Vasculitis in Klinefelter’s syndrome

Sir: Necrotising vasculitis may be local or systemic, secondary to infections, drugs, or associated with other collagen vascular diseases, but it is often idiopathic. As far as we know, vasculitis has not yet been described in association with Klinefelter’s syndrome.

Our patient was a 20 year old man admitted to Cook County Hospital with a history of sore throat, fever, cough, and increasing shortness of breath. Two weeks before admission he had been treated for a streptococcal sore throat. Despite treatment with amoxicillin and clavulanic acid his condition deteriorated, with nausea, vomiting, loose bowel movements, oral ulcers, and increasing shortness of breath, and he was referred to Cook County Hospital.

Apart from pneumonia four months before this illness he was healthy. He denied the use of tobacco, alcohol, or illicit drugs, and had none of the known risk factors for AIDS. He looked ill, dehydrated, and tachypnoeic with moderately severe respiratory distress. Blood pressure was 100/60 mmHg; pulse 108/min; respiratory rate 36/min and temperature 40°C. He had a right subcostal and left lower lobe area of increased breath sounds. The right lower lobe fields were not clear.

In the hospital the following treatment was given. After cultures of urine, blood, and sputum had been obtained, the patient was treated initially with intravenous ampicillin and sulbactam. His condition deteriorated and he required intubation on the second hospital day. In the intensive care unit treatment was started with nafcillin, prednisolone, imiphenoterm, isoniazid, and rifampicin, without improvement. On the third hospital day methylprednisolone 60 mg intravenously every 4 hours was started. A single plaque of a skin lesion showed bullae with lymphocytic infiltration around and within the vesicle wall and confirmed a clinical suspicion of vasculitis, which was strengthened as all cultures were negative.

Acute and convalescent titres for influenza A and B, parainfluenza 1 and 2, coxsackievirus B1-6, adenovirus, respiratory syncytial virus, cytomegalovirus, and Epstein-Barr virus did not point to a viral cause for his illness. The patient improved with steroids, and a month after discharge the renal functions, and liver enzymes had returned to normal and the chest radiograph had cleared.

Hormone studies showed lutinising hormone 51.8 μg/ml (basal 3-30) and follicle stimulating hormone 56.9 μg/ml (basal 2-25). Prolactin was 1.19 mmol/l (normal 0.1-0.92) and testosterone 11.1 mmol/l (normal 10-34). Thyroid functions were normal. A chromosome analysis confirmed a karyotype of 47XXY.

Our patient had a systemic vasculitis with a mild neutropenia and thrombocytopenia. A number of other systems, such as the lungs, kidney, and, probably, liver, were affected in addition to the skin. An exhaustive search failed to show an infection. The vasculitic skin lesions, the poor response to broad spectrum antibiotic coverage, and the dramatic response to steroids point to a systemic vasculitis. Gynaecomastia, small firm testes, and increased gonadotrophins fit the description of the syndrome first described by Klinefelter with positive chromatin and a 47XXY karyotype. Since Ortiz-Neu and LeRoy described three cases of Klinefelter’s syndrome associated with lupus there has been a number of similar cases as well as others associated with rheumatoid arthritis and scleroderma, but none, as far as we know, recording the association of vasculitis and Klinefelter’s syndrome. Porphyria and lupus affect women more often than men, as is true also of other collagen vascular diseases. Reports of the triad of cutaneous hepatic porphyria, lupus, and Klinefelter’s syndrome, together with reports of exacerbations during pregnancy, have prompted many to believe that the female hormones probably play a part in evolution of the disease. Indeed, in murine studies female mice are better humoral responders, and this difference has been reported with a variety of antigens. Reports of lupus and other collagen vascular disease in Klinefelter’s syndrome suggest that lowered testosterone levels, oestrogen, or the X chromosome may play a part in autoimmunity or the body’s immune response. Increased levels of autoantigens, the androgen factor, antinuclear antibodies as well as antibodies to thyroid, testes, and cerebral tissue have been reported in Klinefelter’s syndrome.1,11 Raised levels of thyroid antibodies in patients with an XO Turner’s syndrome12 and in a patient with Turner’s syndrome and juvenile rheumatoid arthritis14 give credence to the hypothesis that the X chromosome may play a part in the modulation of the immune response. In our patient we were unable to detect antinuclear antibodies, antineutrophilic cytoplasmic antibodies, or a rheumatoid factor.

The patient did have neutropenia and thrombocytopenia as opposed to a lupus-like syndrome more commonly described with vasculitis.15 The neutropenia coupled with thrombocytopenia though suggests that autoantibodies might have been directed against these cell lines.

Figure 1 Multiple necrotic lesions over the lower trunk.

Figure 2 Small atrophic testes and penis. Chromosome analysis of 47XXY confirmed the diagnosis of Klinefelter’s syndrome.
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 reactions to non-steroidal anti-inflammatory drugs. Side effects are nausea and diarrhoea, which disappear upon dose reduction or discontinuation of the drug. Severe toxic effects, affecting mainly the gastro-intestinal tract, 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 46-year-old man 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 earlier 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.

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).

Electron microscopy showed complex repetitive discharges and brief polyphasic potentials of low amplitude in the proximal arm and leg muscles, characteristic of myopathy. The recruitment pattern was limited. Furthermore, signs of reinnervation without active denervation were seen in the distal muscles. Motor conduction velocities of the median and peroneal nerves were only slightly reduced. Sensory conduction velocity of the median nerve was normal. A sensory nerve action potential could not be elicited in the sural nerves. These findings were ascribed to a predominantly axonal polyneuropathy.

A diagnosis of chronic 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.

The mechanism of acute colchicine neuromyopathy is unknown. The myopathy is suspected to be an altered axonal 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 temporarily 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.

We thank Dr T W van Weerden and J H van der Hoeven of the department of nephrology, who performed the electromyography.

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3 Wallace S L, Omokodu B, Ertel N H Colchicine plasma levels: implication as to pharmacology.

Figures 1 and 2  Electron micrographs of a muscle biopsy specimen of the quadriceps muscle showing vacuoles with membranous debris.
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doi: 10.1136/ard.51.11.1266

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