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Red cell antibodies and autoimmune haemolysis after treatment with azapropazone

Non-steroidal anti-inflammatory drugs are prescribed widely to the eight million people who consult their general practitioners every year with rheumatic complaints. Haematological side effects are well recognised as anaemia related to gastrointestinal blood loss, aplastic anaemia and agranulocytosis in association with phenylbutazone,[1] and autoimmune haemolysis in relation to treatment with mefenamic acid.[2] Autoimmune haemolysis has also been reported in association with ibuprofen[3] and naproxen.[4]

Azapropazone, a relatively new pyrazolon, is structurally similar to phenylbutazone but is not associated with blood disorders other than anaemia due to gastrointestinal blood loss.[1] We report on four patients with positive direct antiglobulin test results, of whom two showed frank haemolysis after treatment with azapropazone.

Case report

Case 1—A 74 year old woman presented with anaemia. She had osteoarthritis and had been taking azapropazone for four years. Results of laboratory investigations were: haemoglobin concentration 74 g/l, white cell count 6×10^9/l, platelet count 267×10^9/l, reticulocytes 18%, and erythrocyte sedimentation rate 100 mm in first hour. Spherocytes were seen in the blood film. Bilirubin concentration was 79 μmol/l (4·6 mg/100 ml) (unconjugated 60 μmol/l; 3·5 mg/100 ml) and lactate dehydrogenase activity 1333 U/l (normal 240-525 U/l). The direct antiglobulin test result was positive with an IgG coating only. Free antibodies were found in the serum, but no red cell specificity was identified. Antinuclear factor was detected at 1/256, but tests for deoxyribonucleic acid antibodies and rheumatoid factor gave negative results. Azapropazone was stopped and prednisolone 60 mg daily instituted. The haemoglobin concentration started to rise at day 7, and prednisolone was stopped. On day 21 the haemoglobin concentration was 122 g/l and the reticulocyte count 3%. At six months haemoglobin was 143 g/l with the direct antiglobulin test still giving a strongly positive result.

Case 2—A 73 year old woman was referred to the haematology clinic with anaemia. She had osteoarthritis and had been taking azapropazone for 18 months. A direct antiglobulin test had given a negative result four years previously. Haemoglobin concentration was 108 g/l and reticulocyte count 7%, and spherocytes were noted in the blood film. The direct antiglobulin test was positive with an IgG and IgM coating without complement. Free anti-e was detected in the serum (Rh genotype R_1r CDe/cde). Azapropazone was stopped. The result of the direct antiglobulin test remained positive at six weeks, but the haemoglobin concentration had risen to 132 g/l.

We performed the direct antiglobulin test on a further eight patients taking azapropazone. These eight patients were selected at random. Four were identified by the pharmacy department as hospital inpatients taking azapropazone, three were identified by information on the blood count report form completed by their general practitioners, and one was attending the haematology department. In two patients the test result was positive with no evidence of haemolysis.

Case 3—A 71 year old woman who had been taking azapropazone for two years yielded a positive direct antiglobulin test result with an IgG coating. Complement coating was not present and there was no evidence of haemolysis. The drug was stopped and a month later the test result was negative.

Case 4—A 68 year old man with a three year history of chronic myelomonocytic leukaemia was given azapropazone by his general practitioner because of joint pains. His direct antiglobulin test result had been negative six months previously. The result became positive with an IgG coating within three months of starting treatment. Azapropazone was stopped but at one month the test result remained positive.

The other six patients had negative direct antiglobulin test results. No history was available for three of these patients, in whom the duration of treatment with azapropazone was unknown. The other three patients had been taking azapropazone for more than one year.

Comment

The Committee on the Safety of Medicines has been notified of six cases of Coombs positive haemolytic anaemia with azapropazone between January 1984 and March 1985, and the manufacturers of the drug have had reports of six cases of autoimmune haemolysis over 10 years. Our four cases strongly implicate azapropazone as the causal agent for the development of red cell autoantibodies, which in one instance was shown to have anti-e specificity. If the eight patients selected at random in this limited study were representative of all patients taking azapropazone then a quarter may be expected to develop a positive direct antiglobulin test result. This proportion is similar to that found with methyldopa[5] but cannot be used to predict the incidence of autoimmune haemolysis.

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Phaeochromocytoma in the elderly: a poorly recognised entity?

Phaeochromocytoma is an uncommon disease in the elderly, with less than 3% of reported cases occurring in patients over 70 years of age.[1] Malignant phaeochromocytoma has been described in this age group in only one postmortem case report 30 years ago.[2] We report on four elderly patients with phaeochromocytoma seen over a year, two of whom had malignant tumours.

Case reports

Case 1—A 74 year old woman with a five year history of mild hypertension presented with nausea and vomiting. Severe labile hypertension was noted after treatment with β blockers was started. Urinary adrenaline and dopamine concentrations were considerably raised, and computed tomography showed a left sided adrenal mass. At operation a 12 cm tumour was found with local venous invasion. Postoperatively she suffered persistent hypertension and raised excretion of urinary catecholamines, and an iodine-131-metaiodobenzylguanidine scan showed multiple skeletal metastases. Over the following months she became progressively more cachectic and died.

Case 2—A 72 year old woman with neurofibromatosis and a 15 year history of mild hypertension underwent computed tomography of the abdomen for investigation of an abdominal mass, which showed a pancreatic cyst and a left sided adrenal mass. Urinary adrenaline concentrations were slightly raised. Six months later, during surgery for removal of a sigmoid carcinoma, she developed

Clinical details of patients

Case No	Sex	Age (years)	Symptoms	Urinary catecholamine concentrations (nmol/day)*			Findings on computed tomography	Findings of ^{131}I-metaiodobenzylguanidine scanning	Outcome
				Adrenaline	Noradrenaline	Dopamine			
1	F	81	Anorexia, nausea, labile hypertension, syncope, palpitations	405	62	1862	Left sided adrenal mass 10 cm in diameter	Left sided adrenal mass	Normotensive, well
2	F	74	Persistent hypertension, flushes and sweating, nausea, diarrhoea, palpitations	520	1175	332	Right sided adrenal mass 2·8 cm in diameter	Right sided adrenal mass	Normotensive, well
3	F	75	Persistent hypertension, nausea and vomiting, palpitations, sweating	433	350	11000	Left sided adrenal mass 5×7 cm	Multiple skeletal metastases†	Death
4	F	72	Neurofibromatosis, hypertension	110 (279)‡	100 (2185)‡	492 (2370)‡	Left sided adrenal mass 5·5 cm in diameter and pseudocyst of pancreas	Left sided adrenal mass. Repeat scan showed skeletal and hepatic metastases	Refused to have operation, death

*Catecholamine concentrations were measured by reverse phase liquid chromatography. Normal ranges: adrenaline 5-80 nmol/day, noradrenaline 40-780 nmol/day, dopamine 200-3500 nmol/day.
†Scan performed after patient underwent left sided adrenalectomy.
‡Repeat measurements.
Conversion: SI to traditional units—Adrenaline: 1 nmol/day≈0·18 μg/day. Noradrenaline: 1 nmol/day≈0·17 μg/day. Dopamine: 1 nmol/day≈0·15 μg/day.

cardiac arrhythmias and severe labile hypertension. Postoperative ^{131}I-metaiodobenzylguanidine scanning confirmed that the adrenal tumour was a phaeochromocytoma. Measurements taken a year later showed that urinary catecholamine concentrations were raised, and a ^{131}I-metaiodobenzylguanidine scan showed widespread bony and hepatic metastases. She became progressively more cachectic over the next month and died. At necropsy disseminated malignant phaeochromocytoma was confirmed histologically.

Case 3—An 81 year old woman with a two year history of poorly controlled hypertension and recurrent syncope presented with episodes of central abdominal pain associated with palpitations. A small thyroid nodule was noted, and thyrotoxicosis was confirmed biochemically. Urinary adrenaline excretion was raised, and both computed tomography and ^{131}I-metaiodobenzylguanidine scanning confirmed a left adrenal phaeochromocytoma. At operation a 9·5 cm brown bosselated tumour was removed. Postoperatively she remained normotensive and free of symptoms, but hyperthyroidism recurred when carbimazole treatment was stopped.

Case 4—A 74 year old woman with a history of four years of hypertension and a previous myocardial infarct presented with severe back pain. Computed tomography showed a right adrenal mass. During the three months before admission she had suffered two syncopal attacks and complained of flushing, sweating, and nausea. Urinary adrenaline and noradrenaline concentrations were raised, and a ^{131}I-metaiodobenzylguanidine scan showed a right adrenal tumour. A 3·5 cm encapsulated golden brown tumour was removed at operation. She was normotensive when discharged.

Comment

This is the first antemortem description of patients aged over 70 with malignant phaeochromocytoma. All four patients were women, all had hypersecretion of adrenaline, and one of the malignant tumours secreted excess dopamine.

The incidence of phaeochromocytoma in the elderly is reported to be much lower than that in younger patients.[1] A necropsy study that reviewed 54 tumours found, however, that 12 patients with benign tumours were over 68 years old, indicating a higher incidence in the elderly than has been suggested.[3] In nine of the 12 patients the clinical diagnosis was unsuspected. A contributory factor to the rarity of the antemortem diagnosis of phaeochromocytomas in the elderly may be a decrease in sensitivity to catecholamines with age.[4] Another possibility is pronounced variability in catecholamine secretion (see case 4 in table).

Surgery has resulted in cure in over 90% of patients with phaeochromocytoma,[5] but this has been based on populations in which the mean age ranged from 45 to 50. The excellent outcome in cases 1 and 2, despite the patients' ages, suggests that phaeochromocytoma is a potentially remediable condition in the elderly.

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Pyrexia of unknown origin and colorectal carcinoma

Pyrexia of unknown origin is defined as a fever greater than 38·3°C of more than three weeks' duration that remains unexplained despite one week's observation of the patient in hospital.[1] Pyrexia is often associated with occult malignant disease,[2] most commonly of the reticuloendothelial system, lung, pancreas, kidney, and liver, though many other malignancies have been reported.

Patients with colorectal cancer rarely present with pyrexia of unknown origin without associated gastrointestinal symptoms. We report three such cases.

Case reports

Case 1—A 63 year old man presented with a six week history of intermittent fever and malaise. He had experienced sudden bouts of fever of up to 39°C with rigors that lasted for several hours. The fevers were occasionally associated with the passage of stool. Physical examination, including rectal examination, yielded normal results, as did all the tests routinely performed in patients with pyrexia of unknown origin, including a barium enema. Blood cultures grew *Escherichia coli*. As all the tests yielded negative results the patient was referred for laparotomy, at which a mobile Dukes's B carcinoma of the rectum was found and an anterior resection performed. The patient recovered and suffered no further episodes of fever.

Case 2—A 60 year old woman presented with a six month history of intermittent attacks of fever and rigors lasting for up to two hours. She underwent thorough medical investigation in two hospitals. All tests, including a barium enema, yielded normal results. Nine months after the onset of symptoms a transient swelling was noted in the right iliac fossa. Tests for faecal occult bloods yielded positive results, and a repeat barium enema showed a filling defect in the caecum. Laparotomy showed a mobile Dukes's B carcinoma of the caecum. A right hemicolectomy was performed, and the patient recovered and remained well for 12 years after surgery.

Case 3—A 68 year old man presented with a six month history of intermittent feverish episodes associated with malaise, rigors, and headaches. The attacks lasted about six hours, and his temperature rose to 39°C. General physical