Hydralazine induced lupus syndrome with eye disease

A syndrome resembling systemic lupus erythematosus, characterised by prominent polyarthralgia, arthritis, pleurisy, and a positive antinuclear antibody (ANA) test, is a recognised complication of treatment with hydralazine. It is generally considered a benign condition that resolves without permanent sequelae.¹

We describe two patients who developed bilateral retinal vasculitis during otherwise typical hydralazine induced lupus syndrome. In one case episcleritis was also present. So far as we are aware this is the first report to associate eye disease with the drug induced lupus syndrome.

Case 1

A 63 year old woman with essential hypertension presented with a 10 month history of symmetrical hand, wrist, and shoulder arthralgia, blurred vision, malaise, and weight loss. She had taken hydralazine 150 mg/day for three years. Examination showed tender but otherwise normal joints; her blood pressure was 115/80 mm Hg. Corrected visual acuities were 6/18 on each side. There was a right sided nodular episcleritis; both vitreous bodies showed mild inflammatory cell infiltration; and both retinas had widespread dot haemorrhages and macular oedema. The results of investigations included: haemoglobin concentration 10.2 g/dl (normal red cell indices); leucocyte and platelet counts normal; plasma viscosity 1.92 cP (normal range 1.5-1.72 cP); serum ANA test positive (1/1280) with homogeneous immunofluorescence staining; DNA binding negative; urea, serum complement (C3, C4), and immunoglobulin concentrations within normal limits. Chest x ray films and joint radiographs were normal. Fluorescein angiography showed arteriolar attenuation with scattered areas of capillary dilatation and leakage in both fundi. Changes at the right macula were consistent with a small branch vein occlusion; elsewhere abnormalities showed focal capillary damage most appreciable in the peripheral fundi. Tissue typing and acetylase state were not assessed.

Her arthralgia, episcleritis, and malaise resolved within four weeks of stopping hydralazine. Ten months later her ANA test remained positive (1/320), visual acuities were unaltered, and no new retinal lesions had appeared.

Case 2

A 53 year old woman with essential hypertension presented with a three month history of symmetrical hand, wrist, and knee arthralgia, general malaise, and weight loss. She had taken hydralazine 150 mg/day for two years. Examination showed normal joints; blood pressure was 125/85 mm Hg. Visual acuities were 6/12 in each eye unaided. Both retinas showed widespread retinal pigment epithelial changes with pigment clumping and also pronounced retinal capillary tortuosity around the papillary plexuses. The results of investigations included: haemoglobin concentration 10.9 g/dl (normal indices); leucocyte and platelet counts normal; viscosity 1.81 cP; serum ANA test positive (1/320) with homogeneous immunofluorescence staining; DNA binding negative; urea, serum complement, and immunoglobulin concentrations normal. Chest x ray and joint radiographs were normal. Tissue typing and acetylase state were not assessed.

Her arthralgia and malaise resolved within three weeks of stopping hydralazine. After six months' follow up her ANA remained positive (1/160) and her eyes were unchanged.

Comment

With the possible exception of the macular branch vein occlusion in case 1, the retinal changes observed in these patients are not explicable in terms of hypertensive retinopathy alone.² Both patients had raised plasma viscosity, but this was not to the level usually associated with hyperviscosity syndrome and the changes observed are atypical of slow flow retinopathy.² Such abnormalities, however, although non-specific, are fully compatible with the retinal microvascular disturbance described in patients with systemic lupus erythematosus.^{2,3}

Features of both patients' illnesses which are characteristic of hydralazine induced lupus include: prominent polyarthralgia; weight loss; positive ANA test with negative DNA binding; normocomplementaemia; prompt recovery on discontinuing hydralazine and subsequent prolonged ANA positivity.¹ Although drug induced lupus is usually characterised by limited organ disease and a less severe clinical course than idiopathic systemic lupus erythematosus,¹ the occasional development of rapidly progressive glomerulonephritis^{4,5} and vasculitis⁶ has recently been emphasised. The present report suggests that ocular disease is a further potentially serious com-

plication of this syndrome. The frequent coexistence of hypertensive retinopathy in patients selected for treatment with hydralazine may well result in underdiagnosis.

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Onycholysis associated with cytotoxic drugs

Onycholysis is associated with conditions such as psoriasis and hyperthyroidism and with ingestion of drugs, notably tetracycline and captopril.¹ Only one case has been reported in which onycholysis was attributed to cytotoxic drugs: onycholysis developed after treatment with doxorubicin and was associated with appreciable epidermolysis of the feet and hands.² We report three cases of onycholysis that occurred during cytotoxic treatment without any manifestation of skin toxicity.

Case reports

Case 1—A 78 year old man presented in October 1983 with generalised lymphadenopathy and hypercalcaemia (calcium concentration 3.2 mmol/l (13 mg/100 ml) corrected) and normal nails. Histological examination showed a T cell non-Hodgkin's lymphoma. The hypercalcaemia was treated with intravenous mithramycin, and he began chemotherapy comprising intravenous cyclophosphamide (650 mg), doxorubicin (35 mg), etoposide (160 mg), bleomycin (30 mg), and vincristine (2 mg) every three weeks. After five cycles almost complete onycholysis of both great toes had occurred, and this progressed to total nail loss with further chemotherapy. No other drugs were being taken. Thyroid function tests gave normal results, and nail scrapings for fungi and hyphae were negative. Serum zinc concentration was 11 µmol/l (72 µg/100 ml) and zinc clearance 4.5 µmol/l (294 µg/l) (normal ranges 12-18 µmol/l (78-118 µg/100 ml) and 4.6-10.5 µmol/l (301-693 µg/l) respectively). Creatinine clearance was 80 ml/min. By February 1984 he was in complete remission and chemotherapy was therefore stopped. His nails recovered fully. In June relapse occurred and the same combination chemotherapy was restarted. After three cycles onycholysis recurred.

Case 2—A 47 year old clerk with normal nails, lymphadenopathy, and abdominal mass due to diffuse histiocytic lymphoma presented in December 1983. Combination chemotherapy with intravenous cyclophosphamide (730 mg), doxorubicin (40 mg), etoposide (194 mg), and vincristine (2 mg), intramuscular bleomycin (30 mg), and oral prednisolone (100 mg for five days) every three weeks was started in February 1984. By the seventh cycle the nails of both great toes were lost and early onycholysis had developed in all finger nails. Nail scrapings for fungi and hyphae yielded negative results. Results of thyroid function tests were normal. Serum zinc concentration was 8 µmol/l (52 µg/100 ml), zinc clearance 2.0 µmol/l (131 µg/l), and creatinine clearance 88 ml/min. She had not been receiving any other treatment. After chemotherapy was stopped in August the nails began to grow.

Case 3—A 58 year old housewife with breast adenocarcinoma began chemotherapy in January 1984. Her nails were normal. She received anti-hypertensive treatment with propranolol and bendroflumazide throughout the period of chemotherapy. Chemotherapy comprised intravenous vincristine (2 mg) and doxorubicin (45 mg) and oral prednisolone (40 mg daily for five days) every three weeks. Complete onycholysis of both great toes occurred after seven cycles. Results of thyroid function tests were normal,

and nail scrapings for fungi and hyphae were negative. Serum zinc concentration was $14 \mu\text{mol/l}$ ($92 \mu\text{g}/100 \text{ ml}$), zinc clearance $3.5 \mu\text{mol/l}$ ($229 \mu\text{g/l}$), and creatinine clearance 95 ml/min .

Comment

These are the only three cases of onycholysis due to cytotoxic drugs to be reported without associated dermatopathy. This is surprising as our experience indicates that it is not a rare phenomenon: these three cases occurred over nine months. Two of the patients had low serum zinc concentrations and all three had reduced urinary zinc clearance, which with normal creatinine clearance implies zinc deficiency.

The precise importance of these findings is uncertain, though the importance of zinc in growth and nutrition is well known and possibly the combination of zinc deficiency and cytotoxic treatment led to nail loss. Thus zinc supplementation might conceivably have prevented the onycholysis. The cytotoxic agents common to all patients were doxorubicin and vincristine. Doxorubicin causes alopecia in virtually all patients, and the developmental similarity between hair and nails is readily apparent. Vincristine has no such effect on hair. Of the other cytotoxic drugs, methotrexate suppresses growth of finger nails³ and cyclophosphamide and bleomycin cause pigmentation and banding of nails.^{4,5} Therefore, although doxorubicin is most likely to have been the cause, the contribution of the other cytotoxic agents or zinc deficiency cannot be dismissed.

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Cortical blindness complicating Wegener's granulomatosis

Wegener's granulomatosis is characterised by a necrotising vasculitis of the respiratory tract and an associated glomerulonephritis. The condition often includes a generalised vasculitis affecting various organs,¹ sometimes producing neurological and ocular complications such as cranial nerve abnormalities and mononeuritis multiplex, and conjunctivitis, retinal vasculitis, and optic neuropathy.²

We report on a patient with classical Wegener's granulomatosis who suffered bilateral infarction within the occipital cortex with resultant cortical blindness. This complication has not been reported previously.

Case report

A 35 year old woman with a three year history of nasal stuffiness and a chronic clear nasal discharge developed polyarthralgia in early 1983. In August 1983 she developed scleritis and was treated with prednisolone 30 mg and azathioprine 150 mg daily. The scleritis, however, persisted and in January 1984 a chest x ray film showed a cavitating lesion in the upper lobe of the right lung. Despite a negative Mantoux test result and sputum culture, rifampicin 600 mg and isoniazid 300 mg daily were started for presumed pulmonary tuberculosis. There was no response and one month later her polyarthralgia deteriorated and a blistering skin eruption developed. A dipstick urine test showed protein and blood in large amounts and renal function began to deteriorate to the point where haemodialysis became necessary. Skin and nasal septum biopsy specimens showed necrotising vasculitis and a renal biopsy specimen showed focal segmental proliferative glomerulonephritis with crescents in 64% of the glomeruli. Immunofluorescence showed traces of IgG and C3, but no IgA, IgM, C1q, or C4. The crescents stained with high intensity for fibrinogen.

Treatment with cyclophosphamide, prednisolone, and plasma exchange

produced dramatic improvement. Her blood pressure was well controlled and renal function began to recover rapidly (see figure). Nevertheless, her progress was interrupted by two generalised seizures over four days. An

Effect of treatment on renal function. Under vision, episode 1 was transient loss of vision and episode 2 permanent loss of vision.

isotope brain scan after the first seizure was normal. Just before the second seizure she had transient blindness, but after she recovered from the convulsion her vision was normal. A third seizure followed, after which a repeat isotope brain scan was again normal. Nevertheless, two days later she developed sudden blindness, which this time persisted. Direct and consensual reactivity of the pupils was normal but she could not see finger movement at a few inches' distance and a rotating drum test could not induce nystagmus. Computed tomography showed segmental areas of low attenuation consistent with small focal areas of infarction near both occipital poles and in the high parameian parietal regions. Although renal function subsequently improved steadily, she recovered very little vision. Perimetry showed generalised constriction of the peripheral visual fields consistent with bilateral cortical infarction.

Comment

Cortical blindness has been described in association with hypertension secondary to glomerulonephritis.^{3,4} In both these cases complete recovery of vision occurred and blindness was probably secondary to arteriolar spasm (of the branches of the posterior cerebral arteries), which occurs in severe hypertension.³

Our patient had transient blindness preceding a convulsion while her blood pressure was well controlled. The permanent blindness which developed subsequently occurred when the renal and systemic manifestations of her disease were improving, and the two episodes are therefore unlikely to have been due to spasm or to progressive disease. Although combination therapy proved effective against the arteritis in the kidneys, and brought about definite improvement in renal function, the most likely explanation for the blindness is that thrombosis occurred in branches of the posterior cerebral arteries affected by the original disease. If this is so then in Wegener's granulomatosis and other forms of arteritis antiplatelet agents may be important in minimising tissue damage once the original inflammatory reaction has been controlled by steroids, cyclophosphamide, and plasma exchange.

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