We believe that hypercalcaemia after tamoxifen may signify tumour response and be a reason for continuing with tamoxifen and treating the hypercalcaemia. This is supported by a report of tamoxifen "flare" in metastatic breast cancer and the observation that acute exacerbation of bone pain in patients with breast cancer after tamoxifen may be associated with tumour response.⁵ The mechanism of tamoxifen-induced tumour response needs further investigation, since acute hypercalcaemia is not seen in patients responding to chemotherapy or oophorectomy.

Requests for reprints should be sent to Professor M H N Tattersall.

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Hydrallazine-induced SLE-like syndrome presenting as a leg ulcer

The use of hydrallazine for systemic hypertension may be complicated by a syndrome resembling systemic lupus erythematosus (SLE) in 10-15% of patients after cumulative doses exceeding 100 g.¹ We describe a patient who presented with a painful leg ulcer.

Case report

A 50-year-old man admitted in January 1979 had a nine-week history of a painful ulcer above the right heel, which had steadily enlarged and prevented walking. He had a nine-month history of symptoms suggestive of Raynaud's phenomenon, joint pains for three months, malaise for six weeks, and an itchy rash over the left shin and forearm for one week. Malignant hypertension was diagnosed in 1970 (blood pressure 250/130 mm Hg) and treatment instituted with debrisoquine. In 1976 he was admitted with a blood pressure of 270/180 mm Hg and hydrallazine treatment was begun (150 mg daily). There was no diabetes mellitus, vascular insufficiency, or trauma. He smoked 15 cigarettes daily.

He was drowsy, with mild tachycardia (100/min) and low-grade fever (37.5 °C). Blood pressure was 220/150 mm Hg (supine) and 190/135 mm Hg (erect). The ulcer (3.5 cm diameter), directly over the right tendo Achillis, was superficial, but the edge was discoloured and the base encrusted with old blood. There was no arterial or venous insufficiency or regional lymphadenopathy. There was severe wasting of the right quadriceps muscle, equinus deformity of the right ankle, and a diffuse purpuric rash over the left shin and forearm.

Haemoglobin concentration was 12.8 g/dl but white cell and platelet counts were normal. Plasma viscosity was raised (1.92 mPa s; 1.92 cp), serum iron concentration 6.9 µmol/l (38.5 µg/100 ml), total iron-binding capacity 47 µmol/l (262.5 µg/100 ml), blood urea concentration 8.1 mmol/l (48.6 mg/100 ml), and creatinine clearance 52 ml/min. Titre for antinuclear factor (ANF) was 1/320 and DNA antibody binding 21%. IgM concentration was 9.0 g/l, but complement values were normal. Random blood glucose estimations, chest and ankle radiographs, and Wassermann and latex fixation tests showed no abnormalities. The patient was a slow acetylator as assessed by sulphadimidine clearance. A biopsy specimen of the ulcer disclosed fibrosing granulation tissue.

All these features suggested that an SLE-like syndrome may have caused this patient's indolent ulcer. Since total hydrallazine exposure may have been relevant the drug was replaced by atenolol and bendrofluazide. With bed rest, raising the leg, and cleaning the ulcer locally his condition rapidly improved. The rash disappeared five days after stopping hydrallazine, and by one week the ulcer was healing; this was accelerated by applying split-skin grafts. At discharge plasma viscosity was 1.7 mPa s (1.7 cp). After four

months he was in good health and had returned to work. The ulcer had healed, and after physiotherapy his ankle and thigh had returned to normal. Blood pressure was controlled at 140/90 mm Hg. Plasma viscosity, ANF titres, and DNA antibody binding were unchanged.

Comment

Dubois² reviewed 520 cases of idiopathic SLE and found a 5% incidence of leg ulceration but this complication has not been reported in hydrallazine-induced SLE. About 10% of cases of SLE may be caused by drugs, notably hydrallazine. Patients may develop a positive ANF titre with hydrallazine without having SLE-like symptoms.³ This phenomenon was also shown for prazosin.⁴ Drug-induced SLE differs from idiopathic SLE in affecting older people, relatively more men, and the lung and kidney less often; DNA antibody binding is under 30%.³ Some 96% of patients with drug-induced SLE are slow acetylators.^{3,5} Although first described in patients taking large daily doses of hydrallazine (400 mg),³ the syndrome may occur with lower doses (150 mg)⁵; the cumulative dosage appears to be more important. Symptoms usually disappear within four months of stopping hydrallazine, but ANF titres and DNA antibody binding may take up to six years to return to normal.⁵

The relation between toxic symptoms and hypertensive control is not clear. Perry³ suggested that toxicity was associated with control of blood pressure and that suddenly stopping treatment led to rebound hypertension. In our case toxicity was associated with failure of hypertensive control. We suggest that acetylator states of all patients taking long-term hydrallazine should be determined to identify those at risk from drug-induced SLE. Once hypertension is controlled the daily dose should be reduced to the minimum needed to maintain normal blood pressure.

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Gallium-67 scanning in pyrexia of unknown origin

Pyrexia of unknown origin (PUO) is a common problem in clinical medicine, occurring either as a presenting feature or as a postoperative complication. We have assessed the efficacy of ⁶⁷Ga scanning as a non-invasive investigation of PUO.

Methods and results

We reviewed retrospectively 67 consecutive scans performed on 61 patients with PUO referred to our department in one year. The PUO had been present for several days to several weeks, and routine investigations including blood, sputum, and urine cultures, chest radiography, and intravenous urography, had not determined its origin. Imaging was performed 48 and 72 hours after intravenous injection of 75-100 MBq (2-2.7 mCi) gallium citrate (⁶⁷Ga; Radiochemical Centre). Patients were not prepared before injection, but unless contraindicated Dorbanex tablets (danthron-polyoxamer) were given 12-hourly for 72 hours afterwards. Imaging was performed with an Ohio Nuclear 84 double-headed rectilinear scanner with 5:1 ratio minification using a high-energy collimator and an analyser setting that accepted the 185 and 296 keV peaks of ⁶⁷Ga. Patients were imaged from neck to thigh. When indicated, a liver-spleen scan with ^{99m}Tc-sulphur colloid was performed after the ⁶⁷Ga scan at 72 hours, the patient being kept in the same position to permit superimposition of the scans. Gallium-67 scans were regarded as normal when uptake was seen only in sites of physiological accumulation, and abnormal when uptake was seen at other sites, provided relative uptake increased between 48 and 72 hours.

Of the 67 ⁶⁷Ga scans, 50 were abnormal. Most sites of abnormal uptake were in the abdomen (table), miscellaneous sites consisting mainly of

Sites of abnormal ^{67}Ga in 50 scans

Abdomen	32	Chest	12
subphrenic	9	mediastinum	7
renal	8	lung fields	5
hepatic	2	Other	6
miscellaneous	13*		

*Mostly operation sites—for example, uptake in scars—and intraperitoneal collections.

operation sites—for example, uptake in scars—and intraperitoneal collections. Conditions underlying abnormal uptake included localised pus (32 cases), non-infective inflammation (six), tuberculosis (three), neoplasm (five), and transplant rejection (one); in three cases the cause was not clear. Of the 50 abnormal scans, 33 provided new, useful information resulting in an important change in diagnostic probability; 12 resulted in only a borderline change, confirming the presence of a highly probable lesion but excluding others; and five resulted in no change in diagnostic probability, which was already high. In none of the 17 patients with normal scans did follow-up disclose any focal cause for the PUO. Twelve normal scans resulted in an important change in diagnostic probability, and five resulted in a borderline change. All normal scans were of diagnostic value.

Comment

Localisation of ^{67}Ga in inflammatory lesions was first reported by Lavender *et al.*¹ Several authors have reported on its use in other conditions, but there have been few reports on the value of ^{67}Ga scanning in patients with PUO.² A recent review of PUO failed to mention this technique.³ We suggest that ^{67}Ga scanning is valuable in PUO even after blood and urine cultures and radiography. The high sensitivity of the technique is valuable in locating sites for further, possibly invasive diagnostic tests, though it is of low specificity. Conversely, a normal scan is valuable in excluding focal disease. Since this series was collected we have seen one presumed false-positive scan of a patient with focal uptake in the abdomen that resolved without treatment, and two false-negative scans of patients who were already taking appropriate antibiotics at the time of scanning.

There are, of course, difficulties with ^{67}Ga scanning: the isotope is expensive; available only on certain days; and—unless work load warrants a standing order, which may otherwise lead to wastage—must be ordered specially. Waiting for 72 hours for the result may be a problem, and contrary to the suggestion of Hopkins *et al.*⁴ we do not find imaging six hours after injection to be helpful. Normal excretion of ^{67}Ga in the bowel may also make interpretation difficult, especially after abdominal operations, when laxatives may be contraindicated. Despite these problems ^{67}Ga -citrate scanning is a useful addition to non-invasive investigations of PUO.

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Proximal myopathy during beta-blockade

Many side effects of beta-blocking drugs have been identified.¹ We describe a severe proximal myopathy in a patient taking sotalol and subsequently propranolol. The symptoms resolved completely when the drug was withdrawn and recurred on rechallenge with propranolol.

Case report

A 68-year-old woman started taking sotalol 80 mg every eight hours in January 1977. A four-year history of angina of effort had previously been managed with nitrites. The resting electrocardiogram was normal, and with

exercise 1-2 mm ischaemic S-T depression developed at a heart rate of 130/min. Chest radiograph, plasma urea, electrolytes, and full blood count were normal (ESR 27 mm in the first hour).

Six months later she developed painless weakness of the arms and legs. The symptoms were worst in the morning: she had to crawl upstairs and could not stand unsupported. On examination striking proximal muscle weakness was most pronounced in the quadriceps group. Arm reflexes were normal and leg reflexes present with reinforcement. Investigations showed normal full blood count, plasma urea, electrolytes, liver function tests, calcium, phosphate, serum total thyroxine, and thyrotrophin response to thyrotrophin-releasing hormone. Rheumatoid and antinuclear factors were negative. The erythrocyte sedimentation rate (ESR) was raised, varying from 49 to 75 mm in the first hour. Treatment was changed to propranolol 40 mg eight hourly but muscle weakness continued. Serum creatine phosphokinase (SCPK) concentrations, estimated after six months of propranolol treatment, were raised and varied from 700 to 2200 U/l (reference range 30-150 U/l). Isoenzyme estimation showed that its origin was predominantly skeletal muscle. Electromyography (EMG) using a concentric needle electrode showed no abnormalities in the left tibialis anterior or left deltoid. There was no spontaneous activity in the left quadriceps: motor unit action potentials were mainly of normal amplitude (0.5-2 mV) and mostly lasted 8-10 ms. There was, however, an increased number of briefer potentials (<5 ms), some of which were polyphasic. Recruitment was full, making a neuropathic cause for the weakness unlikely. The changes suggested a mild myopathic process. Extensive investigations to identify an occult neoplasm were negative.

Propranolol was discontinued in July 1978 and the proximal weakness rapidly resolved and SCPK concentrations returned to normal (see figure). It was reintroduced in August at a dose of 80 mg eight hourly and the patient remained well until November 1978, when weakness returned with an increase in SCPK of skeletal muscle origin (see figure). Repeat EMG showed changes as described above in the left quadriceps and also intermittent fibrillation in the left tibialis anterior at rest. Appearances in the left deltoid remained normal.

Serum creatine phosphokinase (SCPK) during and after propranolol.

Biopsy of the quadriceps muscle showed normal architecture with no evidence of inflammation, cell atrophy, hypertrophy, or necrosis. Histochemical studies showed normal distribution of type I and II fibres with only minor variation in type I fibre size.

Propranolol was again discontinued with rapid return of normal muscle power. Six months later symptoms had not recurred. Moderate angina of effort was satisfactorily controlled with nitrites and perhexilene. The ESR remained raised at 30-60 mm in the first hour.

Comment

There appears to be a clear relationship between these two beta-blockers and proximal myopathy. The possibility of an underlying polymyositis remains despite the biopsy and is supported by the raised ESR, but the detrimental effect of beta-blockade remains.

Propranolol treatment has precipitated myotonia² and raised SCPK concentrations in a patient with probable occult dystrophic myotonia.³ Neither these nor the effects in our patient can be readily explained on the basis of the known effects of propranolol as a beta-receptor antagonist without intrinsic sympathomimetic activity and as a membrane stabiliser.⁴ Phosphorylase activation and muscle glycogen breakdown may be impaired after beta-blockade from reduced intra-