Case report

Disseminated intravascular coagulation, antiphospholipid antibodies, and ischaemic necrosis of extremities

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Summary A middle aged woman presented with acute, severe, intravascular coagulation leading to ischaemic necrosis of the extremities. Pulmonary involvement required artificial ventilation, and there was evidence of hepatic, pancreatic, and renal damage, which resolved without complication. These events may have been triggered by the ingestion of compound diuretic tablets. The finding of the ‘lupus anticoagulant’ and anticardiolipin antibodies, together with high titre antinuclear factor in the serum, and antibodies to extractable nuclear antigen (RNP), and a past history of spontaneous abortion, suggest that this was a dramatic manifestation of an immune connective tissue disorder.

Key words: gangrene, drug induced.

Case history

A previously healthy 52 year old white woman was admitted as an emergency. She had been lethargic for three months and had recently noted pain and swelling in her hands. Three weeks before admission she had taken one combination diuretic tablet (triamterene 50 mg and hydrochlorothiazide 25 mg), after which she became unwell with weakness, nausea, and vomiting for 24 hours. On the day before admission she again took the diuretic tablet and 12 hours later developed rigors, nausea, vomiting, diarrhoea, and shortness of breath. She complained of severe pains in the arms and legs. On admission she was confused and pyrexial (38.5°C) with a tachycardia of 140/minute. Her blood pressure was unrecordable and there was marked cyanosis of the nose, hands, and feet (Fig. 1).

Her past medical history had been unremarkable apart from the miscarriage of a twin conception 17 years earlier. At no time had there been evidence of arthropathy, Raynaud’s phenomenon, or facial erythema.

Investigations

Laboratory investigations on admission were as follows: haemoglobin 12.9 g/dl (129 g/l); white blood cell count 17×10⁹/l; platelets initially 200×10⁹/l falling to 80×10⁹/l after one week; blood glucose 6.3 mmol/l; plasma sodium 134 mmol/l; potassium 5.1 mmol/l; chloride 99 mmol/l; bicarbonate 99 mmol/l; urea 15.7 mmol/l; creatinine 282 µmol/l. Arterial blood gas analysis showed pH 7.56, Po₂ 9.2 kPa, Pco₂ 2.5 kPa. Serum total protein was 54 g/l, albumin 32 g/l, calcium 2.10 mmol/l, phosphate 1.4 mmol/l, bilirubin 8 µmol/l, alkaline phosphatase 68 IU/l (normal <92 IU/l), aspartate transaminase (AST) 197 IU/l (normal <37 IU/l). Clotting studies showed a prothrombin time of 32 seconds (control 13 seconds), kaolin-cephalin time 72 seconds (normal <40 seconds), thrombin time 38 seconds (normal <40 seconds). The level of fibrin degradation products was 320 µg/l of serum rising to over 500 µg/l; fibrinogen 0.7 g/l (normal 2–4 g/l). Low
titre cold agglutinins were initially detected. Cryoglobulins were not present. Serum complement levels were low: C3 0.68 g/l (normal range 0.75–1.5 g/l), C4 0.15 g/l (normal range 0.14–0.42 g/l).

COURSE AND MANAGEMENT

A provisional diagnosis of disseminated intravascular coagulation secondary to presumed septicaemia was made. She was treated with intravenous plasma protein fraction, blood transfusions, intravenous hydrocortisone (100 mg, intravenously, eight hourly), 35% oxygen, and intravenous antibiotics (ampicillin 2 g and flucloxacillin 2 g, six hourly; metronidazole 400 mg, eight hourly). Atrial fibrillation supervened requiring intravenous digoxin. Later that day intravenous heparin, 15 000 IU/24 hours, was added. An initial central venous pressure of -10 cm was improved to +4 cm. Basal lung crepitations developed and the chest x ray showed diffuse alveolar shadowing.

Twelve hours after admission her blood pressure had risen to 110/80 mmHg, with a pulse rate of 140/minute, sinus rhythm. Her confusion improved and she now responded to questions. There was no abdominal pain or tenderness, but bowel sounds were absent and small bowel fluid levels were visible on plain x ray. Peripheral pulses were all easily palpable and the Pco₂ had risen to 13.8 kPa; the cyanosis of the extremities had, however, become more pronounced. Urine output was satisfactory at 50–100 ml/h.

The following morning she complained of worsening pains in the hands and feet. She was febrile, 38°C, the respiratory rate had risen to 50/minute, and the blood pressure had fallen to 80 mmHg systolic with a pulse of 130/minute and central venous pressure +1 cm. Chest x ray again showed alveolar shadowing and blood gas analysis had deteriorated (pH 7.35; Pco₂ 6.6 kPa; Pco₂ 4.2 kPa). There was tenderness in the epigastrium; serum amylase was 510 IU/l. She was transferred to the intensive care unit (Dr D W Ryan) for intermittent positive pressure ventilation. Abdominal ultrasound showed no evidence of hepatic or intra-abdominal abscess. Bowel ischaemia seemed likely.

No evidence of bacterial infection was found on initial blood and urine cultures or high vaginal swab. Subsequently the results of tests for hepatitis B, mycoplasma, legionella, and virus titres were negative. The antibiotics were changed to intravenous metronidazole 400 mg and erythromycin 1 g, eight hourly. Intravenous dextran 40 and glyceryl trinitrate were given in addition to heparin to try to improve the peripheral circulation. The distal hands, feet, and nose now appeared frankly gangrenous.

The serum AST level rose to a maximum of 900 IU/l on the second day. Her fever resolved and artificial ventilation was discontinued five days after admission; bowel sounds returned the next day. The serum amylase continued to rise to a maximum of 2543 IU/l on the seventh day. The serum albumin had fallen to 26 g/l and marked oedema of the lower limbs and sacrum developed. The chest x ray and renal function rapidly returned to normal.

Antibiotics were discontinued after 12 days. Treatment was simplified to oral prednisolone 60 mg daily, potassium supplements, and buprenorphine for pain in the limbs. There was by now well...

Fig. 1 Appearance of hands on second day after admission.
demarcated ischaemic necrosis of the distal hands, feet, and nose (Figs 2 and 3). During the ensuing two months she underwent a series of plastic surgical procedures to treat the ischaemic limbs (Mr M J M Black). Serial amputations of the left fingers and thumb, distal amputation of both feet, amputation of the right fingers and thumb, and skin grafting to the left hand were carried out. Three months after admission she was able to walk with the help of two physiotherapists and all operation sites were healing well. The nose healed without surgical intervention. She was now being treated with oral prednisolone 35 mg daily, and azathioprine 100 mg daily was added. Four months after the onset of the illness painful peripheral paraesthesiae developed, and nerve conduction studies confirmed motor and sensory peripheral neuropathy. A course of cyclophosphamide 150 mg daily was commenced instead of azathioprine. Six weeks later she developed troublesome urinary frequency. This was attributed to the cyclophosphamide, which was therefore stopped and replaced by azathioprine 150 mg daily. During the following 12 months this immunosuppressive treatment was gradually reduced to a maintenance dose of prednisolone 5 mg and azathioprine 25 mg orally daily. Her general health was now excellent and there had been a gradual improvement in the paraesthesiae. Full blood count, platelets, erythrocyte sedimentation rate, liver function tests, blood urea, electrolytes, and serum amylase have remained consistently normal.

**IMMUNOLOGICAL TESTS**

After recovery from the initial illness serum immunoglobulins were normal (IgM 1.7 g/l; IgG 9.7 g/l; IgA 1.0 g/l). Serum complement estimation showed a normal C3 (1.02 g/l), reduced C4 (0.13 g/l), and low CH50 (1200 units/ml, normal 1260–2880 units/ml). IgG antinuclear factor was present at a titre of 1/1280; antibodies to extractable nuclear antigens (anti-RNP) were found in a titre of 1/4. The DNA binding was consistently negative. Both IgM and IgG anticardiolipin antibodies were detected in high titre.

A forearm skin biopsy one month after admission showed generalised dermal atrophy with mild perivascular lymphocytic infiltrates. Direct immunofluorescence showed granular C3 and IgM deposition in dermal capillaries and small arterioles, consistent with small vessel vasculitis. No IgM, IgG, or C3 deposits were demonstrable at the dermo-epidermal junction; thus the ‘lupus band’ typically found in established systemic lupus erythematosus (SLE) was not present. Sixteen months after the presenting illness both IgM and IgG anticardiolipin binding assays had become negative; antinuclear factor remained positive, titre 1/40; serum levels of C3 and C4 were now within the normal range.
Discussion

This patient became acutely and severely ill a short time after the ingestion of a compound diuretic tablet. During the early stages of this illness she was seen by several physicians and surgeons, none of whom had seen a similar presentation previously. She was thought to have an overwhelming septicaemia, or septic shock syndrome, or an acute drug induced vasculitis. The treatment given was therefore empirical and non-specific. The ‘lupus anticoagulant’ or antiparacardiolipin antibody tests were not locally available at that time and the positive result became known only after she had recovered. In retrospect the history of abortion, the precipitation of illness by drugs, the vascular occlusion, and the immunological findings suggest that this may have been a further example of the protean presentations of antiphospholipid antibodies.

Although antiphospholipid antibodies (‘lupus anticoagulant’, antiparacardiolipin antibodies, false positive Venereal Disease Research Laboratory (VDRL) test) have been most frequently associated with venous occlusions,3-5 arterial thrombosis has also been reported with increasing frequency. Occlusion of large cerebral vessels resulting in stroke is not uncommon in SLE.6,7 and involvement of other arteries such as mesenteric,8 retinal,9 and coronary10 has also been recorded. Large vessel arterial involvement with gangrene of the extremities has recently been described.11,12 Although most of the patients reported were diagnosed as having SLE according to the American Rheumatism Association criteria,13 it is now clear that many do not conform to these criteria.14 Such patients have been described as having ‘lupus-like’ disease, ‘variant lupus’, or simply ‘autoimmune disorders’ or ‘the antiphospholipid syndrome’. Presenting features include venous or arterial occlusions, fetal loss,15 thrombocytopenia, false positive VDRL test, and less frequently pulmonary hypertension16 and chorea.17 It seems possible that the fetal loss incurred by our patient 17 years earlier may also have been related to the presence of antiparacardiolipin antibodies.

The association of antiphospholipid antibodies with drug therapy has also been recorded. Much et al in 1980 described eight patients with psychiatric illness treated with phenothiazines, who demonstrated the ‘lupus anticoagulant’, and thrombotic events (thrombophlebitis, pulmonary embolus, cerebral thrombosis) occurred in three of these.18

Hydralazine had been administered in two others and procainamide in one. All of these compounds have been associated with the development of a drug induced ‘lupus syndrome’. The development of symptoms in our patient on two occasions after diuretic administration suggests that the severe illness reported here may also have been drug induced. Whether the low C4 level in this patient was associated with a null allele at the C4 locus as in the case of patients with hydralazine toxicity remains to be investigated.

The high levels of fibrin degradation products, the low fibrinogen, and the prolonged prothrombin and kaolin-cephalin times are consistent with the syndrome of disseminated intravascular coagulation (DIC) in our patient, though the platelet count was at first normal. DIC has been reported in SLE, but this is rare.20,21 It has also been recorded in SLE with association with acute pneumonitis, and in that case the authors report that the ‘lupus anticoagulant’ may have played a part in their patient’s illness.22

Although our patient did not have diagnosable SLE, she manifested a high antinuclear antibody and precipitating antibodies to nRNP. She had no clinical features suggestive of any other connective tissue disease, such as mixed connective tissue disease. The pulmonary changes present in our patient may have represented an acute interstitial pneumonitis as in the patient referred to above.23 Failure to appreciate the probable nature of the illness in this patient at the outset led to treatment with antibiotics that was probably inappropriate while essential immunosuppressive therapy was delayed. Sudden unexplained vascular events of this type should cause suspicion that antiphospholipid antibodies may be present, leading to earlier diagnosis and perhaps to the development of more rational early therapy.

References

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