Case report

A 28-year-old European woman presented with nausea and mild diarrhoea. She was taking pyrimethamine 25 mg twice weekly for malaria prophylaxis. A blood film showed malaria parasites. Unfortunately facilities were not available for species identification, but the malaria in the district was generally assumed to be due to *Plasmodium falciparum*. She was given a course of chloroquine by mouth to a total of 1800 mg. For a body weight of 45 kg that amply met the WHO recommended standards. She had no diarrhoea or vomiting while taking the drug. She had never had malaria before nor had she previously taken chloroquine. The treatment did not relieve her symptoms—in fact, they were added to by the drug's side effects. Five days after her initial presentation a blood film, examined at a different laboratory, showed abundant parasites. Her haemoglobin concentration was 12 g/dl. She was therefore given Fansidar (pyrimethamine 25 mg, sulphadoxine 500 mg) three tablets immediately.

Four days later she again attended, feeling weak and dizzy, with a temperature of 38°C. There were still a few plasmodia in the blood film. She was given chloroquine 800 mg immediately, to be repeated once weekly for three weeks—although only one of these doses was taken. She slowly improved, and two weeks after her first attendance her blood film was clear. No parasites were found in a repeat film after a further two weeks.

Comment

While we have no absolute proof of the existence of chloroquine-resistant malaria in our part of Africa we strongly suspect it because of several cases like this one, mostly in Africans. I have chosen to report this case because it is well documented although it is atypical in that the patient was a European taking regular prophylaxis. I am sure I am by no means alone in believing that resistance of *P falciparum* to chloroquine exists in Africa and that our regimens of treatment and chemoprophylaxis therefore need to be reconsidered.

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Captopril-induced pemphigus

Captopril (SQ 14225), an oral inhibitor of angiotensin-converting enzyme, offers a new approach to treating several forms of hypertension. The commonest unwanted effects are morbilliform or maculopapular rashes and fever, which usually resolve on stopping or reducing the dose.¹ Other unwanted effects include aphthous ulcers of the mouth, temporary ageusia, the nephrotic syndrome, and reversible renal failure.¹ We report a case of pemphigus induced by captopril.

Case report

A 45-year-old previously fit English Jew began captopril 25 mg thrice daily in July 1979 for essential hypertension. The dose was increased weekly for four weeks to 150 mg thrice daily. Propranolol 10 mg thrice daily was added, being increased at weekly intervals until control was achieved with 80 mg thrice daily. He remained on the same dose of both drugs until January, when he presented with a two-week history of lesions on the trunk, scalp, and face and painful tongue erosions. The skin lesions were sore, red patches which had rapidly lost their surface, oozed, and crusted. Pemphigus erythematosus was diagnosed. Captopril was stopped, and after five weeks the skin and mouth ulcers had healed, though one new cutaneous lesion appeared. Blood cell count, erythrocyte sedimentation rate, blood glucose concentrations, liver and renal function values, protein electrophoresis, and immunoglobulin and serum complement concentrations were normal; antinuclear factor was speckled positive at 1/10.

Autoantibody to epidermal intercellular cement substance was positive at 1/40. Skin biopsy of the trunk showed an intraepithelial bulla high in the epidermis, containing a few acantholytic cells. On direct immunofluorescence upper epidermal intercellular IgG and lower epidermal intercellular C3 were detected in a biopsy specimen of a lesion. There was basement-membrane

deposition of C3 in perilesional skin. These appearances were consistent with pemphigus erythematosus. The HLA genotype was HLA-A1, 3/8, 18/BL, -1/6/DRW3, DRW5.

Comment

Though several hundred patients have been treated with captopril for at least six months, this is the first report of captopril-induced pemphigus. In Jewish patients with pemphigus vulgaris there is a particularly high prevalence of HLA-A10 and DRW4.² Our patient had neither of these.

Chemical structures of captopril and penicillamine.

Prolonged penicillamine treatment may also induce pemphigus. It has been estimated that 7% of patients taking penicillamine for at least six months develop pemphigus.³ Most patients have had pemphigus foliaceus, a few pemphigus erythematosus (as in our patient), and one pemphigus vulgaris. The side effects of captopril,¹ such as maculopapular and urticarial eruptions, which occur in the first few weeks of treatment, mouth ulcers, temporary ageusia, the nephrotic syndrome, and now pemphigus, are the same as those of penicillamine.

The chemical structures of penicillamine and captopril are strikingly similar (figure). Each compound has a highly reactive, negatively charged sulphhydryl group in a stable stereochemical relation to a similarly negatively polarised oxo group. The stereochemical similarities between penicillamine and captopril, combined with the clinical evidence of their ability to produce similar disorders, suggest that the toxicity of both drugs may prove disconcertingly similar.

We thank Dr F Marsh, Dr H Baker, and Dr J Pegum for advice during investigation of this patient and preparation of the manuscript.

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Systemic lupus erythematosus and nephritis: severe relapse with disappearance of antinuclear antibodies

Exacerbations of systemic lupus erythematosus with active renal disease are almost always associated with high plasma titres of antinuclear factor (ANF) and DNA-binding antibody (anti-ds DNA).¹ We describe a patient with classical systemic lupus erythematosus and initial high titres of antinuclear antibodies in whom severe relapse resulting in renal failure coincided with a prolonged reversion to normal of these serological indices.

Case report

A 20-year-old woman developed the nephrotic syndrome and a butterfly rash. Results of investigations were: haemoglobin concentration 9.6 g/dl; platelet count $87 \times 10^9/l$ ($87\,000/mm^3$); serum electrolyte, urea, and creatinine

concentrations normal, though with creatinine clearance 37 ml/min; serum albumin concentration 20 g/l; and 24-hour urinary protein loss 24 g. There was microscopic haematuria but no casts were seen. LE cell preparation was strongly positive, ANF titre 1/160, and anti-ds DNA 99% (normal 0-20%). She was treated with prednisolone and azathioprine. The rash cleared but the nephrotic syndrome persisted without change in creatinine clearance. Anti-ds DNA remained high and ANF continued strongly positive.

Four months later the patient developed status epilepticus with acute oliguric renal failure. Her temperature was 38.8°C and there was generalised oedema. Haemoglobin concentration was 5.7 g/dl, white cell count $10.2 \times 10^9/l$ ($10\ 200/mm^3$), potassium concentration 6.4 mmol(mEq)/l, and creatinine concentration 666 $\mu\text{mol/l}$ (7.5 mg/100 ml); urine microscopy showed profuse red-cell casts. Blood, cerebrospinal fluid, and urine cultures were sterile. ANF and LE cell preparations were repeatedly negative and anti-ds DNA normal (18%). Serum concentrations of C3 (0.48 g/l) and C4 (0.13 g/l) were low (normal ranges 0.65-1.25 g/l and 0.20-0.50 g/l respectively), and circulating immune complexes were detected. Immunosuppressive treatment was intensified with high-dose corticosteroids, cyclophosphamide, azathioprine, and subsequently plasma exchange (figure). Renal biopsy showed

Biochemical and clinical course over 10 months. (Plasma creatinine: 1 $\mu\text{mol/l}$ $\approx$ 0.01 mg/100 ml.)

diffuse proliferative glomerulonephritis. Eight of the nine glomeruli contained epithelial crescents; immunofluorescence disclosed granular deposition of IgG, IgM, and C3 on the glomerular capillary basement membrane. Electron microscopy showed subendothelial dense deposits. There was a gradual improvement in both clinical condition and renal function.

During month 5 generalised herpes zoster and further grand-mal seizures occurred. Azathioprine was temporarily withdrawn and the steroid dose reduced. ANF remained negative, and anti-ds DNA and C3 and C4 concentrations were normal. Six months later the creatinine clearance had risen to 60 ml/min, ANF remained negative, and C3 and C4 concentrations were normal, though anti-ds DNA was raised at 44% for the first time since relapse.

Comment

ANF-negative systemic lupus erythematosus is well recognised; such patients tend to have mild disease, and renal impairment is rare.² In most patients with the disease ANF is positive and titres of anti-ds DNA are specifically raised. Anti-ds DNA is closely implicated in the pathogenesis of immune complex nephritis.³ The diffuse proliferative lesion found in over half the patients with lupus nephritis is almost invariably associated with high titres of these antinuclear antibodies. At our patient's initial presentation the serological findings were strongly positive, yet during a severe flare of her disease, with proliferative nephritis and presumptive acute cerebral lupus, these findings were repeatedly negative. The absence of detectable antinuclear antibody at the time of maximal disease activity may be explained by antigen binding, either in the circulation or in the kidney, of all available antibody.⁴ This would account for the low complement concentrations, circulating immune complexes, and immunofluorescent granular deposits on the glomerular basement membrane. Thereafter persisting seronegativity may have resulted from suppression of autoantibody synthesis by treatment or spontaneous improvement.

High titres of anti-ds DNA are associated with active systemic lupus erythematosus. Nevertheless, in a longitudinal study⁵ flares of disease activity with renal impairment were associated with a sharp fall in anti-ds DNA and coexistent depression of complement concentrations (though anti-ds DNA still remained above normal). Our case is an

extreme example of this phenomenon; complete disappearance of antinuclear antibody was associated with an acute and severe exacerbation of the disease.

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Requests for reprints should be sent to Dr JGG Ledingham.

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Echinococcus granulosus infection and malignancy

Yong *et al*¹ reported a possible antigenic similarity between pulmonary carcinoma and cysts of *Echinococcus granulosus*. They found a broad precipitin band due to real antigen-antibody reaction in the immunoelectrophoresis test, but the line did not join the so-called echinococcus-specific arc-5 band in the reference system that was run simultaneously. Since similar cases are rare² our experience may be of interest.

Methods and results

In our institute serological diagnosis of hydatid disease is routinely carried out by indirect immunofluorescence using protoscolices of horse cysts in combination with a classical complement-fixation test with polysaccharide antigen. In positive cases a questionnaire is sent to the physician to obtain background information as well as the final diagnosis. Out of a total of 1500 examinations in the past five years there were at least eight cases in which a positive result in the serological test for *E granulosus* was associated with a confirmed malignant neoplastic growth instead of surgically confirmed hydatidosis (table).

Malignancies in eight patients with serological evidence of hydatid disease

Case No	Immuno-fluorescence test*	Complement-fixation test*	Final diagnosis
1	320	negative	carcinoma of sigmoid
2	40	negative	adenocarcinoma of colon
3	negative	32	planocellular carcinoma (bronchus)
4	20	64	renal carcinoma + pulmonary metastases
5	5	2	bronchial carcinoma
6	5	negative	bronchial carcinoma
7	10	2	liver metastases
8	20	negative	carcinoma of the pancreas

*Reciprocal antibody titre.

Comment

As the evidence for an antigenic similarity between *E granulosus* and some tumour types increases we should keep in mind that the presence of specific antibodies in the serum is not always diagnostic of hydatid disease or a related-helminth infection. Similar cross-reactions between bacteria and tumour cells have been reported. For example, *Mycobacterium bovis* (BCG) and guinea-pig line 10 hepatocarcinoma cells as well as human melanoma cells share surface antigens. This