SHORT REPORTS

Acute leukaemia after four years of melphalan treatment for melanoma

Numerous reports of the development of acute leukaemia as a complition of haematological malignancy, in particular of multiple myeloma, have recently been reviewed,[1] but we have found no mention of acute leukaemia after the successful treatment of malignant melanoma without prior radiotherapy.

Case Report

A 44-year-old woman was referred to this centre with a history of two month's intermittent epistaxis and haematuria and five month's weakness and bruising. In 1966 a melanoma had been excised from her left calf, followed by a block dissection of the groin one year later for metastatic melanoma. Over the next four years she remained well on intermittent maintenance courses of melphalan 1-2 mg daily to a total of about 1500 mg.

On examination she was pale and had widespread ecchymoses and an enlarged liver and spleen (4 cm and 3 cm below the costal margin respectively).

Investigations showed haemoglobin 8·9 g/dl; mean corpuscular volume (MCV) 85 fl; mean corpuscular haemoglobin (MCH) 23·3 pg; leucocyte count $13{\cdot}1\times10^9$/l (neutrophils $3{\cdot}1\times10^9$/l); blast cells $8{\cdot}2\times10^9$/l; platelet count 15×10^9/l; plasma calcium 2·4 mmol/l (9·6 mg/100 ml); albumin 2·9 g/l; blood urea 6·6 mmol/l (40 mg/100 ml); urate 9·35 mmol/l (5·9 mg/100 ml). Cultures of blood and urine were sterile but there was heavy proteinuria and macroscopic haematuria. Bone marrow aspirate consisted largely of myeloblasts, some of which contained azurophilic granules. The Sudan black stain was strongly positive.

Treatment was started with one dose of 100 mg daunorubicin intravenously, 150 mg cytarabine daily for five days and allopurinol 100 mg three times a day. She was transfused with whole blood and platelet concentrates. A pyrexia of 39°C was unaffected by 80 mg gentamicin, 150 mg clindamycin, and 500 mg cephalexin three times a day, and 500 mg cloxacillin four times a day. Acute renal failure supervened, the blood urea rising to 80·5 mmol/l (500 mg/100 ml) and the patient died six days after admission. Necropsy showed widespread haemorrhages. There were gross submucosal haemorrhages producing obstruction in both ureters, which appears to have been the cause of the renal failure. Diffuse leukaemic infiltrates replaced bone marrow and were also found in lymph nodes, heart, lung, liver, spleen, and kidneys. All these tissues contained multinucleate giant cells which resembled megakaryocytes and showed considerable mitotic activity, coarse nuclear lobulation, and high nucleocytoplasmic ratio, but they did not appear to be forming platelets. Histochemical stains were unsuccessful due to the age of the post-mortem cytological specimens.

Discussion

There is no doubt that the clinical and haematological syndrome was of acute myeloblastic leukaemia, though the origin of the multinucleate cells remains unclear. They were seen only in post-mortem specimens and could not be found in the pretreatment aspirate. Possibly they were osteoclasts, an atypical cytological reaction to chemotherapy or megakaryocytes, whose proliferation is known to occur as part of acute myeloblastic leukaemia.[2]

The occurrence of dual malignancies has been long recognised. In a recent review of multiple myeloma terminating in acute leukaemia Rosner[1] points out that acute leukaemia rarely develops in solid tumours occurring outside the lymphoproliferative and myeloproliferative groups not treated with prior radiotherapy.

There are now 56 well-documented cases of acute leukaemia occurring in myeloma.[1 3] All were myeloblastic or myelomonocytic and 50 out of the 56 patients had received prolonged therapy with an alkylating agent—either melphalan or cyclophosphamide.

Whether the acute leukaemia is part of the natural history of the myeloma or is directly due to prolonged chemotherapy is controversial. The occurrence of this case treated with an agent commonly used in the treatment of myeloma adds weight to the concept that this complication is related to the chemotherapy rather than the nature of the primary neoplasm.

We thank Dr R Seidelin, Mr D S Adams, and Professor G P McNicol for permission to report this case.

[1] Rosner, F, Grunwald, H, *American Journal of Medicine*, 1974, **57**, 927.
[2] Gelin, G, Wasserman, L R, *Sang; Biologie et Pathologie*, 1959, **30**, 829.
[3] Karchmer, R K, *et al*, *Cancer*, 1974, **33**, 1103.

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Recovery after "lethal" quantity of paint remover

We wish to report a case in which recovery took place after the ingestion of an apparently lethal quantity of Nitromors paint remover. The active ingredient in this preparation is methylene chloride, an halogenated hydrocarbon which has been widely used as an industrial solvent. It also contains methanol, cellulose acetate, triethanolamine, paraffin wax, and detergent. There are reports concerning the toxic effects of inhalation of methylene chloride vapour. These are pulmonary oedema[1] and central nervous system depression.[2] Dykes[3] reviewed the toxic effects of ingestion of several halogenated hydrocarbons, hepatic damage and acute renal failure being the most common adverse effects.

Case report

A 38-year-old man ingested between one and two pints of Nitromors in a suicide attempt. One and a half hours afterwards he was deeply unconscious and unresponsive to painful stimuli. His pupils were equal and reactive but tendon jerks were depressed; plantar response was absent. Areas of skin where liquid had spilled from his mouth were erythematous and blistered. At intubation the vocal cords and epiglottis were oedematous and ulcerated. There was tachypnoea, but the pulse and blood pressure were well maintained. An obvious feature was gross haemoglobinuria. The results of initial investigations showed a metabolic acidosis. A diuresis was initiated to prevent acute renal damage as a result of the intravascular haemolysis which was clearly occurring. Normal saline alternating with 5% dextrose solution with added potassium was infused at a rate of 1 litre per hour and 80-mg doses of frusemide were given. Urine output and central venous pressure were carefully monitored. Hydrocortisone 200 mg every 4 hours was administered. During the first 24 hours of treatment the patient passed 18 litres of urine and the haemoglobinuria gradually ceased. The levels of plasma electrolytes remained satisfactory throughout and the blood urea rose to a maximum of 10·5 mmol/l (63 mg/100 ml). The patient had regained consciousness 14 hours after the initial event, and it soon became clear that he had suffered no detectable cerebral damage. His recovery was hindered by episodes of gastrointestinal haemorrhage requiring blood transfusion and severe chest infection consequent on a disturbance of the swallowing mechanism and requiring tracheostomy. Barium meal examinations showed ulceration of the duodenojejunal junction and first 30 cm of the jejunum accompanied by luminal narrowing. Six months after the event these ulcers were shown to have developed into diverticula. Hepatic damage was not a feature of the illness, and there was no evidence of any toxic effect on the heart. Creatinine clearance after recovery was 101 ml/min.

Discussion

On admission to hospital the patient's condition was grave. His illness was characterised by deep unconsciousness, acidosis, and intravascular haemolysis. Recovery seemed unlikely and this opinion was confirmed by reference to one of the United Kingdom poisons

information centres. Nevertheless, the onset of recovery was rapid. The important late effect of the poisoning was the development of jejunal ulceration and diverticula formation, and hence the formation of strictures remains a real possibility. The induction of a diuresis seemed to play a particularly important part in preventing acute renal damage.

The prognosis in methylene chloride poisoning then is far from hopeless. With scrupulous intensive care recovery may be anticipated.

We thank Dr H M Leather for permission to report on a patient under his care.

[1] Hughes, J P, *Journal of the American Medical Association*, 1954, **156**, 234.
[2] Stewart, R D, *American Journal of Nursing*, 1967, **67**, 85.
[3] Dykes, M H M, *International Anesthesiology Clinics*, 1970, 357.

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Rosacea and migraine

An association between certain clinical conditions may remain unrecognised for years. There are many ways with which the skin and other systems are linked. Examination of the skin may help the clinician in assessing systemic disease: many patients with dermatitis herpetiformis have intestinal malabsorption and patients with vitiligo show an increase of organ-specific autoimmune diseases.[1] During our investigation into a new approach to the treatment of facial flushing in rosacea we found three consecutive patients who not only had rosacea but also migraine. This stimulated us to attempt to establish the association between the two conditions.

Methods and results

One hundred and thirty-seven patients with rosacea and 161 controls were asked whether they had migraine. The control group were predominantly fit hospital personnel; a few had either viral warts, basal cell carcinoma, or gravitational eczema. The definition of migraine was episodic vascular headache with at least two of the following features: unilateral headache; associated nausea or vomiting; visual aura; family history of migraine; and past history of bilious attacks.[2] The patients with rosacea were mainly women, 89 women and 48 men, aged 20-87 (mean 46·0±1·3 years). The controls were not significantly different: 114 women and 47 men, aged 18-80 (mean 42·0±3·1 years).

Sixty of the 137 patients with rosacea (44%) had suffered from migraine; this contrasted with 21 of the 161 controls (13·1%). There was thus a significant association ($P<0.0005$) between migraine and rosacea (see table). Twenty-nine of the controls had intermittent facial flushing with no other features of rosacea and 16 of these had migraine. Exclusion of these controls further increased the significance of the association between rosacea and migraine.

Incidence of migraine

	Rosacea	Controls	Significance
With migraine	60 (44%)	21 (13%)	$P<0.0005$
No migraine	77	140	
Total	137	161	

Discussion

We know of no report in which the association between migraine and rosacea has been described. Crawford[3] reported a 29-year-old woman with migraine who had an unusual eruption and flushing of the right leg, occurring independently of headaches, possibly representing a cutaneous equivalent. Facial migraine—which consists of episodic facial neuralgia, flushing, and reddening of the skin and lachrymation—usually occurs in middle-aged women with a past history of migraine[4]; the presence or absence of rosacea has not been reported in these patients.

The incidence of migraine in our controls is higher than that in other control series.[5] Thus our observation that 44% of patients with rosacea suffered from migraine is significant when compared with not only our own but also other control series. The association between rosacea and migraine is not surprising, since both are associated with abnormal vascular reactivity, and both are aggravated by stress. Although migraine tends to occur in younger patients than rosacea, this lack of a temporal relationship does not make the association less likely because it is also seen in other conditions such as eczema and asthma.

The association between rosacea and migraine has several implications. The presence of rosacea may help clinicians in diagnosing migraine variants. Oral contraceptives may significantly increase the frequency and severity of headaches in migrainous women, and hence should patients with rosacea avoid them? Some patients with migraine develop their attacks after eating cheese or chocolate because of failure to metabolise such compounds as tyramine or phenylethylamine. Do such factors aggravate rosaceous flushing? Study of the facial blood vessels in rosacea may help to understand better the physiological and biochemical abnormalities of the intracranial, extracerebral blood vessels of migraine. Conversely, could drugs prescribed for migraine help facial flushing in rosacea? In low doses clonidine reduces facial flushing and helps migraine at the menopause, and our preliminary investigations show that clonidine probably helps in reducing the facial erythema and flushing of rosacea.

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[1] Cunliffe, W J, *et al*, *British Journal of Dermatology*, 1968, **80**, 135.
[2] World Federation of Neurology Research Group on Migraine and Headache in *Background to Migraine*, p 181. London, Heinemann, 1969.
[3] Crawford, P F, *British Journal of Dermatology*, 1961, **73**, 419.
[4] McArdle, J, in *Background to Migraine*. London, Heinemann, 1969.
[5] Brewis, M, *et al*, *Acta Neurologica Scandinavica*, 1966. **42**, Suppl 24.

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Intestinal obstruction complicating orphenadrine treatment

Gastrointestinal symptoms associated with drugs are common in clinical practice and may take several forms. A reduction in bowel motility with consequent constipation may be caused by drugs with an atropine-like action, including anti-Parkinsonian agents. Parkinsonism itself may cause constipation,[1] and treatment with a constipation-provoking agent might be expected to produce troublesome symptoms. Severe constipation is perhaps less common than would be predicted but can occasionally be severe enough to cause intestinal obstruction.[2] A case is presented here in which orphenadrine appears to have precipitated such an event, an association not previously reported.

Case report

The patient was a 77-year-old man who was diagnosed as suffering from Parkinsonism in 1972, when immobile facies, bradykinesia, and a typical tremor were noted. Orphenadrine was started at a dose of 50 mg three times a day, which improved his symptoms. In 1973 an episode of urinary retention was treated by transurethral resection of the prostate, with complete