SHORT REPORTS

Bone marrow necrosis after treatment with sulphasalazine

We describe a patient in whom extensive necrosis of the bone marrow occurred while taking sulphasalazine. Unlike most cases of extensive bone marrow necrosis he made a full recovery.

Case history

A 22 year old Jamaican man diagnosed as suffering from ulcerative proctitis was prescribed sulphasalazine 1 g thrice daily and prednisolone enemas. His blood count at the time was normal. Three weeks later he presented to his family practitioner complaining of headache, sore throat, and facial swelling; amoxycillin was prescribed. His condition continued to deteriorate and a generalised rash developed. He was admitted to hospital five days later. Examination showed facial swelling, generalised tender lymphadenopathy, an exfoliative dermatitis, and a tender, enlarged liver. Haemoglobin concentration was 12.6 g/dl, white cell count $12.6 \times 10^9/l$, and platelet count $224 \times 10^9/l$. The differential white cell count showed only 12% neutrophils and 88% lymphocytes, some of which were atypical. Result of the Paul-Bunnell test was negative and remained so throughout. All drugs except the prednisolone enemas were stopped.

The patient took his own discharge but his symptoms worsened and he presented again, this time to St Thomas's Hospital. Results of examination, in addition to the above, included fever and severe pharyngitis. Haemoglobin concentration had fallen to 9.8 g/dl with reticulocytopenia, platelet count to $146 \times 10^9/l$, and white cell count to $3.3 \times 10^9/l$. The differential white cell count showed no neutrophils, 15% monocytes, 4% atypical mononuclear cells, and the remainder lymphocytes. Haemoglobin electrophoresis showed a normal pattern. A bone marrow aspirate contained fragments that stained abnormally, lacking cellular details and surrounded by clumps of platelets. Residual haemopoietic cells were normal morphologically but an excess of atypical lymphoid cells were present. The marrow spaces of a trephine biopsy sample consisted largely of necrotic tissue, and small areas of residual haemopoietic tissue were infiltrated by lymphocytes and plasma cells (figure).

Trephine biopsy specimen showing normal bone trabeculae in upper half of field and complete marrow necrosis in lower half. Elastic van Gieson $\times 100$ (original magnification).

Staphylococcus aureus was cultured from an oropharyngeal ulcer and treatment with flucloxacillin begun. A repeat bone marrow and trephine biopsy three days later, from different sites, confirmed bone marrow necrosis at each site. Lymph node biopsy showed sinus histiocytosis. Ferrokinetic studies further to assess the extent of bone marrow necrosis could not be performed as the patient was receiving reverse barrier nursing.

Absolute neutropenia persisted for five days, recovery being preceded by a monocytosis. A blood transfusion was required to maintain his haemoglobin value, and the platelet count fell to $58 \times 10^9/l$. The platelet count took the longest to return to normal, but complete recovery occurred and he subsequently remained well.

Comment

Sulphasalazine is effective against ulcerative colitis but the incidence of side effects is reportedly as high as 20%.¹ In the colon sulphasalazine is broken down to sulphapyridine and 5-aminosalicylic acid. Sulphapyridine is absorbed and appears to be responsible for many of the side effects reported. These include toxic erythema, hepatitis, Heinz body haemolytic anaemia, megaloblastic anaemia, and pancytopenia. Patients who are slow acetylators tend to have high plasma sulphapyridine concentrations and to be most at risk from sulphasalazine toxicity.

The occurrence of bone marrow necrosis in an otherwise fit young man shortly after beginning a course of sulphasalazine and in the presence of other problems associated with sulphasalazine (hepatitis and exfoliative dermatitis) make it likely that sensitivity to sulphasalazine was responsible for this problem. Bone marrow necrosis is an uncommon haematological finding but was once noted after treatment with another sulphonamide, sulphathiazole.² It is also a recognised complication of sepsis,³ but in our patient the neutrophil count was already falling before he became feverish. In other cases of sulphasalazine induced cytopenias the patients lacked precursor cells of one or more of the normal haemopoietic cell lines.³⁻⁵ Infiltration of the bone marrow by lymphocytes and plasma cells has been noted.⁵

Extensive bone marrow necrosis is usually associated with a high mortality and is often recognised only at necropsy.² Recovery in our patient was fortunately complete.

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Diabetic thoracic polyradiculopathy presenting as abdominal swelling

Many workers have reported abdominal pain and paraesthesiae as manifestations of diabetic neuropathies.¹⁻⁵ Such truncal neuropathies are usually characterised by an absence of clinical features of motor abnormality,²⁻⁴ the coexistence of peripheral and autonomic neuropathies,¹⁻⁵ and a good prognosis for recovery.¹⁻⁵ We describe a patient with type 2 diabetes and truncal polyradiculopathy who presented with an abdominal swelling but no other symptoms of peripheral or autonomic neuropathy.

Case report

A 71 year old white man with a 15 year history of type 2 (non insulin dependent) diabetes mellitus was referred for investigation of a right sided abdominal swelling. Six weeks previously he had noticed a bulge in the right side of his abdomen, which became more prominent when he coughed or tried to sit up from the supine position. There was no localised pain, though a

few days later he noticed an area of numbness and paraesthesia below the right rib cage. These symptoms were more pronounced at night. He was otherwise well, though four years previously he had undergone an operation for a left renal stone. He was taking lente insulin 35 units and soluble insulin 10 units each morning, metoprolol for hypertension, and disopyramide and digoxin for a cardiac arrhythmia. He had been admitted to a district general hospital for investigations including ultrasound examination and computed tomography of the abdomen, barium enema, barium meal examination, and intravenous urography. None had shown any abnormality.

On examination he was overweight with a pulse of 60 beats/minute, atrial fibrillation, and blood pressure 160/76 mm Hg without postural hypotension. Fundal examination was normal. There was a definite right sided abdominal swelling (figure) with weakness of the right sided abdominal muscles, though no masses were palpable. Neurological examination showed an area of hyperesthesia with decreased touch in the right T6 and T7 dermatomes anterolaterally. Abdominal reflexes were absent. Sweating was normal in the hands and feet.

Right sided abdominal swelling caused by diabetic truncal polyradiculopathy.

A random blood glucose concentration was 12.3 mmol/l (221 mg/100 ml) and glycosylated haemoglobin 8% (range in non-diabetics 5-7%). Urea and electrolytes, serum B₁₂, and results of liver function tests and urine analysis were normal. A Venereal Disease Research Laboratory test gave a negative result. Nerve conduction studies in the peroneal nerve were normal, though the sural nerve showed evidence of peripheral sensory neuropathy. Electromyography showed fibrillations and positive waves, an increase in the proportion of polyphasic motor unit potentials, and decreased interference patterns in the rectus abdominis innervated by T6-T12 on the right. Similar changes were seen in the right external oblique and thoracic paraspinal muscles. All studies on the left side gave normal results.

Thoracic polyradiculopathy was diagnosed, and the sensory symptoms resolved over two months. No change was seen in the abdominal swelling.

Comment

This patient presented with asymmetrical motor abnormalities in the abdominal muscles and mild and transient sensory symptoms affecting the right T6 and T7 dermatomes. He had electrophysiological evidence of only a mild sensory peripheral neuropathy, and, furthermore, there was no postural hypotension or clinical evidence of decreased sweating in the feet to suggest autonomic neuropathy. We could not perform standard heart rate dependent tests of autonomic function as the patient was in atrial fibrillation. Kikta *et al* reported on one patient with thoracic polyradiculopathy who was found to have abdominal swelling, though the patient was not diabetic and had an eight month history of abdominal pain. The diagnosis was confirmed by electromyography, and although a glucose tolerance test did not confirm diabetes it was suggestive of impaired glucose tolerance,

which may have contributed to the aetiology of the polyradiculopathy.⁵

Truncal polyradiculopathy should be considered in diabetic patients with unexplained abdominal pain or areas of muscle weakness. This case shows that such patients may present with no other neuro-pathic manifestations. If the diagnosis is considered early many unnecessary investigations might be avoided. Electromyography is the most helpful investigation in diagnosing this condition.^{3 5}

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Accumulation of midazolam after repeated dosage in patients receiving mechanical ventilation in an intensive care unit

Midazolam hydrochloride (Hypnovel) is a recently introduced imidazobenzodiazepine. Its potency and rapid onset and short duration of action after a single intravenous bolus make it an ideal agent for premedication or induction in anaesthesia for short surgical, endoscopic, and dental procedures. These same pharmacokinetic features would seem to make the drug an ideal sedative for patients receiving mechanical ventilation. A chance observation of an unusually high plasma midazolam concentration (750 µg/l) in a seriously ill 75 year old needing prolonged intermittent positive pressure ventilation for unexplained respiratory depression, however, led us to examine the problem in three other patients with a similar clinical course.

Present series and results

Samples of serum (after stopping treatment with midazolam) were analysed retrospectively by a sensitive and specific gas-liquid chromatographic method developed at the poisons unit (unpublished data). The terminal half lives were determined by log linear least squares regression analysis.

The figure shows the serial plasma midazolam concentrations in the three patients.

Case 1—A 68 year old man (weight 65 kg) with chronic renal failure, hypertension, and angina developed cardiac failure and pneumonia after a myocardial infarction. Respiratory and cardiac failure necessitated intermittent positive pressure ventilation and inotropic support as well as daily haemofiltration. Sedation was achieved with intravenous midazolam (total daily dosage 5 mg, 40 mg, 40 mg, 70 mg, 45 mg, 5 mg) and papaveretum. He regained full consciousness six days after the last dose of midazolam and eventually recovered.

Case 2—A 46 month old girl (3.6 kg) required intermittent positive pressure ventilation after total correction of her tetralogy of Fallot. She was sedated with intravenous midazolam (total daily dosage 11.5 mg, 32.5 mg, 26.5 mg, 8 mg), papaveretum, and chloral hydrate. She regained consciousness 48 hours after the last dose of midazolam, adequate sedation then being maintained with papaveretum and chloral hydrate at the same dosage. Abnormal coagulation values were ascribed to mild hepatic dysfunction secondary to cardiac failure.

Case 3—A 56 year old man (100 kg) with brittle asthma suffered an acute exacerbation requiring intermittent positive pressure ventilation after failure