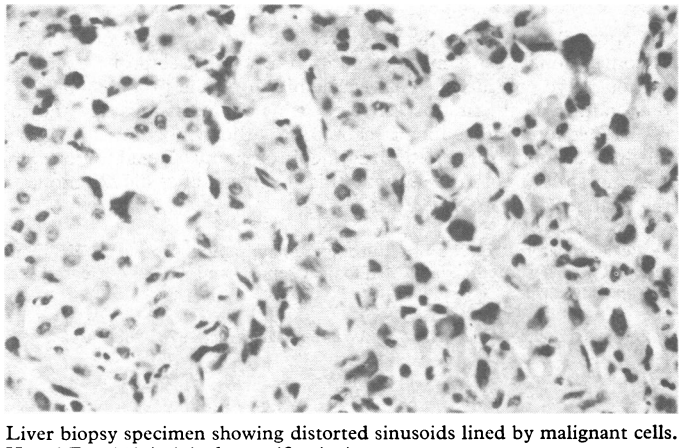
Angiosarcoma of liver associated with phenelzine

Angiosarcoma of the liver is extremely rare.[1] It has been associated with thorium dioxide, organic arsenic, and vinyl chloride monomer.[2] Phenelzine (phenethylhydrazine; Nardil), a monoamine oxidase inhibitor, causes angiosarcoma of the liver in mice.[3] We describe a woman who developed angiosarcoma while taking phenelzine.

Case report

A 64-year-old woman admitted for investigation of anaemia gave a four-month history of malaise, bruising tendency, and cough productive of small blood clots. She had been taking phenelzine for at least six years. The initial dose was 45 mg daily, which was reduced to 15 mg daily after three years. Diazepam 5 or 10 mg occasionally was the only other regular medication. There was no history of exposure to thorium dioxide, arsenic, or vinyl chloride. Examination showed pallor, generalised wasting, and several large bruises. The liver was enlarged and palpable. Full blood count showed haemoglobin concentration 7·8 g/dl, white cell count 7×10^9/l (7000/mm^3), platelet count 155×10^9/l (155 000/mm^3), and reticulocytes 6·5%. Blood film showed fragmentation of red cells. Prothrombin time, thrombin clotting time, and activated partial thromboplastin time were all prolonged. Concentration of fibrin degradation products (FDP) was 160 mg/l. Moderate haematuria was present. Urea and electrolyte concentrations, initial liver function tests, serum α-fetoprotein value, and bone marrow appearances were normal.

The haematological findings suggested mild chronic disseminated intravascular coagulation (DIC). The haematuria and haemoptysis were ascribed to this process after exclusion of other causes. Subsequent platelet counts ranged between 20 and 100×10^9/l, and the raised titre of FDP persisted. Isotope liver scan showed multiple areas of decreased uptake, and computerised axial tomography of the liver confirmed areas of abnormal texture. In the lateral epicondyle of the right humerus there was an osteolytic area suggestive of metastatic disease. Results of barium meal and excretion urography were normal. Laparoscopy of the liver surface showed multiple umbilicated nodules up to 2 cm diameter, unlike cirrhosis or metastatic carcinoma. Laparoscopic needle biopsies disclosed normal liver tissue with focal areas of bile-duct proliferation with large pleomorphic cells suggestive of malignancy. At laparotomy numerous haemorrhagic nodules were seen on the liver and parietal peritoneum overlying the right lobe. These were sampled for biopsy. Histologically the liver showed distorted sinusoids lined by malignant cells adjacent to the focal areas of bile-duct proliferation (see figure). There was no evidence of cirrhosis. The peritoneal nodules comprised blood-filled spaces lined by malignant endothelial cells with pleomorphic nuclei. These changes were considered to be diagnostic of angiosarcoma.



Liver biopsy specimen showing distorted sinusoids lined by malignant cells. H and E ×840 (original magnification).

The patient recovered from laparotomy and the haematuria and haemoptysis lessened. Gross bloodstained ascites developed, however, which required drainage. She died at home five months after presentation.

Comment

In animals substituted hydrazine derivatives induce a variety of tumours, including tumours of blood vessels.[4] Phenelzine given to female Swiss mice significantly increased the incidence of angiosarcoma at various sites, including the liver.[3] Hence the angiosarcoma in our patient may have been related to phenelzine. Although such an association in a patient has not been recorded before, this may represent failure in documenting drug history.

The presenting features of this case were probably manifestations of chronic DIC, which is associated with liver angiosarcoma.[2] This process may have contributed to the bloodstained ascites. Naked-eye appearances of the liver were not diagnostic at laparoscopy or laparotomy. Primary liver tumour was diagnosed by multiple biopsy at laparotomy. We cannot be certain whether the peritoneal angiosarcomatous lesions and the lesion in the right humerus were metastases from a primary liver tumour or represented multifocal tumour growth, which is true in experimental animals.[3 4]

We suggest that inquiry about hydrazine compounds—for example, phenelzine, isoniazid, and procarbazine—should be made in future cases of angiosarcoma of the liver.

We thank Professor P J Scheuer, Royal Free Hospital Medical School, for reviewing the histology; and Dr H McNulty, Regional Drug Information Service, Bristol Royal Infirmary.

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[3] Toth, B, *Cancer Research*, 1976, **36**, 917.
[4] Toth, B, *Cancer Research*, 1975, **35**, 3693.

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Multiple lipomas in pregnancy

Lipomas are benign tumours of adult fat cells. We report a case in which multiple lipomas first appeared during pregnancy.

Case report

The patient, aged 31, was in her second pregnancy. Her first pregnancy, in 1975, had ended in spontaneous abortion at 12 weeks. She had stopped taking a combined oral contraceptive in 1974 after two years' use. Her periods had remained irregular ever since.

She was seen first at the antenatal clinic when 20 weeks pregnant. She was of normal build, with weight 53·2 kg and height 156 cm. Physical examination showed no abnormality and the pregnancy was continuing normally, the uterine size being as expected from the duration of amenorrhoea. At her next visit at 28 weeks (care being shared with her general practitioner) she mentioned isolated, soft, painful subcutaneous swellings on both forearms. These were about 2 cm diameter and had been present for three weeks. Later, a further six swellings on the anterior aspects of her thighs became palpable. The swellings continued to enlarge slowly throughout the rest of her pregnancy, the largest, on her left forearm, reaching 3 cm diameter. Biopsy of a swelling on her right forearm showed the histological features of a simple lipoma. There was no vascular proliferation to suggest angiolipoma.

The pregnancy was otherwise normal: she gained 10 kg. She was delivered at 42 weeks by forceps of a healthy boy weighing 3400 g. In the immediate puerperium the lipomas became less and at the postnatal check six weeks later all but a swelling 0·5 cm diameter on her left forearm had disappeared. No lumps on her thighs could be seen or felt. She was breast-feeding and had begun an oral contraceptive containing only progesterone. So far as she knew none of her relatives had multiple lipomas.

Comment

Lipomas are slow-growing, benign tumours of adipose tissue. Multiple tender lesions, especially if there is a family history, are characteristic of angiolipomas.[1-3] Though her lipomas were tender, she had no family history, and histopathological findings were not consistent with angiolipomas.

Lipomas are common, but this is apparently the first report of multiple lipomas appearing in pregnancy and regressing in the puerperium. Possible explanations include: (*a*) that the hormonal

changes of pregnancy produced a reversible increase in the fat content of the cells of pre-existing tumours, and (*b*) that increased peripheral blood flow in pregnancy caused an alteration in the water content of already existent though impalpable tumours.

We thank Dr P Hutchinson, consultant dermatologist, Leicester Royal Infirmary, for help in preparing this case.

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Reversible renal failure during treatment with captopril

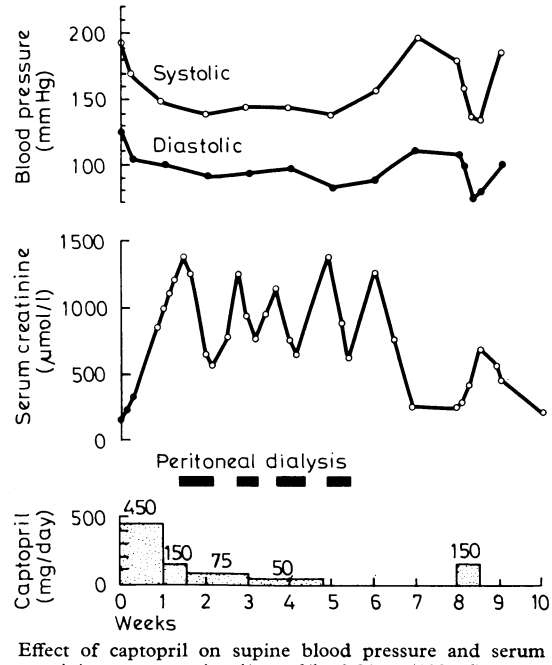
The new orally active angiotensin-converting enzyme inhibitor captopril (Squibb, SQ 14225) is effective in hypertension whether or not of renal origin.[1] Rashes may occur but resolve when the dose is reduced. Other side effects are minor, and nephrotoxicity has not been reported, although transient slight increases in serum creatinine concentrations were observed in two patients.[1] We report a case of acute renal failure in a young woman with transplant artery stenosis and severe hypertension resistant to conventional treatment that occurred during administration of captopril. Renal failure recurred on reintroducing the drug.

Case history

The patient was found to be hypertensive in 1973, when she was aged 22. Full investigation including renal arteriography failed to disclose a cause for her severe hypertension, which was resistant to large doses of standard drugs. Neither minoxidil nor diazoxide were used because of the risk of hirsutes. She progressed to end-stage renal failure and began regular haemodialysis in 1975. With dialysis, blood pressure was controlled satisfactorily (150/90 mm Hg) while taking propranolol 120 mg daily. She was transplanted with a well-matched (two HLA-B and one HLA-A) cadaver kidney in 1976. There were two renal arteries, one of which was anastomosed end-to-end to the left internal iliac artery and the other end-to-side to the common iliac artery. Two months later severe hypertension recurred, and a systolic bruit was heard over the transplant.

The inferior vena cava (IVC) was cannulated via the right femoral vein and plasma samples collected from the left common iliac vein and IVC below and above the renal veins. Plasma renin activities at the three sites were 69, 56, and 59 pmol/l/min (8·8, 7·2, and 7·6 ng/100 ml/min), suggesting that the graft was the probable cause of her hypertension. Arteriography showed tight stenosis at the anastomosis with the internal iliac artery. At surgical exploration correction of the stenosis could not be attempted without risk of losing the kidney because of dense fibrosis around the anastomosis. Blood pressure remained poorly controlled (190/130 mm Hg lying, 180/130 mm Hg standing) despite methyldopa 3 g, propranolol 1280 mg, frusemide 1 g, and hydrallazine 200 mg daily, though standing pressures down to 130/90 mm Hg were recorded at times. Furthermore, she was severely incapacitated by side effects of the drugs, mainly drowsiness and depression. We therefore decided to use captopril, which was approved by the hospital's ethical committee.

All other treatment was stopped the evening before according to the trial protocol under which captopril was being used and the drug given by mouth at an initial dose of 25 mg. This was doubled eight-hourly until 150 mg eight-hourly was reached after 24 hours. Hydrochlorothiazide 50 mg daily was added. The figure shows the blood-pressure response and changes in serum creatinine concentration. The initial fall in blood pressure may have been in part a carryover effect from the previous treatment, but this would not explain control at one week. An erythematous, macular itchy rash appeared after five days but cleared on reducing the dose of captopril to 25 mg eight-hourly. Renal function began to deteriorate on the second day, the lowest recorded blood pressure during captopril treatment before this being 120/80 mm Hg standing. It seemed likely that the renal failure was due to acute tubular necrosis resulting from ischaemia beyond the renal artery stenosis consequent on the reduction in blood pressure, and captopril was continued at 25 mg eight-hourly. After three weeks of renal failure renal biopsy showed patchy atrophy and inflammation suggesting localised scarring but no evidence of rejection or tubular necrosis.



Effect of captopril on supine blood pressure and serum creatinine concentration (1 μmol/l ≈ 0·01 mg/100 ml).

After five weeks captopril was withdrawn and replaced with methyldopa 500 mg twice daily. During the sixth week renal function recovered, serum creatinine finally reaching pre-captopril values. Hypertension recurred (180/120 mm Hg), and 10 days after recovery methyldopa was withdrawn and captopril reintroduced at a dose of 50 mg eight-hourly. Renal function immediately deteriorated (figure), though blood pressure did not fall below 140/80 mm Hg. Captopril was withdrawn and renal function returned to pretreatment values in eight days.

Comment

Captopril was most effective in controlling hypertension resistant to conventional agents in the maximum doses that could be tolerated. Although we considered renal ischaemia to be the probable cause of renal failure on the first occasion, the time course of recovery and the recurrence on reintroducing captopril without documented hypotension strongly suggested drug nephrotoxicity. Renal biopsy appearances were compatible with this diagnosis and showed none of the changes of tubular necrosis.

We are grateful to Squibb (Europe) for supplying captopril. We thank Dr A R Morley for the renal histological report, and Mrs R Grieveson for secretarial help.

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Correction

Postcards or outpatients: an alternative method of follow-up

We regret that owing to a printer's error Mr David J Varnam's name was spelt incorrectly in the list of authors of the above article (19 May, p 1321). Bristol Myers in his address should have been hyphenated.