LETTERS TO THE EDITOR

Serum and synovial fluid levels of interleukin-5 in a patient with eosinophilic fasciitis

Eosinophilic fasciitis was initially described by Shulman\(^1\) as a syndrome involving skin lesions, oedema of the extremities, polyarthralgia, eosinophilia, an elevated erythrocyte sedimentation rate (ESR), and hypergammaglobulinaemia. Its aetiology is not well understood. An increase in circulating immune complex levels was reported as one possibility.\(^2\) Interleukin-5 (IL-5), a T cell replacing factor, induces eosinophilia in the blood and the production of autacoids.\(^3,4\) We investigated the role of IL-5 in a patient with eosinophilic fasciitis.

A 31 year old Japanese woman, a nurse, developed swelling, stiffness, and pain in both hands, elbows, and knees on November 10, 1995. She had not performed any vigorous exercise or physical work before the onset of symptoms. She was initially treated with a non-steroidal anti-inflammatory drug (NSAID), prescribed by a local orthopaedic specialist. However, on November 20 she developed a low grade fever and a granularity of the skin and the lower legs. She was then admitted to our hospital for detailed examination and treatment. Evaluation of the peripheral blood showed marked eosinophilia (31%, 4061 µl\(^{-1}\)) and mild leucocytosis (13.100 µl\(^{-1}\), but no anaemia (RBC 4.51 x 10\(^{12}\) µl\(^{-1}\), Hb 13.1 g dl\(^{-1}\)). Serological testing was negative for antinuclear antibody, rheumatoid factor, antithyroglobulin antibody, and antimicrobial antibody. The serum level of complements, immunoglobulins, and the proportions of the lymphocyte subpopulation and the CD4/8 ratio were all normal, as were blood chemistry findings. The erythrocyte sedimentation rate was raised (21 mm h was present) and positivity for serum CRP was present (2.2 mg ml\(^{-1}\)). Serum iron was 16 mg dl\(^{-1}\), and the total iron binding capacity was 226 µg dl\(^{-1}\). Radiographs of the chest, hand, and knee showed no abnormalities or erosive lesions. The clinical and laboratory findings suggested a diagnosis of eosinophilic fasciitis.

As confirmation, we obtained an endobucal biopsy specimen extending from the skin through the muscle of left lower leg. Histological examination showed hyperkeratosis of the epidermis, with fibrosis and infiltration of lymphocytes and eosinophilic leucocytes around the small vessels in the dermis. Granulomas were found in the subcutaneous tissue, consisting of epithelial cells, macrophages, and multinucleated giant cells surrounded by eosinophilic leucocytes. The adipose tissue and fascia showed similar histological findings, that is, granulomas and infiltration of eosinophilic leucocytes (fig.).

The muscle was unaffected. Pathological findings were compatible with a diagnosis of eosinophilic fasciitis, according to the findings of Barness et al.\(^5\) Because of bilateral swelling of the knee joints, the left knee joint was aspirated to sample the synovial fluid. Ten millilitres of fluid were obtained. It was straw coloured and turbid. The mucin clot was fair and crystals were absent. The white blood cell count in the synovial fluid was 1646 µl\(^{-1}\), with lymphocytes 75%, monocytes 21%, neutrophils 2%, and eosinophils 2%. The patient was not receiving steroids. These findings were also compatible with eosinophilic fasciitis.\(^6\)

Concentrations of IL-5 were measured in the serum and synovial fluid using an ELISA kit (R&D Systems Inc, Minneapolis, MN, USA). IL-5 concentrations in sera were not detectable (less than 8 pg ml\(^{-1}\)) before or after steroid treatment, but the level of IL-5 in synovial fluid was 32 pg ml\(^{-1}\) before therapy. No synovial fluid was obtained after therapy. As controls, the levels of IL-5 in SF from three patients with rheumatoid arthritis and three patients with osteoarthritis were measured and were undetectable.

Treatment was initiated with prednisolone, 40 mg per day, and symptoms such as fever, oedema, polyarthralgia, and eosinophilia disappeared within a week. The dose was gradually tapered. The patient is presently in remission.

To our knowledge, concentrations of IL-5 in serum or synovial fluid have not previously been measured in eosinophilic fasciitis. The IL-5 level in synovial fluid from our patient (32 pg ml\(^{-1}\)) was lower than that in serum previously reported in a patient with the pulmonary infiltration with eosinophilia (PIE) syndrome (59 pg ml\(^{-1}\)). This IL-5 concentration in synovial fluid was higher than in synovial fluid from patients with rheumatoid arthritis or osteoarthritis. There was, however, no striking infiltration of eosinophils in the joint (2%). The possibilities to explain this result are as follows: (1) the effect of human IL-5 on eosinophils is chemokinetic rather than chemotactic in vitro (and Hirashima M, personal communication); (2) the amount of IL-5 detected (32 pg ml\(^{-1}\)) may be not sufficient to induce the massive eosinophil infiltration; (3) IL-5 produced in joint space might not be released into circulation, remaining in joint. Recently, Kopf et al\(^7\) reported that basal levels of eosinophils with normal morphology were produced even in IL-5 deficient mice. They suggested the involvement of IL-3 and granulocytomacrophage colony stimulating factor (GM-CSF) in the development of eosinophils as well as IL-5. The expression of the gene for IL-3 was reportedly activated in a patient with acute lymphocytic leukaemia with eosinophilia.\(^8\) Thus IL-3 or GM-CSF, in addition to IL-5, may also be engaged in the induction of eosinophils in patients with eosinophilic fasciitis.

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Incidence of hepatitis induced by non-steroidal anti-inflammatory drugs (NSAID)

Netter et al. reported the incidence of hepatitis due to NSAID after a French drug surveillance study in 1985. This work, which is regularly cited in reference books and other publications, has been updated with the results of a second cooperative study carried out in the same way, by the same team, to compare and measure any changes in risk after a three-year interval. As we have pointed out, this approach should minimise the bias inherent in such studies of drug surveillance.

In 1989 the drug surveillance centres collected 51 cases (30 women and 21 men) who had received aspirin. These cases were compared with 56 cases—37 women and 19 men—of hepatitis associated with NSAID in patients without any previous history of hepatic disorder. They comprised acute cytolytic hepatitis (7)

[24], acute cholestatic hepatitis (17) [9], or mixed hepatitis (7) [15]. The remainder were subclinical biochemical abnormalities (20) [8].

In 1989 all patients recovered after the drug was stopped [in 1985 three patients died]. On the basis of the later study, NSAID were reclassified according to the incidence of hepatitis expressed as the number of cases per months of treatment, and the 1985 and 1989 classifications are compared (table).

It is noteworthy that: (a) two drugs in groups 1 and 2 in 1985 were withdrawn from the market that year: oxyphenbutazone because of haematochemical toxicity and isoxicam because of skin toxicity; (b) piroxicam, which was eventually withdrawn (in 1990) because of hepatic toxicity with, according to the manufacturer, a frequency of one case per 69 000 months of treatment, was in group 2 in both of our studies; (c) piroxicam and tenoxicam, which were put on the market at different times (1981 and 1988, respectively), were both in group 4 in 1989.

The hepatotoxicity of NSAID has been the subject of reports for some years. From these reports and our pair of studies emerge a number of broad ideas about NSAID induced hepatotoxicity:

- side effects are non-negligible, with regard to either morbidity or mortality
- different chemical structures can produce similar hepatotoxic responses
- older women greatly predominate among affected patients
- a hepatotoxic response is unpredictable and sometimes is unaccompanied by symptoms
- when a drug is reintroduced, side effect is frequently more sudden and severe, thus the readministration of the same drug must be strictly avoided
- these hepatotoxicities are difficult to investigate for a number of reasons: blood test findings are extremely variable and may show cytolytic, cholestatic, or mixed pattern effects; the clinical picture may or may not suggest an immunological response; the histology is rarely pathognomonic; and, finally, little is known about the mechanisms that initiate it, and little basic research has been done on the subject.