

LETTERS TO THE EDITOR

Rheumatic disease following immunotherapy

Sir: Arthralgias and exacerbation of pre-existing arthritis are well known side effects of treatment with interferons and interleukin-2 (IL-2).¹⁻³ We report here, however, on two patients with malignant melanoma receiving immunotherapy, who developed de novo acute arthritis resembling ankylosing spondylitis and psoriatic arthropathy, respectively.

Since 1987 we have treated 64 patients with malignant melanoma with IL-2 and lymphokine activated killer cells⁴ or IL-2 and interferon α .⁵ We present here two patients out of this cohort whose tumours responded completely to treatment.

The first patient, a 34 year old white man, had had a mole excised 12 years previously and presented with multiple rapidly progressing liver metastases. He received four treatment cycles of IL-2 and lymphokine activated killer cells given as regional treatment.⁴ After the third IL-2 cycle he developed severe low back pain and marked stiffness of the spine; the pain improved with motion. Clinical examination showed tenderness over the lumbosacral spine and the sacroiliac joints. Radiographs of the spine and sacroiliac joints were normal. Laboratory studies showed negative rheumatoid factors. During the fourth treatment he developed asymmetrical pain and swelling of shoulders and wrists, in addition. Symptoms resolved within four weeks of the end of the last treatment cycle. Twelve months later when he received a single five day IL-2 infusion as maintenance treatment the same symptoms recurred.

The second patient, a 44 year old white woman with a history of psoriasis, had had a few recurrent cutaneous lesions for more than 20 years, but no previous episodes of arthritis. Ten years before treatment with IL-2 the primary tumour was excised. She presented with multiple subcutaneous and lymph node metastases; two months previously metastases in the stomach and the left adrenal gland had been resected. She received four treatment cycles comprising interferon α and high dose continuous infusion of IL-2 for five days.⁵ After the second and third treatment cycles the patient had an exacerbation of psoriatic skin lesions and in the following treatment-free interval, she experienced transient arthritic pain of several finger joints. Three weeks after completion of the fourth treatment cycle she presented with sausage-like swelling of two fingers, and tender metacarpophalangeal, proximal carpophalangeal, and distal interphalangeal joints. Radiographs of the hands showed soft tissue swelling but no bony involvement. Rheumatoid factors were negative. Complete resolution of the symptoms occurred only several months after the last treatment cycle. After a maintenance treatment cycle 18 months later she again developed pain and sausage-like swelling of the right middle finger during the IL-2 infusion.

The two patients presented here had an excellent response to immunotherapy. In both patients the arthritis was self limited, with

improvement when immunotherapy was stopped but could be reproducibly induced by successive treatment cycles. HLA typing of these patients showed the presence of HLA-B27 and HLA-B38, both major histocompatibility complex antigens associated with the respective diseases.

Several studies have reported the development of autoimmune thyroiditis in patients treated with IL-2 and lymphokine activated killer cells,⁶ as well as after immunotherapy with interferon α and IL-2.^{7,8} Recently, a rheumatoid arthritis-like disease was also seen in three patients after interferon α treatment.⁹ Our observations provide further evidence that in subjects with an appropriate genetic predisposition activation of the immune system by biological response modifiers may trigger the clinical manifestations of autoimmune diseases.

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Immunosuppressive treatment in stroke and renal failure

Sir: We report on a patient who presented with acute stroke in association with polyarteritis nodosa (PAN), in whom an adequate and sustained renal response to immunosuppressive treatment was accompanied by recurrent ischaemic strokes recorded by computed tomography (CT) and magnetic resonance imaging. When considered with further evidence on the risks of stroke in PAN the case suggests that a more aggressive

treatment regimen may be warranted in patients with cerebral disease.

A 43 year old man was admitted 16 hours after the sudden onset of true vertigo, which had been followed by left arm weakness and dysarthria. Hypertension had been diagnosed four months previously after an episode of transient vertigo. There had been recurrent small and large joint arthropathy over the preceding 14 months. Anaemia had been discovered at the blood transfusion centre on two occasions in the preceding 18 months. He had a normal intravenous urogram and barium enema following surgical admission with abdominal pain five months previously.

On presentation there was widespread patchy pigmentation, fine crepitations at the lung bases, and evidence of recent weight loss. Partial (L) sided VII nerve palsy was present with minimal left sided weakness.

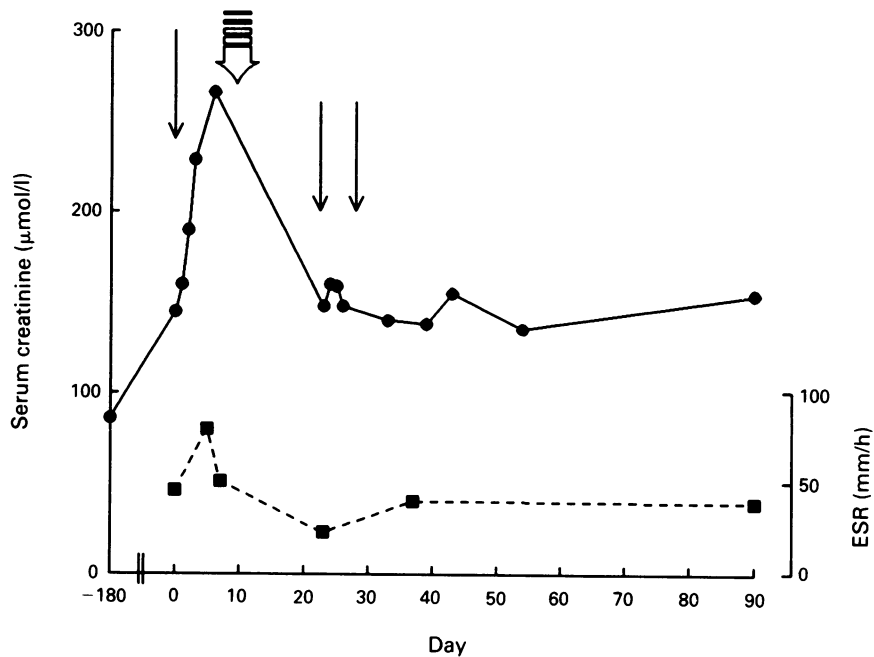
There was iron deficiency anaemia, haemoglobin 74 g/l, mean corpuscular volume 68.3 fl, with significant eosinophilia (0.48 \times 10⁹/litre, 5% of white cell count). Urea was at the upper limit of normal (7.4 mmol/l, normal range 2.5-7.5) and creatinine was raised (145 μ mol/l, normal range 60-110); creatinine clearance was reduced at 54 ml/min. Complement concentrations were normal apart from reduced CH50 at 126 U/ml (normal 150-250). Serum antinuclear cytoplasmic antibody, hepatitis B surface antigen, and a screen for autoantibodies were negative. Blood pressure was 156/94 mmHg and remained raised during the admission. An electrocardiogram and chest radiograph were normal; pulmonary function tests showed moderately severe airflow obstruction and reduced gas transfer. Cerebral CT showed a small infarct in the region of the right basal ganglia. Transcranial Doppler sonography showed a generalised increase in blood flow velocities in the carotid and vertebral basilar circulations, especially in the left middle cerebral artery (mean velocity 117 cm/s, normal 62 (12), mean (SD)).

Daily testing showed deteriorating renal function (figure). Renal and hepatic angiography suggested PAN, and renal biopsy confirmed the diagnosis. Treatment with cyclophosphamide (125 mg daily) and prednisolone (40 mg daily) was started, and renal function improved (figure). Three weeks later left arm power deteriorated and repeat CT showed a new right basal ganglia infarct. Five days later function in both arm and leg deteriorated; CT now showed a further temporoparietal infarct. Magnetic resonance imaging showed multiple ischaemic lesions in the right middle cerebral artery territory. The patient was transfused and heparin infusion started. Renal function did not deteriorate with the recurrent neurological episodes.

The patient was discharged at seven weeks with a mild left hemiparesis. His clinical condition and renal function remain stable eight months after his initial presentation.

The patient fulfils the clinical criteria for PAN.¹ Both angiography and renal biopsy were positive and arterial lesions of different ages were seen, indicating a chronic cyclical course rather than an acute onset.²

Although diffuse cranial arteritis was suggested by the general increase in blood flow velocities, anaemia is likely to have contributed to the transcranial Doppler findings,³ and intracranial artery to artery embolism might have caused the sequential strokes. Probably, however, the primary intracranial disease was arteritis. Moreover, there is evidence of a poor cerebrovascular response to immunosuppressive treatment in follow up studies of PAN; whereas early deaths are associated with



Disease activity in polyarteritis nodosa. Serum creatinine and erythrocyte sedimentation rate (ESR) declined following immunosuppressive treatment (open arrow), but there were further acute neurological events (small arrows). Day 0 = day of admission with first stroke.

renal and visceral disease, late deaths (within two years) are largely attributable to cerebrovascular, and to a lesser extent cardiac, events.²

The addition of cytotoxic agents to corticosteroids may be more efficacious than steroids alone in treatment of PAN³; this approach, or the use of higher dose immunosuppressive treatment, should be considered for patients with PAN who have evidence of cerebrovascular disease. The early recognition and appropriate treatment of PAN significantly improves prognosis;⁵ our case, and the frequent deaths from cerebrovascular disease in PAN, suggests that cerebral involvement in this condition requires further attention and may merit more aggressive treatment.

Improved renal function indicates a good renovascular response to immunosuppressive treatment. In contrast, there were repeated further neurological events recorded as cerebral infarcts. As far as we know this variable response between the cerebral and renal circulations has not been described previously.

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Synovial fluid T cells in HTLV-I positive RA

Sir: Human T lymphotropic virus type I (HTLV-I) is closely associated with the aetiology of adult T cell leukaemia/lymphoma and HTLV-I associated myelopathy/tropical spastic paraparesis.¹ Molecular features of the virus, which involve the relative tropism for CD4 positive T cells and a unique ability to immortalise the infected cells,¹ suggest that HTLV-I may have a role in modifying the inflammatory process.

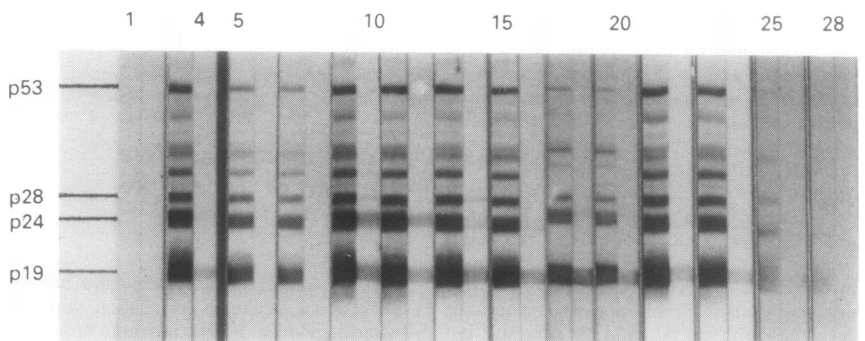
Recently, HTLV-I has been implicated in chronic arthritis as a manifestation of carrier state infection.²⁻⁵ Similarly, a study of transgenic mice demonstrated the arthritogenic capacity of HTLV-I.⁶ It remains to be determined, however, whether HTLV-I has a role in triggering rheumatoid arthritis (RA), modifying inflammation in the synovial compartment, or inducing a new clinical manifestation. In this study we estimated the

influence of HTLV-I on cellular immune responses in the affected synovial compartment in a random sample of 12 patients with RA, six positive for HTLV-I antibody (particle agglutination method) (group A) and six negative for the antibody (group B); T cell subsets in the synovial fluid were also analysed.

All 12 patients had RA, according to the American Rheumatism Association criteria, with affected knee joints from which the synovial fluid was collected. The paired peripheral blood samples were obtained concurrently. Western blot analysis confirmed the presence of IgG and IgM antibodies to HTLV-I antigens in the serum samples and synovial fluids of group B patients (figure). Atypical lymphocytes with nuclear convolutions were detected in synovial fluids obtained from five patients in group B. Peripheral blood and synovial fluid mononuclear cells were isolated and cryopreserved in liquid nitrogen until tested. Dual immunofluorescence staining was used to determine the distribution of T cell subsets as previously described.⁷ Student's two tailed *t* test was used to compare differences between groups A and B, and *p* values less than 0.05 were considered significant. Paired samples from peripheral blood and synovial fluid were evaluated by two tailed paired Student's *t* test, and *p* values less than 0.01 were considered significant.

The table summarises the distribution of T cell subsets in the patients' peripheral blood and synovial fluid samples. No significant differences in the percentages of each T cell subset in synovial fluid were noted. Changes in synovial fluid T cell subsets as compared with those in peripheral blood, including increases in the percentage of CD8+, HLA-DR bearing CD4+ and CD8+, and CD11b negative CD8+ lymphocytes and a decrease in the percentage of CD45RA bearing CD4+ lymphocytes, were determined as previously described.⁸ No significant differences in these changes were found between groups A and B.

These results showed that the patients with RA who were HTLV-I infected had the same pattern of distribution of T cell subsets in synovial fluid and peripheral blood as patients with RA negative for the HTLV-I antibody, showing that HTLV-I infection does not affect phenotypic cell populations in the affected synovial compartments. In addition, to evaluate the relation between HTLV-I and arthritis it will be necessary to carry out further studies on arthritic patients, including both patients with RA and patients with



Western blot analysis in the serum and synovial fluid samples from the patients with rheumatoid arthritis positive for antibody to HTLV-I by particle agglutination method. Odd numbered lanes show the results for HTLV-I IgG antibodies, and even numbered lanes show that for HTLV-I IgM antibodies. Lanes 1 and 2 are negative controls, lanes 3 and 4 positive controls. The samples of lanes 5, 6, 9, 10, 13, 14, 17, 18, 21, 22, 25, and 26 are the serum samples, and those of lanes 7, 8, 11, 12, 15, 16, 19, 20, 23, 24, 27, and 28 are the synovial fluids of the patients.