Letters to the Editor

Synchronous multiple lymphomatous polyposis and adenocarcinoma in the large bowel

Sir,

The occurrence of multiple primary malignancies is well-recognised: most cases have involved two or more carcinomata, often of the skin, stomach, colon or breast, and most commonly found in the same organ homolaterally or contralaterally. Cases of synchronous carcinoma and a non-epithelial neoplasm are rarer but still well-documented. Synchronous adenocarcinoma and lymphoma of the large bowel is rarer still and may involve risk factors (see box).^{1–4} We report a case in which two separate adenocarcinomata occurred in the presence of lymphomatous polyposis and diffuse lymphoma in the large bowel. This is novel in several respects: the patient had no known risk factors, the two tumours collided and, as far as we can determine, adenocarcinoma in association with lymphomatous polyposis has not previously been described.

A 74-year-old woman presented with a three-month history of pain in the right iliac fossa and weight loss. Examination revealed a palpable fixed caecal mass and an ulcer 7 cm from the anal margin. Contrast radiography additionally revealed numerous small polyps throughout the colon. A computed tomographic (CT) scan demonstrated large para-aortic lymph nodes. A rectal biopsy showed infiltrating adenocarcinoma and a dense, nodular, mucosal lymphoid infiltrate, displacing and infiltrating crypts, with atrophy of the overlying epithelium. It was composed of monotonous small lymphoid cells with indented nuclei resembling centrocytes, and a small proportion of large transformed lymphoid cells and macrophages, consistent with lymphomatous polyposis. The patient underwent panproctectomy. The resected large bowel showed diverticular disease and contained three separate tumour masses: a 3 cm polypoid rectal carcinoma with ulceration, an 8 cm polypoid caecal lymphoma and a 7 cm adjacent ulcerating caecal carcinoma. Numerous small polyps were present in the rectum, colon and at the ileal resection margin. Histological examination of both carcinomata revealed Dukes C lesions. The polypoid caecal lymphomatous mass consisted of diffuse sheets of lymphoma cells similar to those in the polyps, with penetration through the bowel wall and spread to adjacent lymph nodes. In some parts of the caecum as well as in the lymph node metastases, the diffuse lymphoma had collided with the carcinoma. Immunohistochemistry confirmed a B-cell phenotype (CD45 +, CD45ra +, CD20 +, MB2 +, κ +, λ –, CD45ro –, CD43 –, CD3 –).

The term malignant lymphomatous polyposis⁵ is now used to describe a specific entity comprising a polypoid mucosal lymphoma of the gastrointestinal tract, regarded as a variant of centrocytic lymphoma^{6,7} and probably identical to mantle zone lymphoma,⁷ which may transform into high grade B-cell lymphoma.⁸ Our patient showed a diffuse low grade lymphomatous mass in the caecum, but no areas of large-cell lymphoma. The lymphoma had involved adjacent mesenteric lymph nodes: both these and the caecal lymphomatous mass showed invasion by carcinoma. This might suggest that local factors such as absent immune surveillance in the lymphoma may have allowed carcinoma cells to grow there preferentially.

Previous reports of concurrent lymphoma and carcinoma

- splenic leukaemia with carcinoma¹
- leukaemia or lymphoma and coexistent primary malignancy (120 cases)²
- lymphoma and adenocarcinoma of the large bowel (separated lesions)³
- lymphoma and adenocarcinoma of large intestine in IgA deficiency⁴

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Manubrio-sternal joint sepsis in rheumatoid arthritis

Sir,

Involvement of the manubrio-sternal articulation in rheumatoid arthritis has been documented. Investigators using computed tomography (CT) have noted abnormalities in 50–70% of patients.^{1,2} It is, however, almost invariably sub-clinical.

A 56-year-old man with sero-positive rheumatoid arthritis, developed a large painless, fluctuant swelling over the anterior

aspect of his sternum. Investigations revealed a white cell count of $12.5 \times 10^9/l$ with 93% granulocytes, C-reactive protein 222 mg/l (normal range <10); erythrocyte sedimentation rate 70 mm/h (Westergren); urea, electrolytes and blood sugar were normal. CT scan showed a large fluid-filled cyst extending beneath the sternum in the anterior mediastinum. The bone on either side of the manubrio-sternal joint appeared eroded and ragged. He developed a pyrexia and urine culture grew *Staphylococcus aureus*. The cystic swelling was incised and several hundred mls of pus aspirated. Culture of the fluid grew *S aureus* sensitive to flucloxacillin. He was commenced on intravenous flucloxacillin 500 mg qid. Over a two-week period the manubrio-sternal cystic swelling and pyrexia resolved. He was treated for a further four weeks with intravenous flucloxacillin and discharged. Six months later he presented with a further large cystic swelling over his manubrio-sternal joint. The aspirate grew *S aureus* and he was commenced on intravenous flucloxacillin and fusidic acid for a further six weeks. CT scan at this time showed irregular margins, erosion and destruction of bone on either side of the manubrio-sternal joint (figure). To date he has had no further recurrence.

A 59-year-old woman with sero-positive rheumatoid arthritis complained of pain and swelling over her manubrio-sternal joint. On examination there was a tense, cystic swelling 3–4 cm in diameter over the manubrio-sternal junction. She had a low grade pyrexia of 37.8. White cell count was $13 \times 10^9/l$, erythrocyte sedimentation rate was 92 mm/h and C-reactive protein was 93 mg/l, urea and electrolytes, blood sugar and plasma proteins were normal. Urine and blood cultures were sterile. She then developed a hot, painful, swollen elbow joint. The aspirate grew *S aureus*, sensitive to flucloxacillin. Aspiration of the manubrio-sternal cystic swelling was attempted but fluid was not obtained. CT scan of the manubrio-sternal junction showed erosion and destruction of bone. Intravenous flucloxacillin and fusidic acid were continued for six weeks. Her temperature settled and the manubrio-sternal swelling resolved.

The pathogenesis of manubrio-sternal abnormality in rheumatoid arthritis is not certain; it may relate to primary involvement by the rheumatoid disease process, as both

Figure Erosion and destruction of bone on both sides of the manubrio-sternal joint in case 1.

Manubrio-sternal joint problems in rheumatoid arthritis

- infection
- synovitis
- subluxation
- ankylosis
- degeneration

the manubrio-sternal and sternoclavicular joints possess synovium,^{3,4} extension of synovial disease from adjacent costochondral joints, degenerative processes or trauma. Histological and microradiographic analysis has indicated active inflammation of the articulation in some patients and the absence of inflammation and presence of fibrous replacement in others.⁵ Pathological problems with clinical manifestation in the manubrio-sternal joint of patients with rheumatoid arthritis are shown in the box. In the former case, bacteraemia and joint sepsis probably occurred secondary to a urinary tract infection in a joint previously compromised by rheumatoid arthritis. This case also illustrates the difficulty in eradication of joint sepsis despite adequate and prolonged administration of appropriate antibiotics. Both cases demonstrate the importance of excluding sepsis in any disproportionately warm and painful joint in a rheumatoid patient. In both patients, fever and peripheral blood leucocytosis were present, characteristic of infection. These responses may be reduced or abolished in rheumatoid patients especially in those debilitated or immunocompromised. Elimination of infection from a joint requires prolonged high-dose antibiotic administration, repeated arthrocentesis and sometimes arthrotomy and surgical drainage. Infection is rapidly destructive of intra-articular structures, congruity and stability.

We suggest that clinically obvious manubrio-sternal joint arthritis in a patient with rheumatoid arthritis should be regarded as septic until proved otherwise.

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Allergic and toxic reaction to alprazolam

Sir,

We report the case of a patient who suffered an alprazolam overdose, and an allergic reaction probably induced by it.

A 19-year-old woman was found unconscious after ingesting 1.2 mg of alprazolam. Six months previously, she had been taking 0.25 mg alprazolam daily and 20 mg fluoxetine daily for two months. One hour later, at the emergency room, a gastric lavage was done, and treatment with fluids was started. Fifteen hours after drug ingestion, the patient's mental status was characterised by total amnesia of what had happened, and a relative had to relate the story. Alcohol and other drug ingestion was ruled out. The patient then presented a crisis of bronchospasm and laryngospasm, with severe dyspnoea and dysphagia.

Physical examination revealed bilateral palpebral and soft palate angioedema and laryngeal stridor. Pulmonary auscultation showed a reduction of the vesicular murmur and disseminated high-pitched wheezes over both pulmonary fields. Cardiac auscultation and abdominal examination were normal. Maleolar oedema with pain on mobilisation, probably secondary to her fall after taking alprazolam, was observed in the left lower limb.

Laboratory analysis showed: $17.6 \times 10^9/l$ white blood cells (84% polymorphonuclear cells, 9% lymphocytes, 6.5% monocytes, 0.1% eosinophils). The remaining cell count, serum electrolytes and urinalysis were normal. Baseline arterial blood gases showed moderate hypoxaemia ($PaO_2 = 76$ mmHg) corrected after oxygen therapy at FiO_2 of 31%. Chest X-ray and electrocardiogram were normal. IgG, A, M and E levels, complement, C1 inhibitor and protein electrophoresis fell within normal limits. Neither HBV antibodies or antigens nor HIV antibodies were detected.

Successive doses of subcutaneous epinephrine and intravenous corticosteroids, antihistamines, oxygen therapy and inhaled β -adrenergic drugs were administered, with good clinical response. On discharge, eight days later, the patient was asymptomatic. Sensitisation to the most frequent allergens was ruled out through clinical history and skin test. A series of standard prick tests for pollens, house dust mites and molds, latex, foods and hymenopter poisons were negative. Finally, an *in vitro* study with alprazolam was conducted on the patient and on three healthy subjects with a negative basophil degranulation test,¹ and a negative histamine release test.^{2,3} No *in vivo* studies on the patient were conducted, being forbidden by current Spanish legislation.

The loss of consciousness and the transient global amnesia, can be attributed to the sedation and the amnesic effects of the alprazolam overdose. This reaction occurred with a dose slightly higher than the upper limit of the dose range for the treatment of panic disorder.⁴

The symptoms that occurred 15 h after ingesting the drug suggest an allergic reaction to alprazolam. Other factors (material used for gastric lavage, other medications, foods or substances) were ruled out by different standard tests. The previous contact of the patient with alprazolam a few months before, supports the idea of a sensitisation. The timing of the clinical manifestations suggests an

independence of the toxic reaction, considering the elimination half-life of the drug.⁵ Ethical considerations made confirmation through *in vivo* tests of our explanation of this clinical picture impossible.

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Chronic myeloid leukaemia and allogenic bone marrow transplantation in a patient with toxic oil syndrome

Sir,

We have observed the development of chronic myeloid leukaemia in a woman who had been affected 10 years earlier by the toxic oil syndrome, produced by the ingestion of adulterated rapeseed oil, and in whom an allogenic bone marrow transplant had been accompanied by severe toxic manifestations.

The toxic oil syndrome^{1,2} is a multisystemic disease in which the basic lesion is endovascularitis involving vessels of all sizes and located anywhere in the organism. The vascular lesion first affects the intima, followed by inflammatory infiltration and cell proliferation producing, in advanced stages, narrowing and occlusion of the vascular lumen, leading to ischaemia and parenchymal atrophy in some organs (box).^{3,4} No cases of development of leukaemia in patients affected by the toxic oil syndrome had been previously reported.⁴

The 35-year-old woman whose case we present here, was diagnosed as having toxic oil syndrome 10 years earlier. The only sequel at the time that the leukaemia was detected, was a mild, predominantly sensory, neuromuscular involvement in the upper limbs. After the diagnosis of Ph-positive chronic myeloid leukaemia, she started treatment with interferon α -2b, but no cytogenetic remission was observed in subsequent haematologic studies.