antigen was detected as long as three and 17 years after yersinia infection,\textsuperscript{1} suggesting that the microbial structures can persist in the tissues. The antigens are found in mesenteric and cervical lymph nodes and in the skin,\textsuperscript{11} and, during the acute phase of infection, in peripheral blood cells of almost every patient, including patients who will not develop reactive arthritis.\textsuperscript{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 stimulant in vitro and in vivo,\textsuperscript{13,14} as do patients with anklyosing spondylitis, at least in vitro.\textsuperscript{14} Furthermore, neutrophils from patients who have a history of severe acute yersinia triggered reactive arthritis,\textsuperscript{13} or with sequelae,\textsuperscript{1} show increased generation of oxygen radicals in vitro. NAP-1/IL-8 stimulates neutrophil chemotaxis and oxygen radical production\textsuperscript{10} 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 from 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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Hand radiography: an indicator of upper cervical rheumatoid arthritis

Sirs: 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 number of radiological techniques used.\textsuperscript{3,4} Although direct radiographic investigations can show atlantoaxial subluxations, computed tomography (CT) and magnetic resonance imaging are the best procedures for investigating the myelopathy and bone soft tissue pathologies in this region.\textsuperscript{5,6} 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\textsuperscript{7} were the first group reporting a relation between atlantoaxial subluxations and severe peripheral joint destruction.\textsuperscript{8} Later, reports from Stevens et al\textsuperscript{9} and Rasker and Cos\textsuperscript{10} supported this view. We attempted to determine if the CT findings correlate with hand radiographic findings or not. We studied 100 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.\textsuperscript{11} Anteroposterior and lateral radiographs were taken and then we carried out CT of the cranio cervical junction in the axial and coronal planes with the patient’s neck in maximum flexion and neutral position by using a computerized tomography scanner.

We noticed not only atlantoaxial subluxations but also erosions of the odontoid process or atlas arcus, thickness of the ligaments, dis- tension of the synovial cavities, and ligament ruptures.

Of the 40 patients studied, 12 had completely normal or slightly abnormal (periarticular soft tissue swelling, periarticular bony erosions, and 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 biconcave transverse vertebra. 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 9 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 subluxations should not be expected in rheumatoid arthritis and there is no need for sophisticated examination of this region.

M NAFIZ AKMAN


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.\textsuperscript{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 was admitted to hospital because of hemiparesis of his left arm and leg, which lasted a couple of days with fever of 39–35 °C. He was checked thoroughly in a neurological and a medical clinic with a light 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

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this clinic by his family doctor for a diagnosis to be made he was receiving 7.5 mg predni-
solone and except for the arthralgias and the Raynaud’s phenomenon he had no complaints. When the prednisolone was dis-
continued, 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 pro-
voked. Wstergren sedimentation rate was 105
mm/h, his platelet count was 648x109/l and an antinuclear antibody titre of 1/640 on
HEP-2 cells with a speckled pattern was found. Anticentromere antibodies were negative and bone 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 fibroptic bronchoscopy showed cells of squamous cell
carcinoma. Perihilar and mediastinal lymph node metastases were present. Radiotherapy was carried out but the patient died nine months later. Raynaud’s phenomenon
and arthralgias 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 rheuma-
tology with an antinuclear antibody titre of 1/40 on
HEP-2 cells. The antinuclear pattern comprised a
complex unexplained combination of symp-
toms and findings. Two months earlier she had received bypass surgery on her left femoropopliteal artery because of chronic artery 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. Diag-
nostic 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 slightly thickened pancreas, which were interpreted as cysts. The patient was discharged.

Ten days later she presented in the out-
patient clinic again. She complained of thoracic and 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 com-
puted tomography scan of the abdomen was repeated, and the suspected lesion of the pancreas was biopsied. Histological tests showed adenocarcinoma. Radiation treat-
ment improved her condition temporarily. 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 connective tissue disease. In the second case it is possible that the anticientro-
mere antibodies belonged to the longstanding primary Raynaud’s phenomenon, which can be associated with anticientromere antibodies not only in CREST (calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclero-
dactyly, telangectasia) syndrome but in

Raynaud’s phenomenon alone. Anticentromere antibodies had not been determined previ-
ously, however, because the patient had not considered her Raynaud’s phenomenon disturbing or painful.

In case 1 the antinuclear antibodies were negative eight weeks 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 consid-
ered a hallmark of systemic rheumatic diseases,1 and are a diagnostic criterion for systemic lupus erythematosus,2 they can occur in other conditions. In a recent survey 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 disease, 15-9% had organ specific autoimmune diseases, 8-3% had infections, 2-9% had neoplasms, 10-9% had miscellaneous other diseases, and 13-4% remained without a diag-

nosis. Another study, 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 antinuclear antibodies in immunofluorescence on HEP-2 cells had the specific antibodies to DNA, Sm, SSA, SSB, RNP or Sc-l, 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 Bonfà et al6 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 any 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 anti-
body titre should direct our diagnostic tests not only towards finding a connective tissue disease but also towards searching for a malignancy.