antigen was detected as long as three and 17 years after yersinia infection,⁷ suggesting that the microbial structures can persist in the tissues. The antigens are found in mesenteric and cervical lymph nodes and in the skin,¹¹ and, during the acute phase of infection, in peripheral blood cells of almost every patient, including patients who will not develop reactive arthritis.¹² Thus the presence of antigens in the blood provides an explanation for extensive antigen dissemination, but not for the development of reactive arthritis and other clinically significant extraintestinal manifestations.

Possibly, extraintestinal symptoms derive from inflammatory hyperreactivity of the patient to the antigenic stimulus. It has been reported that neutrophils of HLA-B27 positive subjects without a history of yersinia infection and of patients with previous yersinia reactive arthritis show enhanced neutrophil migration in response to a chemotactic stimulus *in vitro*³ and *in vivo*,¹³ as do patients with ankylosing spondylitis, at least *in vitro*.¹⁴ Furthermore, neutrophils from patients who have a history of severe acute yersinia triggered reactive arthritis,¹⁵ or with sequelae,⁴ show increased generation of oxygen radicals *in vitro*. NAP-1/IL-8 stimulates neutrophil chemotaxis and oxygen radical production⁵ and might thereby contribute to the neutrophil hyperactivity.

In conclusion, the results show that both control and lipopolysaccharide induced NAP-1/IL-8 production by monocytes was similar in subjects with past yersinia arthritis or enteritis and unaffected subjects, and did not differ between HLA-B27 positive and negative subjects. This seems to rule out an aberrant function of monocytes, at least for the synthesis and release of NAP-1/IL-8, one of their major products, in the triggering of reactive arthritis.

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C, Taylor-Robinson D. Chlamydia trachomatis and reactive arthritis: the missing link. *Lancet* 1987; i: 72-4.

- 7 Granfors K, Jalkanen S, von Essen R, *et al*. Yersinia antigens in synovial-fluid cells from patients with reactive arthritis. *N Engl J Med* 1989; 320: 216-21.
- 8 Granfors K, Jalkanen S, Lindberg A A, *et al*. Salmonella lipopolysaccharide in synovial cells from patients with reactive arthritis. *Lancet* 1990; 335: 685-8.
- 9 Leirisalo-Repo M, Suoranta H. Ten-year follow-up study of patients with yersinia arthritis. *Arthritis Rheum* 1988; 31: 533-7.
- 10 Walz A, Peveri P, Aschauer H, Baggiolini M. Purification and amino acid sequencing of NAF, a novel neutrophil-activating factor produced by monocytes. *Biochem Biophys Res Commun* 1987; 149: 755-61.
- 11 Hoogkamp-Korstanje J A A, de Koning J, Samsom J P. Incidence of human infection with Yersinia enterocolitica serotypes O3, O8, and O9 and the use of indirect immunofluorescence in diagnosis. *J Infect Dis* 1986; 153: 138-41.
- 12 Granfors K, Jalkanen S, Lahesmaa-Rantala R, Saario R, Möttönen T, Toivanen A. Bacterial antigens in peripheral blood cells in yersinia-triggered reactive arthritis [abstract]. *Scand J Rheumatol Suppl* 1990; 85: 45.
- 13 Koivuranta-Vaara P, Repo H, Leirisalo M, Kiistala U, Österman T, Vapaatalo H. Enhanced neutrophil migration *in vivo* in HLA-B27 positive subjects. *Ann Rheum Dis* 1984; 43: 181-5.
- 14 Pease C T, Fordham J N, Currey H L F. Polymorphonuclear cell motility, ankylosing spondylitis, and HLA-B27. *Ann Rheum Dis* 1984; 43: 279-84.
- 15 Koivuranta-Vaara P, Repo H, Leirisalo-Repo M. Polymorphonuclear leucocyte function and previous yersinia arthritis: enhanced chemokinetic migration and oxygen radical production correlate with the severity of the acute disease. *Ann Rheum Dis* 1987; 46: 307-13.

Hand radiography: an indicator of upper cervical disease in rheumatoid arthritis

Sir: One of the most dangerous complications of rheumatoid arthritis is upper cervical disease, which can cause sudden deaths and serious neurological problems. In previous surveys, reported prevalences of atlantoaxial subluxations range between 19 and 71% according to the patient selection and radiological techniques used.¹⁻³ Although direct radiographic investigations can show atlantoaxial subluxations, computed tomography (CT) and magnetic resonance imaging are the best procedures for eliciting the myelopathy and bone soft tissue pathologies in this region.⁴⁻⁷ As these methods are expensive, however, the question then has to be asked: which patients with rheumatoid arthritis should be evaluated by CT or magnetic resonance imaging?

Conlon *et al* were the first group reporting a relation between atlantoaxial subluxations and severe peripheral joint destruction.² Later, reports from Stevens *et al*¹ and Rasker and Cosh³ supported this view. We attempted to determine if the CT findings correlate with hand radiographic findings or not. We studied 40 patients chosen randomly from 138 outpatients at Ankara Hospital, diagnosed as having rheumatoid arthritis according to the 1987 revised criteria of the American Rheumatism Association.⁸ Anteroposterior and lateral radiographs were obtained and then we carried out CT of the craniocervical junction in the axial and coronal planes with the patient's neck in maximum flexion and neutral position by using a third generation scanner. We noticed not only atlantoaxial subluxations but also erosions of the odontoid process or atlas arcus, thickness of the ligaments, distension of the synovial cavities, and ligament ruptures.

Of the 40 patients studied, 12 had completely normal or slightly abnormal (periarticular soft tissue swelling, periarticular osteoporosis, slight joint space narrowing) hand radiographs. In this group there was no evidence of upper cervical disease or atlantoaxial subluxations in CT scans, except in one patient who had a slightly thickened transverse ligament. In the remaining group of 28 patients, who had erosions and marked joint space narrowing in hand radiographs, we found CT abnormalities of all kinds in 25 and atlantoaxial subluxations in 19 patients. As expected, atlantoaxial subluxations were associated with severe and mutilating abnormalities in the hand radiographs. We suggest that if the hand radiographs are normal, upper cervical spine disease should not be expected in rheumatoid arthritis and there is no need for sophisticated examination of this region.

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- 1 Stevens J C, Cartledge N E F, Saunders M, Appleby A, Hall M, Shaw D A. Atlanto-axial subluxation and cervical myelopathy in rheumatoid arthritis. *Q J Med* 1971; 159: 391-408.
- 2 Conlon P W, Isdale I C, Rose B S. Rheumatoid arthritis of the cervical spine. An analysis of 333 cases. *Ann Rheum Dis* 1966; 25: 120-6.
- 3 Rasker J J, Cosh J A. Radiological study of cervical spine and hand in patients with rheumatoid arthritis of 15 years' duration: an assessment of the effects of corticosteroid treatment. *Ann Rheum Dis* 1978; 37: 529-35.
- 4 Daniels D L, Williams A L, Houghton V M. Computed tomography of the articulations and ligaments at the occipito-atlanto-axial region. *Radiology* 1983; 146: 709-16.
- 5 Castor W R, Miller J D R, Russell A S, Chiu P L, Grace M, Hanson J. Computed tomography of the craniocervical junction in rheumatoid arthritis. *J Comput Assist Tomogr* 1983; 7: 31-6.
- 6 Toolanen G, Larsson S E, Fagerlund M. Medullary compression in rheumatoid atlanto-axial subluxation evaluated by computerised tomography. *Spine* 1986; 11: 191-4.
- 7 Reynolds H, Carter S W, Murtagh F R, Rechting G R. Cervical rheumatoid arthritis: value of flexion and extension views in imaging. *Radiology* 1987; 164: 215-8.
- 8 Arnett F C, Edworthy S M, Bloch D A, *et al*. The American Rheumatism Association 1987 revised criteria for classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.

Positive antinuclear antibodies in malignancies

Sir: I read with interest the recent case report of a patient with Raynaud's phenomenon and positive antinuclear antibodies in a malignancy.¹ I would like to report two additional cases of malignancies, which were associated with Raynaud's phenomenon and a high titre of antinuclear antibodies, and make some comments on the subject.

CASE 1

A 61 year old man presented for rheumatology evaluation with a six month history of arthralgias in both hands and a six week history of severe Raynaud's phenomenon. Eight months earlier he had been admitted to hospital because of hemiparesis of his left arm and leg, which lasted a couple of days with fever of 39.5°C. He was checked thoroughly in a neurological and a medical clinic, but no underlying cause of the prolonged neurological deficit and the fever was found. Finally, he was suspected to have an unknown vasculitis and given high dose steroids, which relieved his symptoms. Antinuclear antibodies were negative at that time. When he was referred to

- 1 Arnett F C. The Lyme spirochete: another cause of Reiter's syndrome? *Arthritis Rheum* 1989; 32: 1082-4.
- 2 Repo H, Ristola M, Leirisalo-Repo M. Enhanced inflammatory reactivity in the pathogenesis of spondyloarthropathies. *Autoimmunity* 1990; 7: 245-54.
- 3 Leirisalo M, Repo H, Tiilikainen A, Kosunen T U, Laitinen O. Chemotaxis in yersinia arthritis. HLA-B27 positive neutrophils show high stimulated motility *in vitro*. *Arthritis Rheum* 1980; 23: 1036-44.
- 4 Repo H, Koivuranta-Vaara P, Leirisalo-Repo M. Polymorphonuclear leucocyte function and previous yersinia arthritis: correlation of enhanced superoxide production with late manifestations. *Ann Rheum Dis* 1988; 47: 452-7.
- 5 Baggiolini M, Walz A, Kunkel S L. Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. *J Clin Invest* 1989; 84: 1045-9.
- 6 Keat A, Thomas B, Dixey J, Osborn M, Sonnex

this clinic by his family doctor for a diagnosis to be made he was receiving 7.5 mg prednisolone and except for the arthralgias and the Raynaud's phenomenon he had no complaints. When the prednisolone was discontinued, however, he had sweats at night.

Physical examination disclosed pitting scars on the second and third fingers of both hands and Raynaud's phenomenon could be provoked. Westergren sedimentation rate was 105 mm/h, his platelet count was $648 \times 10^9/l$, and an antinuclear antibody titre of 1/640 on HEp-2 cells with a speckled pattern was found. Anticentromere antibodies were negative. A bone scintigram and radiographs of hands and feet were normal. Routine chest radiography showed a 4 cm mass in the lingula region of his left lung. Histological evaluation of material obtained by fibreoptic bronchoscopy showed cells of squamous cell carcinoma. Perihilar and mediastinal lymph node metastases were present. Radiation therapy was carried out, but the patient died nine months later. Raynaud's phenomenon and arthralgia were present until the end. No rheumatological diagnosis could be established. The rheumatological symptoms of the patient and the positive antinuclear antibodies were considered as a paraneoplastic syndrome.

CASE 2

A 69 year old woman was referred to rheumatology with an antinuclear antibody titre of 1/5120 with a centromere pattern and a complex unexplained combination of symptoms and findings. Two months earlier she had received bypass surgery on her left femoropopliteal artery because of chronic artery occlusion disease stage II-IIIb.

One month later she was admitted to hospital again because of phlebothrombosis in both legs and pulmonary embolism in her right lung. Local lysis therapy using urokinase was performed, a filter was implanted in her vena cava, and she received warfarin. Diagnostic tests were performed to find out the cause of the thrombosis. Alkaline phosphatase was slightly raised at 283 U/l and tumour marker CA 19-9 at 24 000 U/l was greatly increased. Radiology of the stomach was normal. An abdominal computed tomography scan showed small irregular areas of the liver and a slight irregular pattern in the head of the pancreas, which were interpreted as cysts. The patient was discharged.

Ten days later she presented in the outpatient clinic again. She complained of thoracic and low back pain. Because of the positive antinuclear antibodies a connective tissue disorder was suspected. She had had Raynaud's phenomenon since childhood, but did not consider it a disturbing problem. The computed tomography scan of the abdomen was repeated, and the suspected lesion of the pancreas was biopsied. Histological tests showed adenocarcinoma. Radiation treatment was started and her condition improved slightly. Five months later she had a fracture of her right femoral head and required an operation. Two days later her general condition deteriorated rapidly and she died.

An increased antinuclear antibody titre in a patient with a carcinoma can occur with a coexisting connective tissue disease. In the second case it is possible that the anticentromere antibodies belonged to the longstanding primary Raynaud's phenomenon, which can be associated with anticentromere antibodies not only in CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) syndrome but in

Raynaud's phenomenon alone. Anticentromere antibodies had not been determined previously, however, because the patient had not considered her Raynaud's phenomenon disturbing or painful.

In case 1 the antinuclear antibodies were negative eight months before presentation. Raynaud's phenomenon and raised antinuclear antibody titre developed together with the lung cancer and have to be considered as paraneoplastic phenomena.

Although antinuclear antibodies are considered a hallmark of systemic rheumatic diseases,² and are a diagnostic criterion for systemic lupus erythematosus,³ they can occur in other conditions. In a recent survey⁴ it was reported that of all patients with positive antinuclear antibodies and no established diagnosis referred to a rheumatologist for evaluation, 51.4% had connective tissue diseases, 15.9% had organ specific autoimmune diseases, 8.3% had infections, 2.9% had neoplasia, 10.9% had miscellaneous other diseases, and 13.4% remained without a diagnosis. Another study,⁵ in which patients with different malignancies were examined for the presence of antinuclear antibodies without an underlying connective tissue disease, showed that many patients with tumours have low antinuclear antibody titres of about 1/40 in immunofluorescence. Titres above 1/640, however, do occur occasionally, especially in patients with cancer of lung, breast, or colon. However, none of the patients with high titre antinuclear antibodies in immunofluorescence on HEp-2 cells had the specific antibodies to DNA, Sm, SSA, SSB, RNP or Scl-70, which are markers for autoimmune diseases. There are only two reports in which antinuclear antibodies of patients with malignancies were analysed on a protein level to determine the autoantigens. Freundlich *et al* describe a patient with adenocarcinoma of ovarian origin whose serum reacted in immunoblot with several hitherto unknown protein bands.⁶ Bonfa *et al*⁷ analysed antinuclear antibodies from patients with melanoma by western blot and reported several groups of antigenic protein bands.

The molecular level of these antigens is not yet known and we do not understand the meaning of these antinuclear antibodies in malignancies. The antigens might be tumour specific and the production of antibodies an attempt to neutralise them. The occurrence of antinuclear antibodies might also represent a loss of self/non-self discrimination. Another view is that patients with cancer develop lots of autoantibodies resulting from the tissue damage and necrosis that occurs in cancer, which allows proteins which are not normally seen by the immune system to be presented.

These examples teach us that in patients with a significant antinuclear antibody titre, especially in the absence of specific antibodies to DNA and extractable nuclear antigens, the possibility of an underlying carcinoma should be considered. In younger patients there is still the likelihood of a manifestation of a connective tissue disease later in life. In older patients an unexplained high antinuclear antibody titre should direct our diagnostic tests not only towards finding a connective tissue disease but also towards searching for a malignancy.

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- 1 Tolosa-Vilella C, Ordi-Ros J, Vilardell-Tarres M, Selva-O'Callaghan A, Jordana-Comajuncosa R. Raynaud's phenomenon and positive antinuclear antibodies in a malignancy. *Ann Rheum Dis* 1990; 49: 935-6.
- 2 Tan E M. Autoantibodies to nuclear antigens (ANA): their immunobiology and medicine. *Adv Immunol* 1982; 33: 167-240.
- 3 Tan E M, Cohen A S, Fries J F, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
- 4 Shiel W C, Jason M. The diagnostic associations of patients with antinuclear antibodies referred to a community rheumatologist. *J Rheumatol* 1989; 16: 782-5.
- 5 McCarty G A. Autoimmunity and malignancy. *Med Clin North Am* 1985; 69: 599-615.
- 6 Freundlich B, Makover D, Maul G G. A novel antinuclear antibody associated with a lupus-like paraneoplastic syndrome. *Ann Intern Med* 1988; 109: 295-7.
- 7 Bonfa E, Bystrom J-C, Elkon K B. Detection of immunoglobulin G antibodies in melanoma sera reactive with intracellular proteins. *J Invest Dermatol* 1988; 90: 207-12.

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Conjunctival ulceration in Behçet's syndrome

Sir: Previously, we reported in the *Annals* the case of a 45 year old woman with coexistent Behçet's syndrome and ankylosing spondylitis.¹ Recently, this patient developed an unusual manifestation of Behçet's syndrome deserving publication—namely, conjunctival ulceration.

In June 1990 she presented with pain in her left eye. An ophthalmological examination showed no sign of uveal or retinal involvement but only an ulceration, similar to oral aphthae, on the lower palpebral conjunctiva (figure). The patient indicated, however, that the ocular pain was similar to the oral pain caused by buccal aphthae.

Mucous ulcers are important features of Behçet's syndrome. Recurrent oral aphthous ulcerations are so common that according to the recently proposed diagnostic criteria their presence is an indispensable condition for diagnosing Behçet's syndrome.² Mucous ulcers, often showing aspects similar to oral aphthae, have also been seen on the epiglottis,

'Aphthous-like' conjunctival ulceration on the lower palpebral conjunctiva (arrow).