Lesson of the Week

Apparent haematuria: an early sign in polymyositis

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Myoglobin, the protein containing haem, is released from striated muscle in conditions causing rhabdomyolysis. The myoglobinuria which may follow may be recognisable as dark urine and causes a positive reaction on reagent strip testing for blood. We report three cases in which this phenomenon featured prominently in the presentation of dermatomyositis, a subset of polymyositis with characteristic skin lesions.

Case 1

Three months before admission a 20 year old man noticed reddening of his knuckles followed a month later by difficulty in climbing stairs. He attended his general practitioner a month afterwards when he thought he was passing blood in his urine. Reagent strip testing gave a positive result. He remained under observation until he developed generalised aches and pains, headache, malaise, and progressive symmetrical limb weakness four weeks later, when viral illness was diagnosed. Mild dysphagia and a rash ensued, leading to his admission.

Examination showed erythematous plaques on knuckles, elbows, and knees and a diffuse erythematous rash on his face and trunk. Muscle tenderness was present but not wasting. Proximal muscles were weaker than distal. Peak expiratory flow rate was 550 l/min. Urine testing with Multistix yielded 4+ blood and 2+ protein. Microscopy of fresh urine showed 3+ granular casts but no erythrocytes; culturing showed no pathogens. Myoglobin, however, was detected. Plasma urea and electrolyte values were normal. Antinuclear factor was present at a titre of 1/1280 but DNA binding was normal. Taken together with the classical clinical picture, a serum creatine phosphokinase activity of 38 680 IU/l (normal <200) was considered to confirm the diagnosis of dermatomyositis.

Chemotherapy consisted of prednisolone 120 mg/day plus azathioprine 150 mg/day, boosted by three days of intravenous methylprednisolone 1 g/day and a further three days of intravenous cyclophosphamide 150 mg daily when his cough weakened considerably and his peak expiratory flow rate dropped to 200 l/min with pronounced fatigability. Improvement was marginal but enough to avert the need for assisted ventilation. Five months after admission and despite prednisolone 90 mg plus azathioprine 150 mg daily he was still having difficulty going up and down stairs and sitting up unaided. His serum creatine phosphokinase activity was 525 IU/l.

Case 2

A 55 year old man presented with a history of maculopapular rash for four months; pain, stiffness, and swelling of knees and shoulders for two months; myalgia and weakness for one month; and dark brown, frothy urine for three weeks. There was periorbital oedema, periungual erythema, and an erythematous rash on the trunk and upper arms, which were wasted. Muscle power was graded 3/5 proximally and 4/5 distally in the arms and 2/5 proximally and 3/5 distally in the legs. He could barely lift his head or sit

Apparent haematuria in a flu-like illness may be the first sign of polymyositis in the subclinical stage and lead to earlier diagnosis and treatment

up. Multistix urine analysis yielded 3+ blood and 3+ protein. Urine microscopy showed only the occasional erythrocyte and cast. Antinuclear factor titre was 1/2560 with normal DNA binding. Serum creatine phosphokinase activity was 23 290 IU/l. The clinical diagnosis of dermatomyositis was supported by open muscle biopsy. The patient received prednisolone 80 mg plus azathioprine 100 mg daily and was discharged 10 weeks later with a serum creatine phosphokinase activity of 309 IU/l. He returned to work as an itinerant preacher shortly afterwards. Improvement was maintained 12 months later with prednisolone 15 mg plus azathioprine 100 mg daily.

Case 3

A 32 year old garage proprietor complained of dizziness, lethargy, sore throat, generalised aches, low back pain, and tiredness for one week. Two days before admission his urine turned brownish red and he was therefore referred. Examination showed patchy erythema on face, arms, and trunk and livedo reticularis on the thighs. Though he felt weak, testing of his considerable muscle bulk disclosed normal power in the legs and reduction only to 4/5 in the upper proximal muscles. Multistix analysis yielded 3+ blood and 2+ protein. No cells or casts were seen and no growth was obtained from a urine specimen. Myoglobinuria, however, was confirmed by spectroscopy. Serum creatine phosphokinase activity was 187 250 IU/l. Dermatomyositis was deemed the likeliest diagnosis, though a subsequent open deltoid muscle biopsy sample was normal. Antinuclear factor and antibody to extractable nuclear antigens were not detectable. After one week of prednisolone 80 mg plus azathioprine 150 mg daily the rash and weakness disappeared and he was discharged a few days later with a serum creatine phosphokinase activity of 31 000 IU/l. Two months later he had remained well at work and his creatine phosphokinase activity was normal, allowing gradual withdrawal of treatment.

Discussion

It is generally accepted that corticosteroids with or without steroid sparing immunosuppressants are the mainstay of treatment of polymyositis and dermatomyositis.^{1,2} In high doses they induce remission, but it is usually necessary to continue for at least two years with a suitable maintenance dose to suppress activity of the disease. It is uncertain whether the speed of remission influences the duration of maintenance treatment. The earlier treatment is begun, however, the better is the outcome in terms of mortality, morbidity, and residual disability.^{1,8} Functional recovery is important irrespective of age. Even if there is associated malignancy the quality of life may be enhanced.

Chronicity is recognisable largely in retrospect, implying late diagnosis in some cases. Once the disease becomes chronic or "burnt out" treatment is unlikely to improve the muscle atrophy,

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contractures, and resultant disability.^{1,2} A median interval of 4.9 months was calculated from the onset of symptoms of polymyositis to diagnosis, with 22% of diagnoses taking longer than one year.⁴ The corresponding figure was 25% in another study,⁸ with a mean interval of 13 months from first manifestation of the disease to diagnosis.

Diagnosis is based on clinical findings and serum creatine phosphokinase activity, supported by either electromyography or muscle biopsy. Only a few patients have all the criteria.² Muscle strength may be normal in some cases⁶ but, conversely, objective testing may disclose weakness when the patient had not complained of it.² Cutaneous signs may be subtle, transient, or absent. Serum enzyme activity is the most reliable diagnostic test, creatine phosphokinase activity being raised in virtually all cases of acute and subacute myositis.¹ There is no correlation between enzyme activity and grade of disability or weakness at presentation,² so that apparent haematuria may be the first obvious manifestation of rhabdomyolysis. It was this sign that brought our first patient to his doctor and led to the third patient's prompt referral, diagnosis, and treatment. Though doctors may be expected to respond by testing the urine with a reagent strip and collecting a midstream urine specimen for culture, the potential relevance of "stix haematuria" against a background of a flu-like illness, non-specific generalised aches, or weakness may not be appreciated immediately. It should be remembered that both haemoglobin and myoglobin cause a positive reaction. Conceivably some patients might be treated inappropriately with antibiotics or be investigated from an erroneous

approach, causing undue delay. We can only guess at how many patients pass through the phase of "haematuria" into the oblivion of chronicity.

In conclusion, we suspect that apparent haematuria as a reported symptom and on strip testing may be more common than realised and therefore an important sign of polymyositis. It seems reasonable to assume that it is most apparent when rhabdomyolysis is most active, though the muscle damage may be subclinical. We suggest, however, that this may be the optimum time to begin treatment.

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For Debate . . .

Causes of venous ulceration: a new hypothesis

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Abstract

Previous hypotheses about the causes of venous ulceration are inconsistent with recently published data. In patients with chronic venous insufficiency the number of functioning capillary loops visible in the skin on microscopy fell after the legs had been dependent for 30 minutes. Another study had shown that leucocytes became trapped in the circulation in dependent legs. A new hypothesis linking these two findings proposes that the trapped white cells occlude the capillaries and result in ischaemia of the skin of the leg.

Introduction

Venous ulceration is a major unsolved problem: over half a million patients currently receive treatment for it in the United Kingdom.^{1,2} Treatment is unsatisfactory, only bed rest and compression being effective. The association between venous ulcers and underlying damage to the deep veins is well established.³ The damage results in a persistently raised pressure in both the deep and superficial veins of the leg.⁴ The mechanism by which venous ulceration is caused is less clear. Several hypotheses have been advanced, the most recent being the pericapillary fibrin cuff hypothesis.⁵ The cuff is seen in the skin of patients with chronic venous insufficiency, and Browse and Burnand propose that it prevents diffusion of gases and results in tissue hypoxia, which causes ulceration. No one has shown, however, that the fibrin cuff presents a true barrier to diffusion.

Using capillary fluorescence microscopy, Bollinger *et al* found that in patients with chronic venous insufficiency there were areas of skin with no apparent flow of blood.⁶ The flow was restored when the patients wore compression stockings. Bollinger *et al* suggested that some of the capillaries were not functioning because of thrombosis.

In rats white cells become trapped in the capillaries in response to slowing of the circulation, which causes increased peripheral vascular resistance owing to capillary occlusion.⁷ White cells trapped in this way release proteolytic enzymes and superoxide radicals that cause endothelial damage.⁸ We have shown that white

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