Manubrio-sternal joint problems in rheumatoid arthritis

- Infection
- Synovitis
- Subluxation
- Ankylosis
- Degeneration

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 dyspnea 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. Molecular oedema with protein mobilisation probably secondary to her fall after taking alprazolam, was observed in the left lower limb.

Laboratory analysis showed: 17.6 x 10^9/L white blood cells (84% lymphocytes, 9% monocytes, 6.5% monocytes, 0.1% eosinophils). The remaining cell count, serum electrolytes and urinalysis were normal. Baseline arterial blood gases showed moderate hypoxemia (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, Cl inhibitor and protein electrophosphatase 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 hymenoptera 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, and a negative histamine release test. No in vivo study 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 anesthetic 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.

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. 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 is a multisystemic disease in which the basic lesion is endovascularly 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, occlusion and occlusion of the vascular lumen, leading to ischaemia and parenchymal atrophy in some organs (box). No cases of development of leukaemia in patients affected by the toxic oil syndrome had been previously reported.

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.
She was conditioned for an allogenic HLA identical bone marrow transplant from a sister who had received total body irradiation (12 Gy) and cyclophosphamide (60 mg/kg body weight X 2); as prophylaxis for graft-versus-host disease, she received cyclosporin A (1.5 mg/kg body weight every 12 h, starting on day +1) and a short course of methotrexate, according to the Seattle protocol.

On the day of the bone marrow infusion, she developed fever and was put on broad-spectrum antibiotics and a regimen with amphotericin B, which was added later. Her haematological study and chest X-ray were normal. She had, meanwhile, progressive weight gain, abnormal liver function test (increased of bilirubin and y-glutamyl transaminase) and deterioration of renal function. By day +10 she had ascites, tender hepatomegaly and oedema of her lower limbs, all suggestive of hepatic veno-occlusive disease. A thoracoabdominal computed tomography (CT) scan was carried out which showed hepatosplenomegaly, ascites and retroperitoneal lymphadenopathy. Soon after the transplant she developed severe mucositis.

On day +13 she was dyspnoeic and a chest X-ray showed consolidation in the lower left lobe, left pleural effusion and a poorly defined nodule in the upper right lobe. Two days later, the nodule enlarged and consolidation at the base of both lungs with bilateral pleural effusion were observed. Because of the suspicion of pulmonary aspergillosis, the dose of amphotericin B was increased.

On day +20, neutrophil engraftment was detected (neutrophil count >0.5 x 10^9/L). On day +22, the patient presented respiratory distress syndrome and was transferred to the Intensive Care Unit, where she eventually required mechanical ventilation, and died six days later (day +30).

Necropsy showed right pulmonary aspergillosis, radiation pneumonitis with severe diffuse alveolar damage, hepatomegaly with severe cholestasis and venous wall oedema, visceral congestion, and intense generalised mucositis.

The role that the precedent of toxic oil syndrome played in the post-transplant course of this patient is a matter of speculation.

## Criteria for the diagnosis of toxic oil syndrome

1. Intake of cooking oil sold in bulk, and/or other cases among relatives
2. Interstitial-alveolar pattern on chest X-rays during the first 4 months
3. Esophagitis (>500 eosinophils/μl), myalgia, or rash during the first 4 months
4. Pulmonary hypertension, hepatic disease, aseptic osteomyelitis, skin syndrome, polyneuropathy, joint contractures, Raynaud disease, muscle cramps, chronic lung disease

For diagnosis, either
- at least two of criteria 1, 2, or 3
- or at least criteria 1, 2, or 3, and two or more of the features included in criterion 4 should be fulfilled

## Proptosis, skull infarction and epidural haematoma in sickle thalassemia

Sir,

Infarction of the long bones is a common complication of sickle cell disease. However, there are less than 10 cases of orbital bone infarction associated with sickle cell disease in the literature. A combination of orbital and skull bone infarction with associated epidural haematoma in sickle cell disease has been reported only once in the world literature, with our case being the second. This case is unique in that it is sickle thalassemia and hence occurred at a later age. A 35-year-old man, admitted with painful limitation of eye movements and proptosis of the left eye of eight days duration, had absent extracocular movements in all fields of gaze with the cornea, sclera, fundus, pupils and visual acuity being normal. The patient had a haemoglobin of 8.1 g/dl and sickle cells on a peripheral smear. Sickle cell test was positive and haemoglobin electrophoresis revealed Hb S - 48.8%, Hb F - 49.0% and Hb A2 - 2.2%, consistent with a diagnosis of sickle thalassemia. A bone marrow biopsy depicted areas of infarction. The left orbital ultrasonography demonstrated a mass with soft tissue echotexture in the upper temporal quadrant of the left eye, displacing the eye ball inferomedially. A computed tomography (CT) scan of the orbit showed a non-enhancing soft tissue mass without any adjacent bone erosion, destruction or intracranial extension (figure). CT scan of the brain showed an epidural haematoma. A bone scan using 740 M bq of 99 mTc MDP (methylene diphosphonate), showed abnormal uptake in the skull bones and bone marrow imaging using 370 M bq of 99 mTc colloidal sulphur, done two days after the bone scan showed multiple cold areas in the skull. These radiological findings are suggestive of peripheral and skull bone infarction and adjacent haematoma and swelling secondary to it. The patient received hydroxyurea, blood transfusion and analgesics. After 14 days he regained full movements of the eye and proptosis disappeared.

Sickle cell disease is rarely associated with periorbital and skull bone infarctions.

### Periorbital swelling: causes

- Trauma
- Infarction
- Exophthalmic goitre
- Nephritis
- Lateral gland involvement
- Glaucoma
- Angioneurotic oedema
- Bleeding due to blood dyscrasias
- Leukaemic infiltration
- Metastatic neoplasia
- Cavernous sinus thrombosis

Though intracranial bleeding occurs in sickle cell disease, a combination of epidural haematoma and periorbital and skull infarction has only been reported once before. One should include periorbital bone infarction due to sickle cell disease in the differential diagnosis of periorbital swelling. It is often difficult to differentiate bone infarction from osteomyelitis and a 99 mTc MDP bone scintigraphy is useful in demonstrating activity-deficient areas in infarction and hyperactive areas in osteomyelitis. This is important as both can coexist in sickle cell disease and clinical differentiation is often difficult. The combined use of an orbital CT scan and orbital ultrasonogram are useful in differentiating the various orbital problems in such cases.

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

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Correction
Mur P, Rodriguez M, Martinez-Cano H, et al. Allergic and toxic reaction to alprazolam (letter). Postgrad Med J 1995; 71: 444. In the fifth line of this letter the quantity of alprazolam taken should have been given as 12 mg, not 1.2 mg as printed.