Vasculitis in Klinefelter’s syndrome

Sirs: 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 clavulinate 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 mm Hg; pulse 108/min; respiratory rate 36/min, and temperature 40°C. He had a right subconjunctival haemorrhage, multiple ulcers on the soft palate and posterior pharynx, with dry crusted lesions periorally. He had bilateral gynaecomastia. Multiple necrotic papules were noted over the lower abdomen, but the extremities were spared (fig 1). Lymph nodes were not palpable; the thyroid was normal. There was dullness to percussion over the right lung base with scattered rales bilaterally. Other than a tachycardia, the heart was normal. Mild tenderness without rebound or guarding was detected over the right upper quadrant of the abdomen.

The tests were small and atrophic (fig 2).

The hernial orifices were clear. There was no neurological deficit.

Laboratory findings were as follows: haemoglobin 116 g/l, white cell count 3·7×109/l with a normal differential, platelets 93×109/l, urea 15·4 mmol/l, creatinine 256 mmol/l, glucose 6·8 mmol/l, sodium 129 mmol/l, potassium 4·4 mmol/l, chloride 99 mmol/l, CO2 16·4 mmol/l. Total protein was 37 g/l, albumin 23 g/l, alkaline phosphatase 34 U/l. Cholesterol was 5·4 mmol/l, total bilirubin 6·8 mmol/l, aspartate transaminase 723 IU/l, lactate dehydrogenase, gen 16981 IU/l. Hepatitis serology was negative. Liver showed proteinuria 3+ with 5–6 red blood cells/high powered field. A haematology screen, including antinuclear antibodies, rheumatoid factor, SSA, SSB, cryoglobulins, antineutrophilic cytoplasmic antibodies, was negative. C3 was 1·67 g/l (normal 0·85–1·23) and C4 320 mg/l (normal 120–360). Arterial blood gases showed pH 7·52, Po2 60 mm Hg, Pco2 22 mm Hg, bicarbonate 18 mmol/l, saturation of 95% on room air. On 2 litres of O2 the pH was 7·36, Po2 108 mm Hg, Pco2 28 mm Hg, bicarbonate 28 mmol/l, saturation of 98%. Chest radiography showed densities in the right upper, right middle, and both sides of the lungs.

In the hospital the following treatment was given. After cultures of urine, blood, and sputum had been taken, 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 high flow oxygen, inotropes, ioxonide, and rifampicin, without improvement. On the third hospital day methyprednisolone 60 mg intravenously every eight hours was started, and a patch of skin lesion showed bullae with lymphocytic infiltration and around and within the vessel 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 arb. unit (basal 3–30) and follicle stimulating hormone 56·9 arb. unit (basal 10·4–34·6). Thyroid functions were normal. A chromosome analysis confirmed a karyotype of 47.XXY.

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 testis, and increased gonadotrophins fit the description of the syndrome first described by Klinefelter with positive chromatin and a 47.XXY karyotype. Since Ortiz-Neu and LeRoy described three cases of Klinefelter’s syndrome associated with lupus there has been a number of similar cases with 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 also true 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 diseases 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 autoantibodies, rheumatoid factor, antineuritcal antibodies as well as antibodies to thyroid, testes, and cerebral tissue have been reported in Klinefelter’s syndrome. Raised levels of thyroid antibodies in patients with an XO Turner’s syndrome and in a patient with Turner’s syndrome and juvenile rheumatoid arthritis gave 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, antineutrophic cytoplasmic antibodies, or a rheumatoid factor. Our patient did have neutropenia and thrombocytopenia as opposed to a lupus like syndrome, which is more commonly described with vasculitis. The neutropenia coupled with thrombocytopenia though suggests that autoantibodies might have been directed against these cell lines.

Correspondence to: Dr W Sequeira, Cook County Hospital, 1385 W Harrison Street, Chicago, IL 60612-9985, USA.

13. Williams E D, Engle E, Forbes A P. Thyroiditis
Acute neuromyopathy after colchicine treatment

Sir: Colchicine is an effective drug to treat and prevent gout and is the best treatment for patients with contraindications 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 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.1,2 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 66-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. Four years after transplantation, a gradual decline of renal function was noted with impaired creatinine clearance (15·5 ml/min, normal 3·3–6·7) and creatinine 175 μmol/l (before admission 140 μmol/l, normal 62–106). The sodium and potassium were normal. Uric acid concentration was 0·64 mmol/l (normal <0·45), creatine kinase 634 U/l (normal <50), aspartate aminotransferase 312 U/l (normal <30), alanine aminotransferase 276 U/l (normal <30), and lactate dehydrogenase 835 U/l (normal <235). The thyroid stimulating hormone was normal. The cyclosporin concentration was within the therapeutic range (125 μmol/l). The colchicine concentration was 13 μg/l (toxic >5 μg/l). Myoglobinuria was present.

Electromyography 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 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 of colchicine is generally accepted, but the mechanism is not known. Our patient had had colchicine treatment for chronic urate crystal arthritis, and an acute exacerbation of gout occurred during hospitalisation. In the light of our patient’s case we believe that colchicine should not be used during attacks of gout. Colchicine was shown to be effective in prophylaxis of gout attacks by means of long-term prophylactic treatment. However, in our view, long-term prophylactic treatment is contraindicated with the use of colchicine in gout.

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

JOUKE VAN DER NAALT
HANNY HAAXMA-REICHE
Department of Neurology
University Hospital Groningen
The Netherlands

ARIE P VAN DEN BERG
Department of Clinical Immunology
University Hospital Groningen
The Netherlands

BOUKE P C HAazenBERG
Department of Rheumatology
University Hospital Groningen
The Netherlands

WILHELMINA M MOLENAR
Department of Pathology
University Hospital Groningen
The Netherlands

Correspondence to: Dr J van der Naal, University Hospital, Department of Neurology, PO Box 30 001, 9700 RM Groningen, The Netherlands.

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