during pregnancy. A slight stress incontinence had remained after an operation for vaginal prolapse in 1967. Renal function was normal, and the intravenous urogram showed only slight pyelonephritic changes. Urinary cultures were negative. Because blood pressure control with 50 mg chlorthalidone and 300 mg metoprolol daily was insufficient prazosin was added in a dose increasing in four weeks from 1.5 to 6 mg daily. On a dose of 3 mg she developed orthostatic complaints, and she collapsed once. After four weeks she complained of complete incontinence of urine, which started one to two hours after taking prazosin. One day after prazosin withdrawal the incontinence had disappeared.

Urodynamic investigations were then performed before and during treatment with prazosin. Urethral closure pressure profiles were obtained by the catheter-withdrawal technique⁴ with an empty bladder in supine position, and with a full bladder (400 ml) supine and standing. These profiles give a measure for the maximum urethral closure pressure (maximum urethral pressure minus bladder pressure) and the functional urethral length (distance where urethral pressure exceeds bladder pressure). To exclude urinary incontinence caused by "unstable bladder" a cystometro-gram with pressure/flow analysis was also performed.

In the three investigations before taking prazosin the maximum closure pressure and the functional urethral length were low-normal (see figure).

Urethral pressure profiles before (upper panel) and during (lower panel) treatment with prazosin (12 mg daily).

The cystometrogram was normal. During micturition the maximum flow rate was 38 ml/sec (normal value for women 30 ml/sec). There was a detrusor contraction to 12 mm Hg without abdominal strain during micturition. After one week of prazosin (12 mg daily) the maximum closure pressure had decreased to abnormally low values. The height of the proximal part of the pressure profile had diminished, resulting in a substantial decrease of the functional urethral length (see figure). Again, the cystometrogram was normal but the maximum flow rate was now higher (47 ml/sec), while the detrusor contraction had slightly decreased (8 mm Hg). One day after prazosin withdrawal results identical with those before treatment were obtained.

Comment

The urinary incontinence in this patient was probably caused by prazosin. Withdrawal of the drug led to immediate disappearance of the symptoms on two occasions, while reinstitution was followed by complete incontinence. The results of the urodynamic study suggest that this side effect is caused by α -adrenergic receptor blockade. The urethral pressure is determined by the tonus of the smooth muscles of the proximal, presphincteric part of the urethra that are innervated by sympathetic nerves. Administration of phentolamine, a known α -adrenergic receptor blocker, decreases the maximal urethral closure pressure and the functional urethral length. The latter decrease is caused by a pressure fall in the proximal urethra to the level of the bladder pressure.⁴ Identical changes were observed in our patient during treatment with prazosin. Although normal people show differences in profiles with empty and full bladder, we found more impressive changes with full bladder. This might be related to the pre-existing stress incontinence in our patient. This minor dysfunction could have also caused the exaggerated reaction to prazosin. Several authors mention urinary frequency and sometimes incontinence as a side effect of prazosin.⁵ In our own group three out of 30 patients treated with prazosin developed urinary incontinence. One of them had already been operated on for this problem. Apart from the reported postural hypotension and the first dose phenomenon we

found another clinical argument for the hypothesis that prazosin has α -sympathicolytic activity and is not a pure smooth-muscle relaxant.

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Cytomegalovirus and vasculitis

Cytomegalovirus (CMV) infection in adults causes several clinical syndromes. We report a patient with CMV infection who developed vasculitis and believe that this is the first recorded association.

Case history

A 57-year-old woman with longstanding, well-controlled diabetes was admitted to St Martin's Hospital in May 1976 for stabilisation of her disease after three weeks of ill health with an upper respiratory tract infection and itchy rash on both legs. She had had rheumatic fever in childhood. On admission her temperature was 38°C and her throat inflamed. There was one subungual splinter haemorrhage and a macular rash on both legs. Pulse was 92/min, regular; blood pressure was 120/60 mm Hg; and an ejection systolic murmur was audible at the left sternal edge. The jugular venous pressure was not raised but her ankles were oedematous. Scattered crepitations were audible in both lungs. Liver and spleen were palpable. A provisional diagnosis of bacterial endocarditis was made.

Investigations showed (normal ranges in parentheses): haemoglobin (Hb) 10.5 g/dl; white cell count $3.7 \times 10^9/l$ (39% lymphocytes, some atypical); plasma viscosity 1.85 centipoise (1.5-1.72 centipoise); Paul-Bunnell negative; urea 12.4 mmol/l (75 mg/100 ml) (2.5-6.6 mmol/l (15-40 mg/100 ml)); glucose 16.7 mmol/l (301 mg/100 ml) (3.3-5.6 mmol/l (59-101 mg/100 ml)); alkaline phosphatase 400 IU/l (21-92 IU/l); aspartate aminotransferase (SGOT) 78 IU/l (13-42 IU/l); γ -glutamyltranspeptidase 476 IU/l (<40 IU/l). Chest x-ray film and electrocardiogram were normal. Urine was sterile on culture. *Staphylococcus albus* contaminated two of six blood cultures. ASO titre was normal. Hepatitis B antigen was negative. Blood was sent for determination of viral antibodies.

Her insulin dosage was increased, and over the next 10 days two more splinter haemorrhages appeared. Her fever settled, her condition improved without antibiotics, and she was discharged. The results of viral studies available after discharge showed a diagnostic rise in CMV titre from 1/16 to 1/256 between 21 and 27 May 1976 (complement fixation tests: plate microtitre using killed CMV in human fibroblasts from Public Health Laboratory, Colindale). The titres to other viruses were insignificant.

One month later she was readmitted because of increasing fatigue and bouts of sweating. She was febrile, in congestive cardiac failure, and had several new splinter haemorrhages, while the systolic murmur persisted and her liver was tender and enlarged. Investigations showed: Hb 8.7 g/dl, white cells $9.8 \times 10^9/l$, viscosity 2.16 centipoise, urea 17.5 mmol/l (105 mg/100 ml), glucose 24.1 mmol/l (434 mg/100 ml), and SGOT 66 IU/l. A chest x-ray film now showed cardiac enlargement and shadowing in the right lower lobe. Fourteen blood cultures were sterile. Routine autoantibody screen was negative. After admission she developed aching pains in the arms with exquisite tenderness on palpation. Muscle biopsy was performed and prednisone 60 mg daily started for her presumed myositis, but the serum creatinine phosphokinase concentration was normal and histological examination of a biopsy specimen showed a subacute or chronic non-occlusive vasculitis (see figure). The muscle pains and fever abated within two days of starting steroids, and five days later the heart murmur had disappeared. Chest x-ray showed decrease in cardiac size, but her diabetic control had deteriorated. She developed sensory loss and weakness in the right leg and became confused and agitated. Steroids were reduced but fever returned and the

Photomicrograph of muscle biopsy specimen ($\times 133$) showing an arteriole with dense perivascular infiltrate (haematoxylin and eosin stain).

heart murmur reappeared, to disappear again on increasing the steroid dose. On discharge one month later she was well. Haematological and biochemical values were normal and all clinical signs had disappeared. Subsequent review was satisfactory, although a sensory deficit persists in the right leg. Steroids have been stopped.

Comment

Our patient, a known diabetic, developed an illness resembling bacterial endocarditis, but had sterile blood cultures and evidence of active CMV infection. She developed a corticosteroid-responsive vasculitis. Antibiotics were not given at any stage.

Cytomegalovirus infection commonly presents as an infectious-mononucleosis-like illness in which the result of the Paul-Bunnell test is negative,^{1 2} while liver function tests are often abnormal. A fourfold rise in antibody titre is considered diagnostic of active infection.³ The dramatic steroid response in the absence of antibiotics is evidence against bacterial infection in our patient. Moreover, diabetic vascular disease shows no appreciable response to steroids.⁴

Cytomegalovirus infection should be excluded in patients with vasculitis or with suspected bacterial endocarditis and negative blood cultures.

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Acute marrow folate deficiency during intensive care

Reports of the rapid onset of megaloblastic bone-marrow failure in critically ill patients are increasing.¹⁻³ Fatal complications may result, but the cause of the syndrome remains uncertain.^{2 3} It has been

ascribed to folate deficiency, though unequivocal laboratory proof of this is lacking,¹⁻³ and other factors have been thought to be contributory.^{2 3}

The present report suggests that an acute folate deficiency limited to bone-marrow tissue could explain the haematological findings in these patients.

Case report

A man aged 69 was admitted to hospital on 7 July 1977 with a leaking aortic aneurysm. He had had no abdominal surgery. Before admission he had been taking quinine, digoxin, glyceryl trinitrate, and cyclandelate. He had been on a normal diet and drank only occasionally.

At laparotomy on 7 July a large aortic aneurysm was found and a Cooley bifurcation graft inserted. Nineteen units of blood was transfused. By 9 July he had developed pneumonia and was in renal failure. His left leg became gangrenous, and on the 11th it was amputated. He died four days later. During the 10 days in hospital he received diazepam, penicillin, cloxacillin, gentamicin, frusemide, digoxin, lignocaine, chlorpromazine, a cephalosporin, Parentrovite injections (nicotinamide 160 mg, pyridoxine 50 mg, riboflavin 4 mg, thiamine 250 mg, ascorbic acid 500 mg), and vitamin C. Energy intake was maintained with 5% dextrose; he took no food by mouth. Ethanol was not given. No vitamin B₁₂ or folic acid was given as megaloblastic changes were noted only a few hours before death.

Laboratory investigations—The initial blood picture was normal. Two days before death thrombocytopenia ($80 \times 10^9/l$ ($80\,000/mm^3$)) developed. On 15 July bone-marrow biopsy showed gross megaloblastic and dyserythropoietic changes: serum vitamin B₁₂ was 265 ng/l; serum folate 7.8 $\mu g/l$; and red-cell folate 630 $\mu g/l$. Folate concentrations in serum, red cells, and liver were measured using *Lactobacillus casei* as the assay organism. Hepatic folate 14 hours after death was 3.9 $\mu g/g$, giving a total hepatic folate value of 7.8 mg. Eighteen hours before death a deoxyuridine suppression test on bone-marrow cells was performed with the use of ¹²⁵I-deoxyuridine⁴ (see table). This showed folate deficiency, and no inhibition of DNA synthesis was detected. Thus folate deficiency was restricted to bone-marrow cells, while serum, red-cell, and hepatic folate concentrations were normal.

Deoxyuridine (dU) suppression studies on bone-marrow cells from present patient (study A) and normal donor (study B) incubated with patient's serum alone or serum from patient and normal donor. Figures are percentages*

Study A					
Source of bone-marrow cells	Source of serum	dU alone	dU + folic acid (50 μg)	dU + vitamin B ₁₂ (1 μg)	dU + vitamin B ₁₂ (1 μg) + folic acid (50 μg)
Present patient	Present patient	46.0	8.0	47.5	8.0
Study B					
Source of bone-marrow cells	Source of serum	dU alone	dU + folic acid (1 μg)	dU + folic acid (10 μg)	dU + folic acid (50 μg)
Normal donor	Normal donor	6.5	6.0	6.0	8.5
	Present patient	5.0	6.5	5.0	4.0

*The radioactivity of ¹²⁵I-labelled DNA in the bone-marrow sample incubated without added "cold" deoxyuridine is 100% value. Percentages represent degree of suppression of incorporation of ¹²⁵I into DNA by preincubation with cold deoxyuridine with or without added vitamin B₁₂ (1 $\mu g/ml$) and folic acid (50 $\mu g/ml$).

Comment

Our patient received no folic acid by mouth during eight days in intensive care. For most of the time he was infected and intermittently bleeding with both tissue haemorrhage and arterial thromboses. Thus intense demands were made on all three marrow-cell lines—namely, granulocytes, red cells, and platelets—leading to greatly increased folate utilisation by marrow tissue, and eventually to folate deficiency. Our evidence suggested, however, that folate deficiency was limited to marrow tissue and that the major folate storage organ, the liver, maintained a normal folate content and concentration. Demand for folate by the bone marrow was probably so great that liver folate stores could not be mobilised quickly enough to prevent depletion of marrow folate stores. We do not know how rapidly folate can be mobilised from the liver when an acute demand for folate develops, but ethanol may block the release of folate from tissue stores, notably the liver.⁵ Our patient did not receive ethanol, but other drugs or the metabolic changes that occur in renal failure might have impaired release of folate from hepatic stores.