

LETTERS

Multiple rib infarcts: a rare form of osteonecrosis in antiphospholipid syndrome

W-H Yoo

Ann Rheum Dis 2004;**63**:457–458. doi: 10.1136/ard.2003.006197

Osteonecrosis (ON) is a well known morbidity of several rheumatic diseases, usually affecting the hip, knee, shoulder, and ankle. The involvement of multiple or atypical sites by ON has been reported, especially in association with antiphospholipid antibodies (aPL). Rib infarction has been reported as a painful crisis of sickle cell disease, but has not been reported in rheumatic diseases. I describe here the first case of rib infarcts which developed in a patient with mixed connective tissue disease (MCTD) and secondary antiphospholipid syndrome (APS).

CASE REPORT

A 36 year old woman with hand oedema, Raynaud's phenomenon, and polyarthritis of both hands was diagnosed as having MCTD 3 years ago. She had deep venous thromboses in both legs 2 years ago. Laboratory tests showed an antinuclear antibody titre of 1/2560, IgG anticardiolipin antibody 65.42 GPU (normal <15 GPU), and anti-U1RNP antibody (1/1280). Secondary APS associated with MCTD was diagnosed, and treatment with low dose steroid, aspirin, and warfarin was prescribed.

Recently, she presented with a 15 day history of diffuse, bilateral chest pain. Physical examination disclosed tenderness on multiple ribs. Laboratory findings showed an increased leucocyte count of $11.5 \times 10^9/l$, decreased platelet count of $85 \times 10^9/l$, and an increased erythrocyte sedimentation rate of 36 mm/1st h. Coagulation tests showed an activated partial thromboplastin time of 72.4 seconds, and other tests were within the normal range. Immunological studies showed C reactive protein of 125 mg/l (normal <50) and IgG anticardiolipin antibody 45.63 GPU. Other immunological tests including anti-Sm, anti-dsDNA antibody, cryoglobulins, homocysteine were normal or negative.

Bone scintigraphy showed non-uniform uptake, with areas of decreased and increased uptake in the anterior and lateral aspects of multiple ribs, bilaterally (fig 1). Histological analysis confirmed multiple ON of the ribs (fig 2). She was prescribed with simple analgesics in addition to previous drugs. Her chest pain improved dramatically over the following week and her disease was stable on follow up.

DISCUSSION

In this report, I describe a rare case of multiple rib infarcts in a patient with secondary APS who had been managed with low dose glucocorticoid. Two interesting points about this case should be emphasised. The first is the pathogenesis of ON. ON has obvious association with various systemic conditions, including sickle cell disease, prolonged glucocorticoid treatment, alcohol abuse, and Gaucher's disease, and several factors, such as vascular thrombosis, mechanical defects, cellular damage, embolisation, changes in introsseous pressure, or trauma, have been proposed in its pathogenesis.¹ For rheumatological diseases, a pathogenic relationship between aPL and ON has been proposed on the basis of clinical observations of patients with APS who

developed ON in the absence of glucocorticoid treatment.^{2,3} Several studies showed a correlation between aPL and ON in patients with systemic lupus erythematosus,⁴⁻⁶ and Belmonte *et al*⁷ suggested a possible association of aPL with ON in patients with HIV infection.

Multiple rib infarcts in this case strongly suggest that a systemic process may be the underlying pathogenesis. Corticosteroid use and the vasculitic process can be considered to be the causative factors in this case. However, ON in this patient was controlled with a relatively small dose of corticosteroid, and clinical disease was relatively inactive when ON was diagnosed. Whether aPL are directly responsible for this condition or whether they are present as bystanders remains controversial. But, owing to the hypercoagulable potential of aPL, vascular occlusion or thrombotic vasculopathy related to the aPL was also thought to be the underlying pathogenetic mechanism. Thus, the prothrombotic potential of aPL and the above described clinical features of this patient suggest that aPL are directly implicated in the aetiopathogenesis of ON.

The second point which should be emphasised is the atypical presentation of ON affecting the ribs bilaterally. This is an unusual, first described presentation of ON developing on multiple ribs bilaterally. Rib infarction has been reported rarely as a painful crisis of sickle cell disease and associated with vaso-occlusive phenomena.⁸ Although the involvement of multiple or atypical sites (that is, vertebral body and lunette bone) has been reported in association with aPL or catastrophic APS, rib infarcts have not been reported in rheumatic diseases. I suggest that rib infarcts may be an unusual complication of rheumatic diseases with prothrombotic potentials, especially APS.

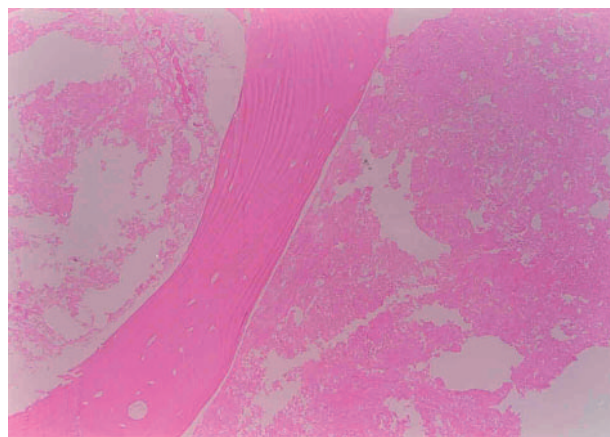


Figure 2 Histological examination of trabecular bone shows the signs of bone death. The trabeculae are preserved, but the lacunae are empty and the marrow is dead (haematoxylin and eosin $\times 100$).

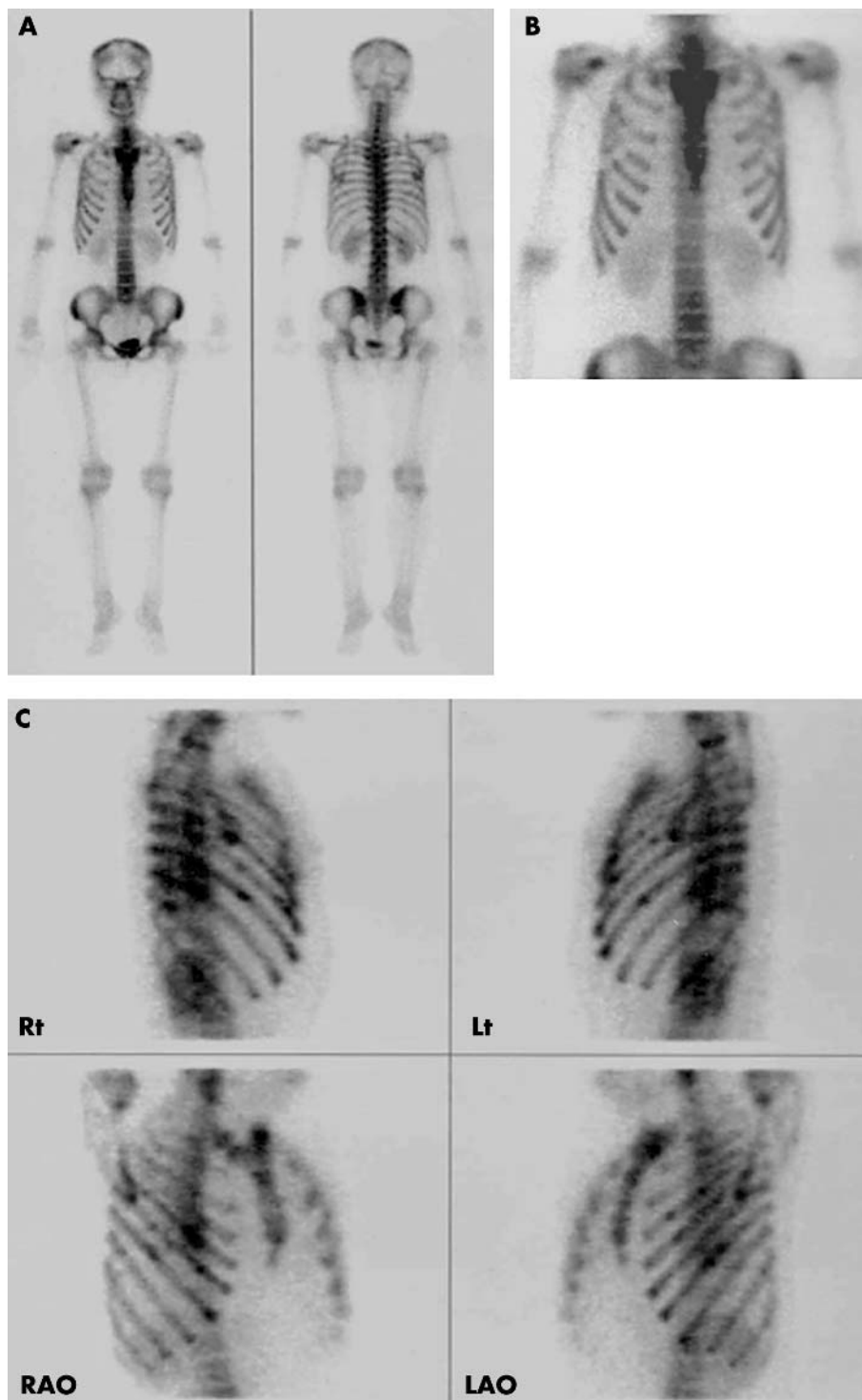


Figure 1 Bone scintigrams of whole body (A), anterior (B), lateral and oblique (C) views of the chest show multiple areas of decreased and increased uptake in the ribs, consistent with bone infarction.

Correspondence to: Dr W-H Yoo, 634-18, Keum-Am Dong, Duck-Jin Gu, Chonju, Chonbuk, 561-712, Korea; ywhim@moak.chonbuk.ac.kr

Accepted 12 June 2003

REFERENCES

- 1 Asherson RA. XVth Internal Congress of Rheumatology. Sydney Australia. 1985:282.
- 2 Seleznick MJ, Silveira LH, Espinoza LR. Avascular necrosis associated with anticardiolipin antibodies. *J Rheumatol* 1991;18:1416-17.
- 3 Alijotas J, Argemi M, Barquinero J. Kienbock's disease and antiphospholipid antibodies. *Clin Exp Rheumatol* 1990;8:297-8.
- 4 Asherson RA, Liote F, Page B, Meyer O, Buchanan N, Khamashta MA, *et al*. Avascular necrosis of bone and antiphospholipid antibodies in systemic lupus erythematosus. *J Rheumatol* 1993;20:284-8.
- 5 Nagasawa K, Ishii Y, Mayumi T, Tada Y, Ueda A, Yamauchi Y, *et al*. Avascular necrosis of bone in systemic lupus erythematosus: possible role of haemostatic abnormalities. *Ann Rheum Dis* 1989;48:672-6.
- 6 Mont MA, Fairbank AC, Petri M, Hungerford DS. Core decompression for osteonecrosis of the femoral head in systemic lupus erythematosus. *Clin Orthop* 1997;334:91-7.
- 7 Belmonte MA, Garcia-Portales R, Domenech I, Fernandez-Nebro A, Camps MT, De Ramon E. Avascular necrosis of bone in human immunodeficiency virus infection and antiphospholipid antibodies. *J Rheumatol* 1993;20:1425-8.
- 8 Mannik K. *Harrison principle of internal medicine*, 12th ed. New York: McGraw-Hill, 1991:1990.

Symmetrical peripheral gangrene complicating *Klebsiella pneumoniae* sepsis associated with antiphospholipid antibodies

J-H Yoo, J-K Min, S-S Kwon, C H Jeong, W-S Shin

Ann Rheum Dis 2004;**63**:459–460. doi: 10.1136/ard.2003.012542

We have encountered a rare case of symmetrical peripheral gangrene^{1–5} complicating *Klebsiella pneumoniae* sepsis associated with antiphospholipid antibodies.

CASE REPORT

A 72 year old woman was admitted to our hospital with fever and symmetrical gangrene of both fingers and toes. She had been well until she began to suffer from fever and pain in the abdomen 3 days before admission. She then attended a local hospital and underwent an abdominal computed tomography scan that showed a liver abscess. Culture of blood and ultrasonography guided aspirates disclosed *Klebsiella pneumoniae*. The day before admission she had deep-bluish discoloration of both fingers and toes, and she was transferred to our hospital.

On admission, most of her fingers and toes already showed gangrenous changes (fig 1A), but the pulse in the bilateral radial, ulnar, and dorsalis pedis arteries was intact. Antithrombin III, protein C and S activities were depressed. IgG anticardiolipin antibody was highly positive, while IgM was negative (table 1). β_2 -Glycoprotein I antibody was also positive. However, there was no evidence of lupus erythematosus by the criteria of the American College of Rheumatology. Computed tomography guided drainage of

the liver abscess and culture of the aspirates subsequently disclosed *K pneumoniae*. Third generation cephalosporin plus metronidazole were given. We initially considered fasciotomy, or even amputation, but the bilaterally intact arterial pulse and the fact that the gangrene was confined to the distal ends of the extremities made us hesitate to intervene surgically. Eventually, we decided to use an anticoagulant, in combination with vasodilators. Tissue plasminogen activator 5 mg/h was given for 16 hours. At the same time we began infusion of prostacyclin (epoprostenol) 2 ng/kg/min for 6 hours a day for 7 days. After 2 days of the tissue plasminogen activator schedule, low dose heparin was given over 5 days, followed by sodium warfarin 2.5 mg/day until the international normalised ratio of 2.0–2.9 was reached. Low dose aspirin 325 mg and nifedipine 30 mg a day were also given. After the anticoagulant and vasodilator treatment had begun, none of the gangrenous lesions progressed any further, and the affected fingers and toes gradually began to regain warmth and colour. About six weeks later, most of the fingers and toes had returned to normal, and four necrotic distal toes of the right foot had been successfully amputated without further complication (fig 1B). As of May 2003, the patient is completely recovered, and now receiving rehabilitation treatment.



Figure 1 (A) Gangrene on fingers and toes on admission. (B) After anticoagulant and vasodilator treatment the fingers and most of the toes are back to normal, although the necrotic distal toes of the right foot have been amputated.

Table 1 Laboratory parameters of the antiphospholipid syndrome

	On admission	6 Weeks later	Convalescent
IgG anticardiolipin antibody*	87	27	7
IgM anticardiolipin antibody	8	3	4
β_2 -Glycoprotein I antibody†	31.0	11.0	11.0

*Normal range of anticardiolipin antibody: 0–20; †normal range of β_2 -glycoprotein I antibody: ≤ 10 U/ml.

DISCUSSION

Because *K pneumoniae* was isolated from the blood, we concluded that hypercoagulability complicating *K pneumoniae* sepsis was the main cause of the clinical feature. We also recognised anticardiolipin and β_2 -glycoprotein antibodies, suggesting that an immunological mechanism, such as catastrophic antiphospholipid syndrome, rather than an infection, might have played a role.^{1–5} IgG anticardiolipin antibody was still positive after 6 weeks^{6–7} but became negative after convalescence (2 months later; table 1). On the basis of these findings, we postulate that both the positive anticardiolipin antibody and the *K pneumoniae* sepsis may be closely correlated with the gangrenous process. Although Amital *et al* reported that amputation could induce remission of the systemic illness,⁸ some reports have recommended that non-surgical management is preferable if there is an intact pulse in the affected limb.^{3–4} The lesson we learnt from this case is that anticoagulant⁹ and/or vasodilator treatment, rather than surgical intervention, should be initiated as soon as possible for a septic patient with apparently symmetric gangrenous extremities.

Only sporadic reports of this rare disease entity have appeared until now, but there has been no report of a case complicating *K pneumoniae* sepsis. To our knowledge, this is

the first report of catastrophic antiphospholipid syndrome following *K pneumoniae* sepsis.

Authors' affiliations

J-H Yoo, J-K Min, S-S Kwon, W-S Shin, Department of Internal Medicine, Holy Family Hospital, The Catholic University of Korea, College of Medicine, Seoul, Korea

C H Jeong, Department of Orthopaedic Surgery, Holy Family Hospital, The Catholic University of Korea, College of Medicine, Seoul, Korea

Correspondence to: Professor J-H Yoo, Department of Internal Medicine, Holy Family (Sung-Ka) Hospital, Sosa-2-Dong, Wonmi-Gu, Bucheon 420-717, Kyongki-Do, South Korea; mogulkor@medimail.co.kr

Accepted 26 July 2003

REFERENCES

- Asherson RA. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;**19**:508–12.
- Zulian F, Costantini C, Montesco MC, Schiavon F, Zaccello F. Successful treatment of gangrene in systemic necrotizing vasculitis with iloprost. *Br J Rheumatol* 1998;**37**:228–230.
- Denning DW, Gilliland L, Hewlett A, Hughes LO, Reid CDL. Peripheral symmetrical gangrene successfully treated with epoprostenol and tissue plasminogen activator. *Lancet* 1986;**ii**:1401–2.
- Hayem G, Kassis N, Nicaise P. Systemic lupus erythematosus associated with catastrophic antiphospholipid syndrome occurring after typhoid fever. A possible role of Salmonella lipopolysaccharide in the occurrence of diffuse vasculopathy—coagulopathy. *Arthritis Rheum* 1999;**42**:1056–61.
- Asherson RA, Cervera R. Antiphospholipid antibodies and infections. *Ann Rheum Dis* 2003;**62**:388–93.
- Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. *Thromb Haemost* 1995;**74**:1185–90.
- Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002;**346**:752–63.
- Amital H, Levy Y, Davidson C, Lundberg I, Harju A, Kosach Y, *et al*. Catastrophic antiphospholipid syndrome: remission following leg amputation in 2 cases. *Semin Arthritis Rheum* 2001;**31**:127–32.
- Uthman I, Taher A, Khalil I, Bizri AR, Gharavi AE. Catastrophic antiphospholipid syndrome associated with typhoid fever: comment on the article by Hayem *et al*. *Arthritis Rheum* 2002;**46**:850.

An unusual case of ankle arthropathy

S Abraham, A Cope

Ann Rheum Dis 2004;**63**:460–461. doi: 10.1136/ard.2003.007757

CASE REPORT

A 65 year old white woman presented with a 5 year history of pain and intermittent swelling of the left ankle. There had been no preceding trauma to the ankle and the symptoms were initially gradual in onset with aching and stiffness but then evolved into a continuous pain, particularly nocturnally. Her previous medical history included a right total hip replacement aged 53, menopause aged 53, and essential hypertension. There was no family history of rheumatological illness and her mother died of a myocardial infarction aged 56 years.

Examination disclosed evidence of osteoarthritis in her hands and an unusual symmetrical bony swelling of her 1st and 2nd metacarpophalangeal joints. Her left ankle was swollen and warm to the touch (fig 1).

Investigations disclosed normal inflammatory markers and autoantibody screen, a mildly raised aspartate aminotransferase 35 U/l (normal 31 U/l) and alanine aminotransferase 42 U/l (normal 30 U/l), and a normal serum glucose. Radiographs of the ankle disclosed changes compatible with moderate to severe osteoarthritis, and those of the hands showed bilateral significant joint space narrowing, hooked osteophytes and sclerosis of the 2nd and 3rd metacarpophalangeal

joints bilaterally, and chondrocalcinosis in the triangular ligament of the wrist. Her transferrin saturation index and ferritin were markedly raised at 98% (normal 20–40) and 4340 μ g/l (normal 12–200), respectively. Genotyping was



Figure 1 Left ankle demonstrating a palpable bony swelling.

Table 1 Cases of ankle arthropathy in haemochromatosis

Age (years)	Sex	Diagnosis haemochromatosis made before or after arthropathy	Systemic manifestations	Reference
45	M	Before	Diabetes	Jacki <i>et al</i> 1999 ³
57	F	After	No mention	Bailey <i>et al</i> 1998 ⁴
75	M	After	No mention	Bailey <i>et al</i> 1998 ⁴
53	M	No mention	No mention	Bailey <i>et al</i> 1998 ⁴
65	F	After	Nil	Case presented

undertaken by polymerase chain reaction from genomic DNA. This showed the patient to be homozygous for the most common haemochromatosis mutation, cysteine to tyrosine (C282Y) on chromosome 6.¹

DISCUSSION

After the description of haemochromatosis in 1935, Schumacher first described an associated arthropathy in 1964.² The prevalence of arthralgia and arthritis in haemochromatosis varies between 28 and 81%. Characteristic radiological features have been reported in the hand, wrist, and hip. Involvement of the ankle joint seems to be rare and only four previous cases have been described, with only one presenting as ankle arthropathy³⁻⁴ (table 1).

The arthropathy of haemochromatosis is usually degenerative and non-inflammatory, first affecting the small joints of the hands and then larger joints such as hips, shoulders, knees, and ankles.⁵⁻⁶ The presentation of haemochromatosis may be confused with either rheumatoid arthritis or pseudogout. A polyarticular, symmetrical involvement, particularly of the 2nd and 3rd metacarpophalangeal joints, in association with other superficial bony swellings consistent with osteoarthritis should alert the clinician to the possibility of haemochromatosis. Acute attacks of synovitis in such patients can be secondary to calcium pyrophosphate dihydrate deposition. Despite treatment of haemochromatosis with phlebotomy, the arthropathy seldom improves.

To date, a number of theories have been reported to explain the relationship between haemochromatosis and arthropathy. Ferric salts are found to promote the formation and deposition of intra-articular calcium pyrophosphate crystals by inhibiting the activity of synovial pyrophosphatase, and hence can precipitate attacks of pseudogout in the joint. It has also been proposed that there is a metabolic abnormality independent of the primary iron absorption disorder which can disrupt the configuration of the cartilage matrix, leading to premature osteoarthritis.

This case report identifies only the second reported case of haemochromatosis presenting as an ankle arthropathy. This

diagnosis should always be considered in the differential diagnosis of an arthropathy in unusual joint sites. Screening tests, such as measurements of iron metabolism, should be performed, followed by, if indicated, the diagnostic genomic DNA analysis for the mutations found in haemochromatosis. The importance of making a correct diagnosis is that effective treatment by phlebotomy can halt progression of the systemic effects of excess iron deposition and progression to resultant damage of internal organs. After a diagnosis of haemochromatosis is made, all close relatives (including parents, siblings, and all offspring) should be genetically tested for the presence of haemochromatosis mutations. Early diagnosis and treatment of family members with the disease is essential to prevent end-organ damage, which might include cardiomyopathy, diabetes, liver cirrhosis, and hepatocellular carcinoma.

Authors' affiliations

S Abraham, A Cope, The Kennedy Institute of Rheumatology, Faculty of Medicine, Imperial College, 1 Aspenlea Road, Hammersmith, London W6 8LH, UK

Correspondence to: Dr S M Abraham; s.abraham@ic.ac.uk

Accepted 29 June 2003

REFERENCES

- Feder JN**, Gnirke A, Thomas W. A novel MHC class 1 like gene is mutated in patients with hereditary haemochromatosis. *Nature Genetics* 1996;**13**:399-408.
- Schumacher HR Jr**. Haemochromatosis and arthritis. *Arthritis Rheum* 1964;**26**:41-50.
- Jacki SH**, Uhl M, Adler CP, Peter HH, Kempis J. Predominant ankle arthropathy in hereditary haemochromatosis. *Rheumatology (Oxford)* 1999;**38**:378-9.
- Bailey EJ**, Gardner BA. Hemochromatosis of the foot and ankle: report of three cases and review of the literature. *Clin Orthop* 1998;**349**:108-15.
- Dymock IW**, Hamilton EDB, Laws JW, Williams R. Arthropathy of hemochromatosis. Clinical and radiological analysis of 63 patients with iron overload. *Ann Rheum Dis* 1970;**29**:469-76.
- Faraawi R**, Harth M, Kertesz A, Bell D. Arthritis in hemochromatosis. *J Rheumatol* 1993;**20**:448-52.

Does etanercept monotherapy enhance the risk of *Listeria monocytogenes* meningitis?

P Pagliano, V Attanasio, U Fusco, D A Mohamed, M Rossi, F S Faella

Ann Rheum Dis 2004;63:462–463. doi: 10.1136/ard.2003.015966

Considerable data have identified tumour necrosis factor α (TNF α) as a pivotal mediator in inflammatory processes, suggesting that it has a role also in the pathogenesis of some autoimmune diseases, such as rheumatoid arthritis (RA).^{1,2} Currently, two drugs that interfere with TNF α , infliximab and etanercept, have been extensively used for the treatment of patients with RA and other immunological disorders; both have been associated with a higher risk of serious infective complications.^{3–7}

Listeria monocytogenes is a Gram positive intracellular organism seen almost always in neonatal sepsis, elderly meningitis, and in patients with chronic diseases and impairment of cellular immunity, which avoids the host immunity by a mechanism of cell to cell spreading.⁸

Association between anti-TNF α agents and listeriosis has already been reported in patients treated with other immunosuppressive agents, but not in patients receiving etanercept monotherapy.^{9,10}

CASE REPORT

We report a case of *Listeria* meningitis in a 45 year old patient with RA. Methotrexate and cyclophosphamide had been given until 20 months before admission to hospital, when low grade renal failure developed and treatment was changed to monotherapy with etanercept 25 mg twice weekly. One day before admission, fever, malaise, headache, and progressive confusion developed.

At entry, examination showed a comatose state, neck stiffness, and fever (38.7°C). Deep tendon reflexes were symmetric, plantar responses were flexor. The findings on a computed tomographic scan of the brain were unremarkable. Blood laboratory analysis showed white blood cells $15 \times 10^9/l$ (91% neutrophils), glucose 8.3 mmol/l, blood urea nitrogen 17.5 mmol/l of urea, creatinine 180 μ mol/l, and no other significant abnormalities. Cerebrospinal fluid (CSF) showed pleocytosis (1.2×10^9 cells/l, lymphocyte 43%), high protein content (2.50 g/l), and glucose 3.6 mmol/l. Etanercept was withdrawn, and treatment with intravenous ceftriaxone (3 g/day), ampicillin (12 g/day), and dexamethasone (16 mg/day) was begun. Further results of the blood analysis obtained on

the second day of hospitalisation showed an erythrocyte sedimentation rate (ESR) of 42 mm/1st h, C reactive protein (CRP) 411 mg/l, CD4+ cell count $1.41 \times 10^9/l$ (CD4+/CD7+ 92%), CD8+ cell count $0.47 \times 10^9/l$ (CD8+/CD38+ 42%), TNF α 32.9 ng/ml. On the fourth day, *Listeria monocytogenes* grew from CSF and blood cultures, ceftriaxone was discontinued, and dexamethasone slowly tapered.

During the next 4 days, the patient's symptoms improved. Ampicillin was given for a total of 28 days, when full normalisation of the CSF variables had occurred. Blood analysis 2 and 4 months after meningitis, while the patient was taking only mild dose of prednisone (40 mg/day), showed a reduction of the ESR and CRP levels and a rise in TNF α (table 1).

DISCUSSION

The main concern about treatment of RA with TNF α neutralising agents is the possibility that latent tuberculosis may be unmasked; subsequent reports disclosed an increase in susceptibility for all infections sustained by intracellular agents. Infliximab, whose use is recommended in association with other immunosuppressive drugs, is implicated in the vast majority of cases.^{6,7} To our knowledge, etanercept has been associated with *Listeria monocytogenes* meningitis only in a 72 year old patient with RA receiving multiple immunosuppressive treatment (etanercept, prednisone, and methotrexate), and no case has been seen during monotherapy.⁹ A study of our patient's lymphocyte subset showed that it did not change during the course of the disease. TNF α levels increased during the follow up, when etanercept was discontinued. Although there is no evidence about association between low TNF α levels and immunosuppression, in our case we suggest there may be an association between etanercept treatment and impairment of cell mediated immunity because of low TNF α circulating levels.

Screening before treatment for latent tuberculosis, close clinical evaluation of every febrile illness, and zero tolerance regimens against *Listeria* and other intracellular preventable pathogens may improve the long term outcome of patients treated with anti-TNF α agents.

Authors' affiliations

P Pagliano, V Attanasio, U Fusco, D A Mohamed, M Rossi, F S Faella, Department of Emergency, Division of Infectious Neuropathies, "D. Cotugno" Hospital, Naples, Italy

Correspondence to: Dr P Pagliano, D Cotugno Hospital, Via G Quagliariello 54, 80131, Naples, Italy; ppagliano@libero.it

Accepted 17 December 2003

REFERENCES

- 1 Feldman M, Taylor P, Paleolog E, Brennan FM, Maini RN. Anti-TNF alpha therapy is useful in rheumatoid arthritis and Crohn's disease: analysis of the mechanisms of action predicts utility in other diseases. *Transplant Proc* 1998;30:4126–7.

Table 1 T cell subset, TNF α , and inflammatory index levels during the follow up

Variable	30th Follow up day	90th Follow up day
CD4+ lymphocyte ($\times 10^9$ cells/l)	1.41	1.87
CD4+/CD7+ (%)	92	95
CD8+ lymphocyte ($\times 10^9$ cells/l)	0.47	0.98
CD8+/CD38+ (%)	36	39
TNF α (ng/ μ l)	157	162
CRP (mg/l)	8	2
ESR (mm/1st h)	40	25

- 2 **Song XR**, Fox F, Gallo MA, Rosenberg A, Jordan R, Shealy D, *et al*. Effects of 2 different anti-Tumor necrosis factor- α in a primate model of subcutaneous abscess formation. *J Infect Dis* 2002;**185**:204–13.
- 3 **Moreland L**, Cohen S, Baumgartner E, Tindall EA, Bulpitt K, Martin R, *et al*. Longterm safety and efficacy of etanercept in patients with rheumatoid arthritis. *J Rheumatol* 2001;**28**:1238–44.
- 4 **Weinblatt ME**, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, *et al*. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;**340**:253–9.
- 5 **Kroesen S**, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF- α therapy. *Rheumatology (Oxford)* 2003;**42**:617–21.
- 6 **Doran MF**, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002;**46**:2287–93.
- 7 **Keane J**, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwiertman WD, *et al*. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralising agent. *N Engl J Med* 2001;**345**:1098–104.
- 8 **Lorber B**. Listeriosis. *Clin Infect Dis* 1997;**24**:1–11.
- 9 **Slifman NR**, Gershon SK, Lee JH, Edwards ET, Braun MM. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor α -neutralizing agent. *Arthritis Rheum* 2003;**48**:319–24.
- 10 **Gluck T**, Linde H-J, Scholmerich J, Muller-Ladner U, Fiehn C, Bohland P. Anti-tumor necrosis factor and Listeria monocytogenes infection: report of two cases. *Arthritis Rheum* 2002;**46**:2255–7.

Autoantibodies against glucose-6-phosphate isomerase are not a diagnostic marker for juvenile idiopathic arthritis

A Schmitt, D Schubert, C Sengler, T Kamradt

Ann Rheum Dis 2004;**63**:463. doi: 10.1136/ard.2003.014225

Rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) are chronic inflammatory diseases that primarily affect the joints. The triggers that activate autoreactive T and B lymphocytes in arthritic patients are still unknown.¹ It has been widely assumed, however, that the autoantigens recognised by arthritogenic lymphocytes are joint-specific. This assumption has been challenged by findings from a murine model of spontaneously developing polyarthritis. There, a ubiquitously expressed soluble antigen, the glycolytic enzyme glucose-6-phosphate isomerase (GPI)

is the target of autoreactive T cells and arthritogenic antibodies.²

It is, therefore, important to determine if GPI is also relevant to human arthritides. A role for antibodies against GPI in the pathogenesis of RA has been claimed³ and refuted.^{4–7} Some characteristics of the murine model, such as the lack of rheumatoid factors, resemble JIA rather than RA. Therefore, we tested whether plasma from patients with JIA contained antibodies against GPI. Recombinant human GPI was expressed as described⁴ and used to test serial dilutions of plasma from patients with JIA or controls matched for age. At a dilution of 1:50, only 1/82 JIA samples and 3/81 controls bound recombinant human GPI (fig 1). Thus, although autoantibodies specific for GPI mediate polyarthritis in a murine model, such antibodies do not occur in a significant fraction of patients with RA or JIA.

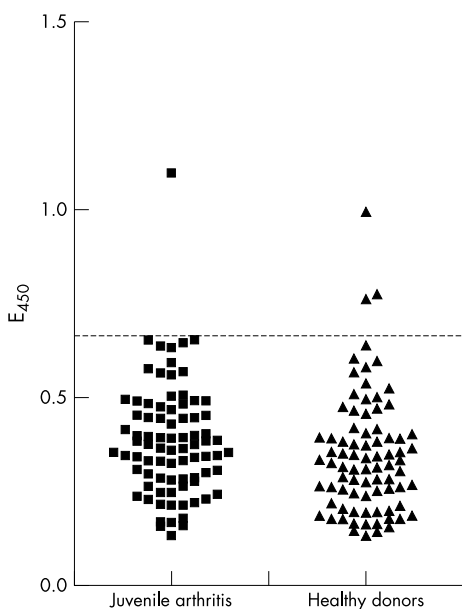


Figure 1 Plasma from patients with JIA or controls rarely contain antibodies against recombinant human GPI. Enzyme linked immunosorbent assays (ELISAs) were performed on sera (diluted 1:50) from 82 patients with JIA or 81 controls matched for age to detect antibodies against recombinant human GPI (produced in *E coli* in our laboratory). The cut off point for a positive value was defined as two standard deviations above the mean optical density of the 81 samples from healthy donors (dotted line).

Authors' affiliations

A Schmitt, D Schubert, T Kamradt, Deutsches Rheumaforschungszentrum Berlin, 10117 Berlin, Germany
C Sengler, Universitätsklinikum Charité, Department of Paediatrics, 10098 Berlin, Germany

Correspondence to: Dr T Kamradt, Deutsches Rheumaforschungszentrum, Schumannstr 20/21, 10117 Berlin, Germany; Kamradt@drfz.de

Accepted 28 July 2003

REFERENCES

- 1 **Kamradt T**, Mitchison NA. Advances in immunology: tolerance and autoimmunity. *N Engl J Med* 2001;**344**:655–64.
- 2 **Matsumoto I**, Staub A, Benoist C, Mathis D. Arthritis provoked by linked T and B cell recognition of a glycolytic enzyme. *Science* 1999;**286**:1732–5.
- 3 **Schaller M**, Burton DR, Ditzel HJ. Autoantibodies to GPI in rheumatoid arthritis: linkage between an animal model and human disease. *Nat Immunol* 2001;**2**:746–53.
- 4 **Schubert D**, Schmidt M, Zaiss D, Jungblut PR, Kamradt T. Autoantibodies against GPI and creatine kinase in rheumatoid arthritis. *Nat Immunol* 2002;**3**:411.
- 5 **Kassahn D**, Kolb C, Solomon S, Bochtler P, Illges H. Few human autoimmune sera detect GPI. *Nat Immunol* 2002;**3**:411–12.
- 6 **Matsumoto I**, Lee DM, Goldbach-Mansky R, Sumida T, Hitchon CA, Schur PH, *et al*. Low prevalence of antibodies to glucose-6-phosphate isomerase in patients with rheumatoid arthritis and a spectrum of other chronic autoimmune disorders. *Arthritis Rheum* 2003;**48**:944–54.
- 7 **Herve CA**, Wait R, Venables PJ. Glucose-6-phosphate isomerase is not a specific autoantigen in rheumatoid arthritis. *Rheumatology (Oxford)* 2003;**8**:986–8.

Haemorrhagic myositis associated with prophylactic heparin use in dermatomyositis

D M Langguth, R C W Wong, C Archibald, P G Hogan

Ann Rheum Dis 2004;**63**:464–465. doi: 10.1136/ard.2003.010272

An 80 year old man was admitted with a short history of fever, dyspnoea, and productive cough. A chest radiograph disclosed right lower lobe infiltrates, and a diagnosis of community acquired pneumonia was made. However, it was noted that he had profound weakness of the proximal, respiratory, and bulbar muscles together with typical features of dermatomyositis, including periorbital oedema and heliotrope discolouration, nailfold infarcts, and Gottron's papules. The serum creatine kinase (CK) level was raised at 1850 IU (reference range <300 IU). An electromyogram and muscle biopsy of the left vastus lateralis confirmed inflammatory myositis. There was no excess bleeding at the site. The diagnosis was revised to aspiration pneumonia secondary to bulbar weakness associated with dermatomyositis. Respiratory muscle weakness progressed after admission, with a fall in the forced expiratory volume (1 second) to 0.95 litres (predicted = 2.5 litres).

Intravenous methylprednisolone (500 mg/day for 3 days) was given, followed by oral prednisone at 80 mg/day. Treatment with prophylactic unfractionated heparin (UFH) (5000 IU twice a day subcutaneously) was started (the patient's weight was 80 kg).

After 9 days of corticosteroid treatment, the patient's strength and serum CK levels were improving. However, on day 10 he complained of a painful right hip of gradual onset. Plain radiographs of the right hip were normal. Avascular necrosis was suspected and magnetic resonance imaging (MRI) of the region was arranged for the next day. Examination before MRI showed a palpable small mass in the left rectus sheath, a tense swollen right thigh, and extensive bruising affecting the left flank. MRI subsequently showed extensive haemorrhagic change in the muscles of the right thigh (fig 1), and computed tomography of the

abdomen showed haemorrhage in the rectus sheath and oblique muscles (fig 2). His haemoglobin had fallen to 50 g/l from 130 g/l overnight, platelets were within the reference range, and the activated partial thromboplastin time (APTT) was slightly raised at 42 seconds (reference range <38 seconds). The APTT, prothrombin, and bleeding time were normal before the muscle biopsy.

The subcutaneous heparin was stopped and 3 units of packed cells and 4 units of fresh frozen plasma were transfused. The patient subsequently developed pulmonary oedema requiring assisted ventilation, but made a successful recovery and returned home after a short period of intensive rehabilitation. There was no history suggestive of a coagulation disorder and after the transfusion his coagulation profile returned to normal.

DISCUSSION

Our patient had a major complication associated with standard dose UFH use for deep vein thrombosis prophylaxis. Significant muscle haemorrhage has not been previously reported in patients with myositis, though recently has been found in a patient receiving therapeutic low molecular weight heparin (LMWH) and warfarin.¹ Heparin treatment is known to be associated with an increased risk of major bleeding, about 0.3%,² with both UFH and LMWH, mostly occurring in the gastrointestinal tract, though haemorrhage at the site of injection has been reported.³

Given the serious nature of this event, we would advise caution in using prophylactic heparin in patients with acute myositis.

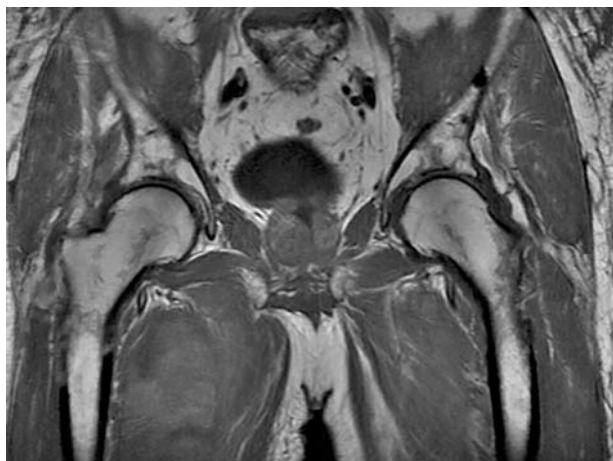


Figure 1 MRI of the pelvis disclosing a large right thigh haematoma.



Figure 2 A computed tomographic scan of the abdomen showing left rectus abdominus and oblique musculature haemorrhage.

Authors' affiliations

D M Langguth, R C W Wong, C Archibald, P G Hogan, Departments of Clinical Immunology and Radiology, Princess Alexandra Hospital, Perth, Australia

Correspondence to: Dr D M Langguth, Immunology Department, Royal Perth Hospital, Wellington St, Perth, WA 6000, Australia; daman.langguth@health.wa.gov.au

Accepted 30 June 2003

REFERENCES

- 1 **Gutknecht DR**. Hematoma of the rectus sheath. *N Engl J Med* 2003;**348**:15.
- 2 **Kleber FX**, Witt C, Vogel G, Koppenhagen K, Schomaker U, Flosbach CW. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. *Am Heart J* 2003;**145**:614–21.
- 3 **Antonelli D**, Fares L, Annene C. Enoxaparin associated with huge abdominal wall hematomas: a report of two cases. *Am Surg* 2000;**66**:797–800.

Isolated cranial nerve syndromes without proximal carotid involvement in aortoarteritis

G R Shroff, D R Karnad, U S Limaye, V M Kothari

Ann Rheum Dis 2004;**63**:465–466. doi: 10.1136/ard.2003.010389

Takayasu's arteritis or aortoarteritis affects the aorta and its proximal branches.¹ Cranial nerve involvement in the form of ischaemic optic neuropathy secondary to proximal carotid involvement is common.² Involvement of other cranial nerves has been reported only once before.³ We report two patients with aortoarteritis who developed isolated cranial nerve palsies. Notably, in both cases it occurred without proximal carotid involvement.

CASE REPORTS

Patient 1, a 30 year old businessman, presented with malignant hypertension because of right renal artery stenosis due to aortoarteritis affecting the abdominal aorta. After successful balloon angioplasty, blood pressure was well controlled with antihypertensive drugs. Two years later he developed sudden headache and diplopia on looking towards the left. Examination showed a convergent squint in the left eye due to abducens nerve palsy. Contrast enhanced brain computed tomography (CT) scan and cerebrospinal fluid (CSF) analysis were normal. Angiography showed that the aortic arch and its branches were normal; the suprarenal abdominal aorta showed irregular narrowing with stenosis of the left renal artery and the previously balloon-dilated right renal artery. On treatment with 1 mg/kg/day of prednisolone he recovered completely in 10 days.

One year later he developed diplopia again. This time he was found to have right abducens nerve palsy. Angiography showed normal carotid vessels but complete occlusion of the left subclavian artery 1 cm distal to its origin. Again, he made a complete recovery with 1 mg/kg of prednisolone over 20 days.

Patient 2, an 18 year old female student, was admitted for accelerated hypertension. A renal Doppler examination showed left renal artery stenosis. On aortography she had an irregular contour with narrowing of the abdominal aorta and occlusion from the origin of the left renal artery, suggestive of aortoarteritis. She refused renal angioplasty and was treated with antihypertensive drugs. Four years later she developed sudden diplopia and right eyelid ptosis. Examination showed complete ptosis on the right, divergent squint, and ophthalmoplegia, suggestive of isolated right oculomotor palsy. The pupil, however, was normal in size and constricted briskly in light. Contrast enhanced brain CT scan, CSF analysis, and four-vessel angiogram were normal. She received 1 mg/kg of prednisolone for 30 days with complete recovery.

DISCUSSION

Both patients satisfied Ishikawa's diagnostic criteria for aortoarteritis,⁴ and presented with sudden onset of isolated cranial nerve palsies. The normal CT scans and CSF examination excluded structural and infective aetiologies of cranial nerve palsies. The sudden onset of deficits in both patients suggested a vascular cause. Moreover, recurrence of the cranial nerve deficit on the contralateral side in patient 1 and the presence of pupillary sparing in patient 2 further supported a vascular aetiology. The pupil is characteristically unaffected in ischaemic oculomotor nerve palsy because the pupillary fibres, which are outermost, receive additional blood supply from the pial (meningeal) vessels and are therefore spared in oculomotor nerve infarction.⁵

The oculomotor and abducens nerves derive their arterial supply from the inferolateral trunk, which originates from the intracavernous siphon of the internal carotid artery.⁶ In our patients the extracranial carotid circulation and the siphon of the internal carotid artery were angiographically normal, suggesting involvement of small sized vessels supplying the cranial nerves. Nuclear brainstem infarcts could also cause cranial nerve deficits⁷ and a magnetic resonance imaging study (not done in our patients) would be most sensitive to diagnose them. However, this is very unlikely owing to the absence of signs of involvement of the brainstem ascending or descending tracts and rapid complete recovery of deficits with corticosteroids.

Similar isolated palsies of the nerves innervating the extraocular muscles may occur in other vasculitides, including Behçet's disease and giant cell arteritis.^{8–9}

Small vessel involvement has been described in some patients with aortoarteritis. Manifestations of these include glomerulonephritis,¹⁰ interstitial lung disease,¹¹ and necrotising vasculitic lesions of the skin.¹² It is likely that cranial nerve palsies in our patients too might be due to similar small vessel involvement in the central nervous system.

Authors' affiliations

G R Shroff, D R Karnad, U S Limaye, V M Kothari, Departments of Medicine and Radiology, Seth G S Medical College and K E M Hospital, Mumbai, India

Correspondence to: Dr G R Shroff, Department of Internal Medicine, Hennepin Country Medical Center, Minneapolis, MN 55415, USA; drgautamshroff@hotmail.com

Accepted 10 July 2002

REFERENCES

- Jennette JC, Falk RJ, Andrasz K, Bacon PA, Churg J, Gross WL, *et al.* Nomenclature of systemic vasculitides: proposal of an international consensus conference. *Arthritis Rheum* 1994;**37**:187–92.
- Schmidt MH, Fox AJ, Nicolle DA. Bilateral anterior ischaemic optic neuropathy as a presentation of Takayasu's disease. *J Neuroophthalmol* 1997;**17**:156–61.
- Gupta R, Kumar S. Relapsing spinal cord and cranial nerve syndromes in Takayasu's arteritis. *J Assoc Physicians India* 1989;**37**:537–9.
- Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. *J Am Coll Cardiol* 1998;**12**:964.
- Rosenstein ED, Sobelman J, Kramer N. Isolated, pupil-sparing third nerve palsy as initial manifestation of systemic lupus erythematosus. *J Clin Neuroophthalmol* 1989;**9**:285–8.
- Lapresle J, Lasjaunias P. Cranial nerve ischaemic arterial syndromes. *Brain* 1986;**109**:207–15.
- Thomke F, Gutmann L, Stoeter P, Hopf HC. Cerebrovascular brainstem diseases with isolated cranial nerve palsies. *Cerebrovasc Dis* 2002;**13**:147–55.
- Lew H, Lee JB, Han SH, Kim HS, Kim SK. Neuro-Behçet's disease presenting with isolated unilateral lateral rectus muscle palsy. *Yonsei Med J* 1999;**40**:294–6.
- Goldberg RT. Ocular muscle paresis and cranial arteritis—an unusual case. *Ann Ophthalmol* 1983;**15**:240–3.
- Yoshikawa Y, Truong LD, Mattioli CA, Lederer E. Membranoproliferative glomerulonephritis in Takayasu's arteritis. *Am J Nephrol* 1988;**8**:240–4.
- Greene NB, Baughman RP, Kim CK. Takayasu's arteritis associated with interstitial lung disease and glomerulonephritis. *Chest* 1986;**89**:605–6.
- Mousa AR, Marafie AA, Dajani AI. Cutaneous necrotizing vasculitis complicating Takayasu's arteritis with a review of cutaneous manifestations. *J Rheumatol* 1985;**12**:607–10.

Myeloablative immunosuppressive treatment with autologous haematopoietic stem cell transplantation in a patient with psoriatic arthropathy and monoclonal gammopathy of undetermined significance

M Mohren, T Daikeler, D Benz, I Günaydin, L Kanz, I Kötter

Ann Rheum Dis 2004;**63**:466–467. doi: 10.1136/ard.2003.010702

Transplantation of peripheral blood stem cells (PBSCT) is currently explored in patients with refractory autoimmune diseases,^{1,2} and results so far show that about two thirds of patients who receive a transplant benefit from this procedure.³ Transplant related mortality in patients with autoimmune disease is similar to that seen in patients with non-Hodgkin's lymphoma.⁴

CASE REPORT

We report on a 34 year old male patient with a 16 year history of psoriatic arthropathy with mutilating bilateral lesions of the wrists, metacarpal, proximal and distal interphalangeal and metatarsal, and lower extremity interphalangeal joints, who was refractory to treatment with multiple disease modifying, immunosuppressive substances, including gold, methotrexate (MTX), MTX plus sulfasalazine, cyclosporin A (CSA), mycophenolate mofetil (MMF) alone or in combination with CSA, steroids, and a combination of CSA, MTX, and MMF. IgA κ monoclonal gammopathy of unknown significance developed later in the course of the disease without evidence for either multiple myeloma or systemic amyloidosis. Treatment of arthritis with a non-steroidal anti-inflammatory drug (NSAID) was complicated by a duodenal ulcer. There were only modest psoriatic skin lesions affecting the extensor surfaces of both knees and elbows.

PBSCT was considered in this patient, because tumour necrosis factor α antagonists had not yet been licensed for use in psoriatic arthropathy at that time. We were particularly concerned about the presence of the IgA κ paraprotein, so therapeutic strategies to control symptoms of arthritis also aimed at eliminating the potentially hazardous plasma cell clone. Haematopoietic stem cells were mobilised with cyclophosphamide (Cy) 4000 mg/m² and granulocyte-colony stimulating factor (G-CSF) 5 μ g/kg. Stem cell apheresis was performed following standard procedures, and T cell depletion of the graft was achieved by CD 34+ selection using the CliniMACS device. CD 34+ cells (11.38 \times 10⁶ cells/kg) were harvested. Myeloablative immunosuppression consisted of Cy 200 mg/kg (50 mg/kg/day, days –5 to –2), and in vivo T cell

depletion was achieved with antithymocyte globulin (ATG) (Fresenius) 80 mg/kg (20 mg/kg/day, days –4 to –1). CD 34+ cells (5.21 \times 10⁶ cells/kg) were retransfused on day 0. An acute flare of arthritis occurred while the patient was receiving G-CSF for stem cell mobilisation, and this was symptomatically treated with an NSAID. Pancytopenia after myeloablative treatment was complicated by neutropenic fever (39.1°C) on day 11, subsiding under standard antibiotic treatment. Mucositis and diarrhoea WHO grade I occurred, lasting for 3 days. Within 3 days after the start of high dose Cy the symptoms of arthritis completely disappeared, as did the psoriatic lesions. As granulocytes did not recover by day 15, G-CSF was started, and no new flare of arthritis was observed. Granulocytes were $>10^9/l$ by day 19, platelets $>20 \times 10^9/l$ by day 21, and the erythrocyte sedimentation rate and C reactive protein subsequently normalised.

Clinical findings were confirmed by negative bone scintigraphy on day 21. Within 6 months after PBSCT the IgA κ paraprotein disappeared.

However, 16 months after PBSCT, polyarthritis recurred, although without laboratory evidence of systemic inflammation (erythrocyte sedimentation rate and C reactive protein were within normal limits), apparently now following a more benign course. At present, the patient is receiving low dose MTX (10 mg/week) and a COX-2 selective NSAID (celecoxib) and has only mild signs of arthritis of the right wrist. Monoclonal gammopathy has not reappeared.

DISCUSSION

To our knowledge this is the first report of PBSCT in a patient with psoriatic arthropathy. In rheumatoid arthritis, disease activity decreased markedly in 8 of 12 patients, with patients free from disease modifying antirheumatic drug treatment for a period of 130 days during a 7–21 month follow up after PBSCT.⁵ Remission of arthritis in patients with rheumatoid arthritis after PBSCT usually lasts for 6–9 months.^{5–7} In our patient relapse of arthritis, with a now more benign course, did not occur until 16 months after PBSCT, possibly owing to a more aggressive immunosuppressive regimen, including in

vivo T cell depletion with ATG and graft manipulation. Three patients with remission of psoriasis (without arthropathy) after PBSCT due to a haematological disease relapsed within 6–14 months as described in a previously published report.⁸ However, skin involvement was not of major concern in our patient.

We conclude that it may be worth exploring PBSCT further in young patients with mutilating psoriatic arthropathy who are resistant to disease modifying antirheumatic drugs and for whom tumour necrosis factor α antagonist treatment has failed.

Authors' affiliations

M Mohren, T Daikeler, D Benz, I Günaydin, L Kanz, I Kötter, Department of Haematology, Oncology, Immunology and Rheumatology, Tübingen University Hospital, Tübingen, Germany

Correspondence to: Dr I Kötter, Department of Internal Medicine II, Haematology/Oncology, Immunology and Rheumatology, University Hospital, Offried-Müller-Str 10, 72076 Tübingen, Germany; ina.koetter@med.uni-tuebingen.de

Accepted 10 July 2003

REFERENCES

- 1 Tyndall A. Haematological stem cell transplantation in the treatment of severe autoimmune diseases: first experiences from an international project. *Rheumatology (Oxford)* 1999;**38**:774–6.
- 2 Tyndall A, Fassas A, Passweg J, Ruiz de Elvira C, Attal M, Brooks P, et al. Autologous haematopoietic stem cell transplants for autoimmune disease—feasibility and transplant-related mortality. *Bone Marrow Transplant* 1999;**24**:729–34.
- 3 Burt RK, Georganas C, Schroeder J, Traynor A, Stefa J, Schuening F, et al. Autologous hematopoietic stem cell transplantation in refractory rheumatoid arthritis. *Arthritis Rheum* 1999;**42**:2281–5.
- 4 Burt RK, Fassas A, Snowden JA, van Laar JM, Kozak T, Wulffraat NM, et al. Collection of hematopoietic stem cells from patients with autoimmune diseases. *Bone Marrow Transplant* 2001;**28**:1–12.
- 5 Snowden JA, Biggs JC, Milliken ST, Fuller A, Brooks PM. A phase I/II dose escalation study of intensified cyclophosphamide and autologous blood stem cell rescue in severe, active rheumatoid arthritis. *Arthritis Rheum* 1999;**42**:2286–92.
- 6 Verburg RJ, Kruize AA, van den Hoogen F, Fibbe WE, Petersen EJ, Preijers F, et al. High dose chemotherapy and autologous hematopoietic stem cell transplantation in patients with rheumatoid arthritis. *Arthritis Rheum* 2001;**44**:754–60.
- 7 Breban M, Dougados M, Picard F, Zompi S, Marolleau JP, Bocaccio C, et al. Intensified-dose (4 g/m²) cyclophosphamide and granulocyte colony-stimulating factor administration for hematopoietic stem cell mobilization in refractory rheumatoid arthritis. *Arthritis Rheum* 1999;**42**:2275–80.
- 8 Cooley H, Snowden J, Grigg A, Wicks I. Outcome of rheumatoid arthritis and psoriasis following autologous stem cell transplantation for hematologic malignancy. *Arthritis Rheum* 1997;**40**:1712–15.

Peripheral blood lymphocyte phenotypes in patients with spondyloarthropathy

A Plonquet, A Gleizes, K Briot, P Maison, X Chevalier, J-P Farcet, P Claudepierre

Ann Rheum Dis 2004;**63**:467–468. doi: 10.1136/ard.2003.006965

A prevalent hypothesis in the pathogenesis of the spondyloarthropathies (SpA) is that gut lymphocytes primed by antigens in the gut lumen may enter the bloodstream and home in on target tissues—for example, the entheses and synovial membranes, where they may initiate a local immune process responsible for further local inflammation.¹ Selective homing of lymphocytes is a well known process that is made possible, in part, by the lymphocyte phenotype acquired as a response to antigenic stimulation and characterised by a subset of receptors (such as integrins) associated with targeted trafficking.² Among integrins, $\alpha_E\beta_7$, is expressed by T lymphocytes in or adjacent to mucosal epithelia, and exhibits features that indicate a possible role in this pathogenic process.^{3,4} To our knowledge, there are no data on the markers for activation and adhesion of circulating lymphocytes in the SpA. The main objective of this study was to look for differences in $\alpha_E\beta_7$ (CD103) blood lymphocyte counts between patients with active and those with inactive SpA, using flow cytometry. We also studied markers for other adhesion molecules, lymphocyte subsets, and lymphocyte activation.

PATIENTS, METHODS, AND RESULTS

Twenty patients meeting European Spondylarthropathy Study Group criteria⁵ or Amor's criteria⁶ for SpA were enrolled in the study, together with control patients followed up for chronic degenerative low back pain. They did not have any other underlying disease and only had a non-steroidal anti-inflammatory drug (NSAID) or acetaminophen as current treatment. All patients and controls gave their

written informed consent to participation in the study, which was approved by the local ethics committee. Table 1 shows the main characteristics of the patients. The 20 control patients had a mean (SD) age of 39.8 (9.6) years ($p > 0.05$ v the SpA group) and six of them were men. Flow cytometry was performed using a Coulter EPICS(r) XL within 24 hours after staining. List mode parameters were analysed and stored on System II software (Beckman-Coulter).

The studied markers (absolute count and/or percentage of positive cells) were compared between the patients with SpA and the controls, and between the patients with SpA with active disease and those with quiescent or controlled disease. Active disease was defined a priori as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score $> 30^7$ with a C reactive protein (CRP) level > 15 mg/l (Mann-Whitney test).

The mean (SD) percentage of CD103 lymphocytes did not differ between the patients with SpA (0.9 (0.4)%) and controls (1 (0.6)%), but was significantly lower in the patients with active SpA (0.66 (0.26)%) than in those with inactive SpA (1.2 (0.7)%, $p < 0.05$). Except for a small but significant decrease in the percentage of CD49d positive cells in the patients with SpA as compared with the controls, no significant differences between the groups with active and inactive SpA were seen for any of the three other integrin markers (CD11a, CD29, and CD49d). The frequencies of the main CD4 and CD8 T cell subsets and NK cells were not significantly different between the patients with SpA and controls or between the groups with active and inactive SpA. However, there was a trend toward an increase in the CD3+ lymphocyte count in the group with active SpA, which was

Table 1 Demographic data and main disease characteristics in the 20 patients with spondyloarthritis (SpA)

Characteristics	All patients with SpA (n = 20)	Active disease (n = 7)	Inactive disease (n = 13)	p*(active v inactive)
Age (years)	35.4 (9.1)	36.4 (7.5)	34.8 (10.1)	>0.05
Sex ratio, M/F	13/7	6/1	7/6	>0.05
Disease duration (years)	8.2 (5.6)	10.1 (3.1)	7.1 (6.5)	>0.05
Sacroiliitis	14	6	8	>0.05
Psoriasis	4	2	2	>0.05
Presence of B27	16†	5	11	>0.05
BASDAI score	50.7 (22.7)	59.4 (13.5)	45.7 (25.9)	>0.05
BASFI score	40 (26.6)	64.2 (13)	23.9 (20)	0.02
ESR (mm/1st h)	22.4 (20)	39.5 (26.4)	14.5 (10.3)	0.05
CRP (mg/l)	18.2 (22)	44.8 (17.8)	5.8 (8.6)	0.002

Results for quantitative parameters are given as means (SD).

*Comparisons were performed using the χ^2 test or Fisher's exact test for qualitative parameters and the Mann-Whitney test for quantitative parameters; †two not done.

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

ascribable primarily to a trend towards higher CD8+ T cell counts. The absolute count of CD8+ cells positive for CD62L was significantly greater in the group with active SpA (140 (28)) than in the group with inactive SpA (77 (82), $p < 0.05$), whereas no difference was noted between the overall SpA patient group and the control group. A trend in the same direction was seen for CD4+ lymphocytes, although the difference was not statistically significant. None of the between-group differences for these molecules (CD25, CD38, DR, CD45RA-RO), which can be considered markers of lymphocyte activation, were statistically significant.

DISCUSSION

This study provides the first data on blood lymphocyte phenotypes according to disease activity in patients with SpA. It found no differences in peripheral blood lymphocyte phenotypes between patients with SpA and controls. However, a decrease of lymphocytes expressing $\alpha_E\beta_7$ integrin was seen in patients with active SpA, which may suggest an accumulation of these cells in tissue and add to earlier evidence⁸ that T cells expressing $\alpha_E\beta_7$ may be involved in the pathogenesis of SpA. The increase in absolute counts of CD8+ T cells expressing L-selectin observed in the same subgroup of patients with active SpA may reflect different immunological processes and also deserves further study.

Authors' affiliations

K Briot, X Chevalier, P Claudepierre, Department of Rheumatology, Henri Mondor Hospital, France

A Plonquet, A Gleizes, J-P Farcet, Department of Immunology, Henri Mondor Hospital, France
P Maison, Clinical Research Unit, Henri Mondor Hospital, France

Correspondence to: Dr P Claudepierre, Service de Rhumatologie, Hôpital Henri Mondor, 94010 Créteil, cedex Créteil, France; pascal.claudepierre@hmn.ap-hop-paris.fr

Accepted 27 May 2003

REFERENCES

- 1 Wolheim FA. Enteropathic arthritis: how do the joints talk with the gut? *Curr Opin Rheumatol* 2001;13:305-9.
- 2 Butcher EC, Picker LJ. Lymphocyte homing and homeostasis. *Science* 1996;272:60-6.
- 3 Cerf-Bensussan N, Jarry A, Brousse N, Lisowska-Grospierre B, Guy-Grand D, Griscelli C. A monoclonal antibody (HML-1) defining a novel membrane molecule present on human intestinal lymphocytes. *Eur J Immunol* 1987;17:1279-85.
- 4 Elewaut D, De Keyser F, Van den Bosch F, Lazarovits AI, De Vos M, Cuvelier C, et al. Enrichment of T cells carrying β_7 integrins in inflamed synovial tissue from patients with early spondyloarthritis, compared to rheumatoid arthritis. *J Rheumatol* 1998;25:1932-7.
- 5 Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondyloarthritis. *Arthritis Rheum* 1991;34:1218-27.
- 6 Amor B, Dougados M, Mijiyawa M. Critères diagnostiques des spondylarthropathies. *Rev Rhum Mal Osteoartic* 1990;57:85-9.
- 7 Garrett S, Jenkinson T, Whitelock H, Kennedy G, Gaisford P, Calin A. A new approach to defining disease status in AS: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). *J Rheumatol* 1994;21:2286-91.
- 8 Elewaut D, De Keyser F, Van den Bosch F, Lazarovits AI, De Vos M, Cuvelier C, et al. Enrichment of T cells carrying β_7 integrins in inflamed synovial tissue from patients with early spondyloarthritis, compared to rheumatoid arthritis. *J Rheumatol* 1998;25:1932-7.

EULAR Teach the Teachers Workshop

5-9 May 2004; Vidago Palace Hotel, Vidago, Portugal

EULAR is proud to announce the organisation of this workshop devoted to the discussion and exchange of best practice in curriculum design, teaching, and assessment methods for musculoskeletal diseases in undergraduate medical courses.

This meeting is designed to guarantee an intensive interactive format in a charming venue.

For more information on the programme, venue, registration fees, and transportation visit the EULAR website at:

<http://www.eular.org>

under "courses" or see:

<http://www.aims-international.com/teachersworkshop>

for registration and programme information.