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.

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 $\times$ 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 microbiological study and chest X-ray were 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 veno-occlusive disease. A thoraco-abdominal 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 $> 0.5 \times 10^9/l$). 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.

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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/ μ l), myalgia, or rash during the first 4 months
- 4 pulmonary hypertension, hepatic disease, scleroderma, sicca 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 thalassaemia

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.¹ 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,² with our case being the second. This case is unique in that it is sickle thalassaemia 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. Sickling 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 thalassaemia. 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 Mbq of 99 mTc MDP (methylene diphosphonate), showed abnormal uptake in the skull bones and bone marrow imaging using 370 Mbq 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 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.

Figure CT scan of the left orbit showing non-enhancing soft tissue mass

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 epidural haematoma and periorbital and skull infarction has only been reported once before.²

One should include periorbital bone infarction due to sickle cell disease in the differential diagnosis of periorbital swelling.³ 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.³ The combined use of an orbital CT scan and orbital ultrasonogram are useful in differentiating the various orbital problems in such cases.⁴

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International Postgraduate Diary

Royal Free Hospital School of Medicine, London

10/11 February 1996: MRCP Part II Mock examinations.

Details: Katia 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 1JQ, 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

14/15 May 1996: The legacy of Jenner: vaccination past, present and future (Joint with Royal Society, Royal College of Pathologists, Wellcome Institute for the History of Medicine)

5 June 1996: Risk factors, earlier diagnosis and preventive possibilities to meet the health of the nation targets

Details: Conference Office, Royal College of Physicians, 11 St Andrews Place, Regent's Park, London NW1 4LE, UK. Tel: + 44 171 935 1174 ext 252/300; fax: + 44 171 487 5218.

Royal College of Surgeons of England: Postgraduate Courses (London, UK)

6/7 and 8/9 February 1996: ATLS Instructor course

12 February – 1 March 1996: Applied basic science for surgeons

13–16 February 1996: Advanced anastomotic techniques

15/16 February 1996: Approaches to anterior cruciate ligament and meniscal suturing

19/20 and 21/22 February 1996: Training the trainers

20/21 February 1996: Management of inguinal hernias

27/28 February 1996: Laparoscopic fundoplication

11–15 March 1996: Art of reconstructive surgery

11–29 March 1996: Applied basic sciences for surgeons

12–14 March 1996: Lumbar spine stabilisation

13/14 March 1996: Training the trainers

20/21 March 1996: Basic skills for safe laparoscopic surgery

21/22 March 1996: Minor surgery for general practitioners

26/27 March 1996: Femoral distal bypass surgery

Details: Raven Department of Education, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London, UK. Tel + 44 171 973 2100; fax + 44 171 973 2117.

Royal National Orthopaedic Hospital Trust

5–6 March 1996: Surgery of the foot and ankle

Details: Carol Winston, Royal National Orthopaedic Hospital Trust, Brockley 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 + 44 171 919 3170; fax + 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 Phoenician 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.

National Association of Clinical Tutors

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Information about the NACT and its activities can be obtained from The Secretariat, National Association of Clinical Tutors, 12 Chandos Street, London W1M 9DE, UK. Tel: + 44 171 636 6334.

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.