Summary
We present the case of a 77-year-old woman who initially presented with pyrexia of unknown origin, anaemia and mild renal impairment. When her omeprazole was stopped she improved rapidly. When omeprazole was re-started she developed fever and acute renal failure, which again settled quickly on discontinuation of omeprazole. This case demonstrates how drugs can cause severe multisystem disorders that may appear to be infective or inflammatory.

Keywords: omeprazole; acute renal failure; anaemia; pyrexia; adverse drug reaction

A 77-year-old woman initially presented with a one-week history of malaise, nausea, rigors and sweats with weight loss of 2.5 kg. She had non-pleuritic left-sided lower back pain and non-productive cough for two days. Oral cefuroxime (250 mg bid) had been started before admission without improvement. She had had malaria and possible pyelonephritis in Africa. She was taking omeprazole 20 mg daily, prescribed empirically for dyspepsia for two months. She had never smoked.

On admission she was pyrexial at 38.5°C and tachypnoeic. No other abnormality was found on clinical examination. The initial full blood count was normal with haemoglobin 12.0 g/dl and white cell count 9.9 × 10^9/l (eosinophils 2.6%). Renal function was impaired with serum creatinine 202 μmol/l. Other biochemistry was normal. The erythrocyte sedimentation rate (ESR) was markedly raised at 96 mm/h. A midstream specimen of urine sent before commencing antibiotics was normal but a repeat specimen demonstrated sterile pyuria. Blood cultures were negative at seven days. A chest X-ray was normal.

Investigations to identify the cause of the pyrexia, including further cultures of blood, urine and stool, specimens for acid-fast bacilli, serology for Legionella and other atypical infections, Mantoux-testing and autoantibody screen, were negative. Ultrasound examination of the abdomen and computed tomography of the chest and abdomen were normal on two occasions, one month apart, as was echocardiography. Lumbar spine X-rays and skeletal scintigraphy were normal. There was no improvement after seven days treatment with intravenous cefuroxime 750 mg eight-hourly.

Bone marrow biopsy and trephine demonstrated profound hypocellularity. There were reactive aggregates of B cell lymphocytes. Myelopoiesis and erythropoiesis were hypoactive with reduced numbers of megakaryocytes. There was no evidence of granulomatous or malignant disease. Haemolysis was excluded by a negative direct Coombs test and normal bilirubin.

The acute phase response, as shown by a raised ESR, a falling haemoglobin and a persistently raised creatinine, continued (figure). With no evidence of infective, autoimmune, haematological or malignant aetiology after 6 weeks of negative investigations, omeprazole was stopped. The temperature settled within 48 hours and our patient felt well enough to leave hospital. Over the subsequent month, the ESR fell to 26 mm/h and haemoglobin and serum creatinine improved to 11.0 g/dl and 123 μmol/l, respectively.

Four weeks after discharge, the patient restarted omeprazole for dyspepsia. Two weeks later, she felt unwell. The ESR was 66 mm/h with serum creatinine 684 μmol/l and haemoglobin 10.3 g/dl. Urine microscopy demonstrated sterile pyuria with white cell casts. The omeprazole was stopped once more and she was admitted with acute renal failure. A renal biopsy showed normal glomeruli with a heavy interstitial infiltrate and tubular flattening. The infiltrate consisted mainly of lymphocytes and plasma cells with occasional eosinophils. She was treated with prednisolone 30 mg daily, reduced over 6 weeks. Serum creatinine began to improve and after 14 days had fallen to 141 μmol/l, with an accompanying reduction in ESR and rise in haemoglobin.

Discussion
There have been a number of cases of acute interstitial nephritis and renal failure attributed to omeprazole. Symptoms can include fever, nausea, malaise, weight loss, rigors, night sweats and anorexia. An erythematosus macular rash may be present. Such features may develop following exposure to omeprazole of a few weeks to 6 months duration. There is azotemia and in some cases eosinophilia. p-ANCA was weakly positive in one case report. Urinalysis may demonstrate proteinuria and haematuria. There is often a sterile pyuria with white cell casts and eosinophiluria. Renal histology shows the typical features of acute interstitial nephritis with an infiltrate of eosinophils in some cases.
Adverse reaction to omeprazole

Figure Changes in ESR, haemoglobin, and serum creatinine on exposure to omeprazole

Unintentional rechallenge has been reported in three cases. In each of these reports, as in our own case, acute renal failure developed more rapidly on re-exposure to omeprazole (within 2 to 14 days) than on initial exposure (2 to 12 weeks). On re-exposure, the rise in serum creatinine was similar to or greater than that at primary exposure. In the third case omeprazole was stopped after only two further doses. The pattern of more rapid and more severe toxicity on re-exposure is suggestive of an immune-mediated reaction following initial sensitisation.

There are two reported cases of blood dyscrasias secondary to omeprazole: one patient developed haemolytic anaemia, and one patient developed agranulocytosis and anaemia with myeloid hypoplasia in the presence of normal erythroid maturation and normal numbers of megakaryocytes. Omeprazole-induced antibodies were postulated to be the mechanism in this case. Mild anaemia has been reported in two other cases. Our patient was anaemic with hypoplastic bone marrow during the initial illness. Peripheral white cell and platelet counts were preserved.

At the time of writing (January 1998), the Committee on Safety of Medicines (CSM) has received nine reports of aplastic anaemia or pancytopenia, eight of interstitial nephritis and three of acute renal failure associated with omeprazole treatment. There have been a further two reports of interstitial nephritis with acute renal failure, and one report of interstitial nephritis with bone marrow depression (CSM, personal communication).

Pyrexia of unknown origin is a common presentation to hospital physicians. In many cases the aetiology can be identified with the benefit of first-line investigations such as chest X-ray, full blood count, biochemical profile, bacteriological culture and auto-immune antibodies. There are, however, some cases in which the cause is not so readily apparent.

In many cases the association of a particular drug with adverse events is difficult to prove. In this patient we have reported three adverse events: pyrexia of unknown origin with acute phase reaction, bone marrow hypoplasia with anaemia, and acute renal failure due to interstitial nephritis. The figure demonstrates the temporal association of withdrawal and re-introduction of omeprazole with the markers of these three adverse events, i.e., ESR, haemoglobin, and serum creatinine. Unintentional

Learning points

- chronic drug treatment can cause severe acute illness
- drugs can cause pyrexia
- drugs can cause severe multisystem disorders that appear to be infective or inflammatory
- if in doubt, all treatment should be stopped, where possible
- rechallenge can be helpful in securing a diagnosis but is potentially dangerous

Treatment is initially by withdrawal of omeprazole. Renal replacement therapy is required in some patients. The role of corticosteroid therapy is unclear. Both oral prednisolone and intravenous methyl prednisolone have been used but other patients have improved spontaneously.

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rechallenge with omeprazole resulted in a much greater deterioration of renal function than was apparent at the time of original exposure, suggesting a process of sensitisation.

Our report demonstrates the need to consider drugs as a cause of unexplained fever. The serendipitous rechallenge with the suspected agent confirms the diagnosis of omeprazole-induced pyrexia with bone marrow hypoplasia and interstitial nephritis.


Oesophageal perforation: a dangerous but potentially curable condition

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Summary
A series of three cases of oesophageal perforation are described. All three presented differently and the X-ray findings were different in the three patients.

Keywords: oesophageal perforation; Boerhaave syndrome

Oesophageal perforation is a potentially fatal condition. It should be recognised and treated appropriately to prevent death. We report three cases, each of which presented differently, followed by a review of the subject.

Case reports

Case 1
A 73-year-old woman was admitted as an emergency at her general practitioner’s request with an 8-hour history of persistent vomiting. There was no previous history of note; this was her first admission to hospital. Physical examination revealed tachycardia at a rate of 122 beats/min and blood pressure of 185/90 mmHg. She was noted to be pale and dehydrated although her routine bloods were within normal limits. Abdominal examination demonstrated minimal epigastric tenderness with no other abnormality.

Plain abdominal X-ray was normal and the vomiting settled overnight. She was reviewed the following morning and by that time had developed subcutaneous emphysema. Review of her chest X-ray demonstrated mediastinal emphysema.

The patient was kept nil by mouth and the clinical suspicion was of a high oesophageal tear. Gastrograin swallow was performed but no tear could be identified. In view of this, fluids and then solids were re-introduced by mouth successfully and the patient suffered no further problems. She was then discharged home after satisfactory review by the ENT surgeons. An alternative diagnosis, which should be considered, is that she had suffered from a rupture of a pulmonary bleb. However, since she was symptomatic on admission with normal X-ray, the diagnosis of oesophageal tear is, in our opinion, more likely.

Case 2
A 50-year-old man presented to the Accident and Emergency department with chest pain and sudden onset dyspnoea. Four hours earlier he had awoken with nausea and he had proceeded to vomit violently with subsequent retching. He denied having drunk excessive alcohol or having consumed a particularly large meal. There was no history of haematemesis or coffee-ground vomitus.

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Figure Chest X-ray
Pyrexia, anaemia and acute renal failure secondary to omeprazole.

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