Allergic and toxic reaction to allopurinol

Sir,

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

A 19-year-old woman was found unconscious after ingesting 1.2 mg of allopurinol. Six months previously, she had been taking 0.25 mg allopurinol 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. Molecular oedema with patients mobilisation probably secondary to the fall after taking allopurinol, was observed in the left lower limit.

Laboratory analysis showed: 17.6 x 10³/μL white blood cells, 46.6% polymorphonuclears, 9% lymphocytes, 6.5% monocytes, 0.1% eosinophils. The remaining cell count, serum electrolytes and urinalysis were normal. Baseline arterial blood gases showed moderate hypoxemia (PaO₂ = 76 mmHg), corrected after oxygen therapy at FiO₂ of 31%. Chest X-ray and electrocardiogram were normal. IgG, A, M and E levels, complement, Cl inhibitor and protein electrophoresis fell within normal limits. Neither HBV antibodies or antigens nor HIV antibodies were detected.

Successive doses of subcutaneous epinephrine and hydrocortisone, anti-histamines, oxygen therapy and inhaled β-adrenergic drugs were administered, with good clinical response. On discharge, eight days later, the patient was asymptomatic. Sensitive to the most frequent allergenic reaction 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 allopurinol 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 with 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 amnestic effects of the allopurinol overdose. This reaction occurred with a dose slightly higher than the upper limit of the dose range for the treatment of painful gout.

The symptoms that occurred 15 h after ingesting the drug suggest an allergic reaction to allopurinol. 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 allopurinol 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 examination of this clinical picture impossible.

P MUR
Department of Allergy, Princess Hospital, Madrid, Spain

H MARTINEZ-CANO
A VELA-BUENO
I FARR
Department of Psychiatry, Autonomous University, Madrid, Spain

M DE ICETA
Department of Psychiatry, San Carlos University Hospital, Madrid, Spain

R POMALIMA
Sleep Disorders Centre, Madrid, Spain

Correspondence to H Martinez-Cano, Camino de Vinateros 12, 8F, 28030 Madrid, Spain


Chronic myeloid leukaemia and allogenic bone marrow transplant-plantation 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 endovascular 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, fibrosis and occlusion of the vascular lumens, 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, neuro-muscular 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 with fractionated 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, was added later. Her haematological and chest X-ray study was normal. She had, meanwhile, progressive weight gain, abnormal liver function test (increased of bilirubin and γ-glutamyl transaminase) and deterioration of renal function. By day +10 she had ascites, tender hepatomegaly and oedemas of her lower limbs, all suggestive of hepatic veeno-occlusive disease. A thoraco-abdominal computed tomography (CT) scan was carried out which showed hepatospleno-megaly, 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 severe oedemas of her lower limbs, all suggestive of hepatic veeno-occlusive disease. A thoraco-abdominal computed tomography (CT) scan was carried out which showed hepatospleno-megaly, ascites and retroperitoneal lymphadenopathy. Soon after the transplant she developed severe mucositis.

Necropsy showed right pulmonary aspergillosis, radio 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. eosinophilia (>500 eosinophils/μl), myalgia, or rash during the first 4 months
4. pulmonary hypertension, hepatic disease, sclerosing cholangitis, pulmonary 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.

Propositis, 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 English 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 extraocular 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 disease was confirmed by a 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 Mibq of 99 mTc MDP (methylene diphosphonate), showed abnormal uptake in the skull bones and bone marrow imaging using 370 Mibq 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 periorbital and skull bone infarction and adjacent haematoma and swelling secondary to it. The patient received hydroxyurea, blood transfusion and anaglics. 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
- lacrimal gland involvement
- glaucoma
- angioneurotic oedema
- bleeding due to blood dyscrasias
- leukaemic infiltration
- metastatic neuroblastoma
- cavernous sinus thrombosis

Though intracranial bleeding occurs in sickle cell disease, a combination of epidual haematoma and periorbital and skull infarction has only been reported once before.1

One should include periorbital bone infarction due to sickle cell disease in the differential diagnosis of periorbital swelling.2 It is often difficult to differentiate bone infarction from osteomyelitis and a 99 mTc MDP bone scintigraphy is useful in differentiating 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.3 The combined use of an orbital CT scan and orbital ultrasonogram are useful in differentiating the various orbital problems in such cases.4

JACOB TONY
GAYATHRI SUBRAMANYA
KG KALLUR
AV CHALAPATHY
SHUBA SHESHADRI
BHUSAN LAKHRAR
Kasturba Medical College,
Manipur 576 119, Karnataka, India

Correspondence to Dr JC Tony, Department of Medicine, Kasturba Medical College, Manipur 576 119, Karnataka, India

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

P. Llamas-Sillero, M. Gómez-Roncero, R. Forés, R. Cabrera, J. L. Díez and M. N. Fernández

doi: 10.1136/pgmj.71.837.444-a

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Royal Free Hospital School of Medicine, London
10/11 February 1996: MRCP Part II Mock examinations.
Details: Kaia Lambour, Department of Medicine, Royal Free Hospital, Rowland Hill Street, London NW3 2PF, UK. Tel: +44 171 830 2108
12–16 February 1996: MRCP Part II course for clinical examination
Details: Dr D Geraint James, Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG, UK. Tel: +44 171 794 0500 ext 5110

Royal Postgraduate Medical School Institute of Obstetrics and Gynaecology
19–21 June 1996: Advanced course in fetal medicine
24–28 June 1996: Advanced course for obstetricians and gynaecologists
Details: Symposium Secretary, RPMS Institute of Obstetrics and Gynaecology, Queen Charlotte’s and Chelsea Hospital, Goldhawk Rd, London W6 0XG, UK. Tel: +44 181 740 3904; fax: +44 181 259 8555

Royal College of Physicians of Edinburgh
1 February 1996: Ethical and economic conflicts in a changing health service (symposium)
7 February 1996: HIV/Infectious diseases (evening teach-in)
4/5 March 1996: Management education for clinicians (Joint symposium with the Royal College of Physicians and Surgeons of Glasgow)
8 March 1996: What’s new in gastroenterology (symposium)
13 March 1996: Vascular disease and the intraluminal environment (symposium)
Aberdeen
26 March 1996: Haematology (evening teach-in)
16 April 1996: Neurology (evening teach-in)
Details: Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh EH2 2JQ, UK. Tel: +44 131 225 7324; fax: +44 131 220 3939

Royal College of Physicians of London
12–15 February 1996: Advanced medicine
29 February 1996: Osteoporosis
6 March 1996: Epithelial cell biology—a science impacting clinically
19 March 1996: The interface between medicine and the insurance industry
25 March 1996: CME day—cerebrovascular disease
19/20 April 1996: Joint congress with the College of Medicine of South Africa (in Cape Town)
8 May 1996: Appraisal: purpose, pitfalls and good practice

Royal National Orthopaedic Hospital Trust
5–6 March 1996: Surgery of the foot and ankle
Details: Carol Winston, Royal National Orthopaedic Hospital Trust, Brookley Hill, Stanmore, Middlesex HA7 4LP, UK. Tel: +44 181 954 2300; fax: +44 181 954 6933

Institute of Psychiatry, London
5–8 February 1996: Cellular and molecular pathology of neurodegenerative disease (course).

Details: Mrs L Wilding, Short Courses Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK. Tel: +44 171 703 5796.

University of California Postgraduate Course
3 February 1996: Third annual update in behavioural/developmental pediatrics
1–2 March 1996: Practical pediatric dermatology (San Francisco, CA, USA)
Details: University of California, Office of Continuing Medical Education, 1855 Folsom St, MCB Room 630, San Francisco, CA 94143–0742, USA. Tel: +1 415 476 4251; fax: +1 415 476 0318

University College London Medical School Institute of Orthopaedics: Lecture courses
January – March 1996: Neuromuscular disorders
April – July 1996: Developing fields in orthopaedics
Details: Postgraduate Secretary, Institute of Orthopaedics, 45 Bolsover St, London W1P 8AQ, UK. Tel: +44 171 387 5070 ext 270.

10th Annual Magnetic Resonance Imaging Conference
3–6 March 1996: Barrow Neurological Institute, St Joseph’s Hospital and Medical Center, The Phoenixian Resort, Scottsdale, Arizona, USA
Details: Beverly Pennington, Neuroscience Conference Coordinator, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, AZ 85013-4496, USA. Tel: +1 602 406 3067; fax: +1 602 406 7196.

First European Forum of Quality Improvement in Healthcare
7–9 March 1996: QEII Conference Centre, London, UK
Details: Claire Moloney, BMA Conference Unit, BMA House, Tavistock Square, London WC1H 9JR, UK. Tel: +44 171 383 6478; fax: +44 171 383 6663.

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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.