient

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Abstract Colchicine is widely employed for the treatment of gout in renal transplant patients where NSAIDs are contra-indicated and allopurinol prophylaxis is often avoided due to concomitant azathioprine immunosuppression. We report here a case of colchicine-induced myoneuropathy in a renal transplant recipient. Our patient had myalgia, muscle weakness, elevated creatine kinase levels, myopathic changes on electromyography and peripheral neuropathy. Withdrawal of colchicine resulted in recovery within 4 weeks. Renal transplant recipients are likely to be at greater risk of colchicine-induced myoneuropathy due to the unique concurrence of risk factors predisposing to toxicity in such patients. These risk factors include the high incidence of gout in this population, widespread use of colchicine as first-line therapy, impaired renal function and concomitant cyclosporin treatment. The diagnosis should be considered in any renal transplant recipient receiving the drug who develops myopathy. Prompt withdrawal of colchicine therapy should result in rapid clinical and biochemical improvement.

Keywords Colchicine · Myoneuropathy · Renal transplant

Introduction

Hyperuricaemia and gout are common in renal transplant recipients as a consequence of impairment of renal function and cyclosporin therapy [11]. Treatment can prove problematic as non-steroidal anti-inflammatory drugs are potentially nephrotoxic and, for those on azathioprine, allopurinol is contraindicated. A majority of such patients are therefore treated with colchicine. Apart from the common gastrointestinal side effects, the drug is generally well tolerated.

Colchicine myoneuropathy was first reported by Kontos in 1962 [6] and may be much more common than previously believed [7]. Renal dysfunction appears to be a risk factor for development of the condition [9, 18] as the drug is partially renally excreted. The resulting higher plasma levels of the drug are associated with increased toxicity. Concomitant use of cyclosporin and colchicine have led to some debate as to which agent is causative [13].

Patients with colchicine myoneuropathy typically present with painless proximal muscle weakness and a sensory motor neuropathy of axonal type [8]. Myalgia has been noted rarely [16]. Here we describe a renal transplant recipient presenting with myalgia, muscle weakness and a peripheral neuropathy due to colchicine.

Case report

A 72-year-old Afro-Caribbean gentleman first presented with end stage renal failure secondary to hypertensive nephrosclerosis in 1984. After 8 years of dialysis he underwent successful cadaveric renal transplantation. Post-operatively, he was maintained on triple immunosuppression with cyclosporin, azathioprine and steroids. In the early post-transplant phase, he experienced an episode of presumptive acute graft rejection which was successfully treated with pulsed intravenous methylprednisolone. Subsequently, he enjoyed

excellent graft function with a baseline serum creatine of around 90 μmol/l.

In July 1997, he developed gout and commenced colchicine 500 μg, which he took initially on an occasional basis, as required. By June 1998 he was taking a regular dose of 500 μg twice daily. The following month, his azathioprine treatment was stopped following a period of leucopenia. At this time his serum creatinine was 102 μmol/l, with a cyclosporin trough level of 103 μg/l on a dose of 75mg b d s. His other drug therapy included prednisolone, 7.5mg daily; amlodipine, 5mg daily; atenolol, 100mg daily; doxazosin, 2mg daily; and codydramol, (paracetamol 500 mg + dihydrocodeine 10mg) two tablets t d s.

One week later, he presented with a 3-day history of generalised weakness, lethargy, and muscular pains in the distal upper limbs and thighs. He described difficulty rising from a chair and diminished grip strength. Neurological examination revealed a mild global weakness (Medical Research Council scale 4/5) with neither specific proximal nor distal distribution. Deep tendon reflexes were absent. Resting muscle tone was normal, and there was no apparent sensory deficit. Plantar responses were flexor and the remainder of his examination was unremarkable. The patient was admitted for further investigation.

Blood tests showed stable graft function with a serum creatinine of 102 μmol/l. A full blood count showed a mild leucopenia with a white cell count of 3.0×109/l. Haemoglobin and platelet count were normal. A full electrolyte profile including calcium and magnesium was within normal limits. C-reactive protein measurement was within normal limits, and the erythrocyte sedimentation rate was just 22mm/h. Thyroid function was found to be normal. An auto-antibody screen including rheumatoid factor and anti-nuclear antibody testing were negative. Septic screen was also negative.

Of note, the muscle enzymes were raised with a creatine kinase (CK) level of 640 iu/l (normal range 0–200), aspartate transaminase (AST) of 170 iu/l (normal < 35), and lactate dehydrogenase (LDH) of 1102 iu/l (normal range 120–500), suggestive of a myositis or rhabdomyolysis. There was no history of cardiac chest pain, and both the CK-MB fraction and a 12-lead electrocardiogram were normal. Cyclosporin level remained within the therapeutic range at 134 μ/l.

Subsequently, the patient complained of muscle tenderness, with a myalgia spreading to affect the muscles of the shoulder girdle and distal upper limbs, bilaterally. This was associated with a progressive rise in CK level which peaked at 766 iu/l by day 3 and persisted above 500 iu/l for the next 4 weeks.

A tentative diagnosis of an acute demyelinating polyneuropathy, possibly Guillain-Barre syndrome was made. However, examination of the cerebrospinal fluid showed only marginally elevated protein content of 0.48g/l (normal range < 0.40g/l), and no other abnormality. Nevertheless, intravenous human immunoglobulin therapy was started on an empirical basis on day 10 of his admission, and continued for 5 days. Vital capacities were monitored throughout, but remained normal.

Electromyography was subsequently performed, it showed florid myopathic changes with short duration, highly polyphasic motor unit activity patterns, (MUAP) most marked proximally. Nerve conduction studies were also abnormal, with reduced compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) responses in both upper and lower limbs, consistent with a mixed sensory motor axonal polyneuropathy. This unusual combination of findings raised the spectre of a drug-induced myoneuropathy, and consequently colchicine treatment was stopped.

Within a week of discontinuation of the drug, the weakness and myalgia substantially improved, and by three weeks the patient was pain-free and able to stand and walk unaided. This marked clinical improvement was accompanied by a rapid biochemical normalisation, with the CK falling to normal within two weeks. The patient was discharged home well, having spent just under a month in hospital.

Discussion

Colchicine exerts its anti-inflammatory action by binding tubulin, a subunit protein of microtubules, preventing their polymerisation [10]. This results in decreased leucocyte motility and impaired phagocytosis. Colchicine myopathy may be the result of this effect on the microtubular system causing derangement of the cytoskeleton.

Concomitant cyclosporin therapy seems to increase the risk of colchicine toxicity. Gruberg et al. [2], in 1999, suggested that this might be due to inhibition of the multi-drug resistance (MDR) transport protein, membrane P glycoprotein (P-gp). P-gp is a transmembrane protein which acts as a transport pump for a wide variety of chemotherapeutic drugs. It protects cells from cytotoxicity by lowering intra-cellular drug concentrations, thereby conferring resistance to these agents. Cyclosporin is known to block P-gp [17], and this may have consequences for the metabolism of colchicine – an MDR substrate. Elimination of colchicine is mainly by the liver, while about 20% is renally excreted. In animal studies, cyclosporin has been shown to profoundly inhibit renal clearance of colchicine and its secretion into the bile, presumably by inhibiting the MDR transporter [14, 15]. This in turn might lead to increased cytotoxicity even at therapeutic doses. By comparison, muscle disorders associated with tacrolimus appear to be less frequent with only isolated reports in the literature [3]. It is thought to be a less potent inhibitor of the MDR transporter [4], and this may reduce the likelihood of potentiating colchicine toxicity.

With regard to diagnosis, muscle biopsy is useful and may help differentiate colchicine myopathy from polymyositis, with which it is often confused. The characteristic histological appearance is of a vacuolar myopathy due to the presence of lysosomes and autophagic vacuoles [7, 12]. Necrotic fibres are rarely present, and inflammatory findings (as one would expect in polymyositis) are absent.

Electrodiagnostic studies may also demonstrate distinctive features [8]. Myopathic motor unit potentials and early recruitment are seen in proximal limb and truncal muscles, frequently with fibrillations, positive sharp waves, or complex repetitive discharges. This is accompanied by a mild axonal neuropathy characterized by reduced amplitude of motor and sensory responses but normal or borderline-slow conduction velocities.

There are few other causes of a sub-acute myopathy associated with axonal neuropathy. Uraemia is one possibility, but our patient enjoyed good graft function, and in any case, elevation of CK would be an unusual finding. Toxins such as ethanol, vincristine, amiodarone and chloroquine can also produce this clinical picture [9], but none of these applied in our patient. What clinches

the diagnosis is the rapid clinical and biochemical improvement following withdrawal of colchicine treatment. Our patient was typical in this respect – the majority of patients recover within 4 weeks of discontinuation of the drug [5, 7, 12].

The incidence of colchicine-induced myoneuropathy is unknown, but it appears to be a rare adverse effect in the general population. Renal transplant recipients, however, are likely to be at significantly greater risk, due to the unique concurrence of risk factors predisposing to toxicity in such patients. These risk factors include the high incidence of gout in this population, widespread use of colchicine as first-line therapy, the presence of impaired renal function and concomitant cyclosporin treatment [1]. All those involved in the care of such patients should therefore be alert to this condition. The diagnosis should be considered in any renal transplant recipient receiving the drug who develops myopathy. Prompt withdrawal of colchicine therapy should result in rapid clinical and biochemical improvement.

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