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Natural killer cell function in ankylosing spondylitis

SIR, Natural killer (NK) function has been assessed in several studies in rheumatoid arthritis,[1] but rarely in ankylosing spondylitis (AS).

Recently, many reports have argued for the responsibility of bacterial agents in the development of AS. Anomalies of the immune response against bacterial antigens could favour the occurrence and development of AS.[2]

The purpose of this study was to evaluate NK function in patients with AS.

NK cells, in addition to their role in immunological antitumoral surveillance,[3] appear to be implicated in anti-infectious and antibacterial defences. This is illustrated by the Chédiak-Higashi syndrome, characterised by functional deficiencies of NK activity with a normal number of NK cells, and the occurrence of severe bacterial infections.[4 5]

Twenty eight patients (23 male, five female) with definite AS were investigated: mean age 39·5 (SD 5·2) years, 21 were HLA-B27 positive, and 17 were receiving non-steroidal anti-inflammatory drugs (NSAIDs) at the time of investigation. Duration of the disease was less than five years in nine cases and more than 10 years in 12 (mean (SD) 9·4 (2·8) years).

Lymphomonocytes were isolated from peripheral venous blood using a Ficoll-Hypaque density centrifugation gradient.

NK function was investigated, firstly, by spontaneous cytotoxicity against a K 562 cell line preincubated with a fluorogenic substrate, and evaluated by a flow cytometric assay as described by McGinnes *et al*,[6] and, secondly, by the use of a Leu-7 (HNK-1) monoclonal antibody (Becton-Dickinson) that recognises NK lymphocyte subpopulation.[7 8] Nineteen healthy blood donors represented the control group; all were HLA-B27 negative.

Monoclonal fixation of OKT3, OKT4, OKT8 (Ortho Diagnostics), and several inflammatory parameters (erythrocyte sedimentation rate (ESR), β_2 microglobulin, serum IgA concentration) were investigated on the same blood samples.

Statistical comparison of the different groups or subgroups of patients was obtained by a Mann-Whitney test, and correlation between different parameters was sought with a linear regression test and R^2 coefficient evaluation.

We found no difference in NK cell activity either between patients with AS and controls (as in previous research with a ^{51}Cr release assay[9–11]), or between B27 positive and B27 negative patients with AS. Similarly, we found no statistical difference in the number of Leu-7 bearing cells between B27 positive and B27 negative patients with AS. Thus this study provides no evidence for NK function control by the B27 gene.

Moreover, no correlation was found between NK activity and any of the other parameters investigated (ESR, β_2 microglobulin, IgA, Leu-7, OKT3, OKT4, OKT8, T4/T8 ratio).

NK activity was significantly decreased ($p=0{\cdot}006$), however, in patients with AS receiving NSAID treatment compared with non-treated patients. As has been shown in vitro[12] and in vivo[13–15] NSAIDs tend to enhance NK cell activity. Thus the decrease observed in this study could be due to activity of the disease itself rather than to a direct effect of NSAIDs upon cell activity. This has already been suggested by Vinje *et al*, who found a negative correlation between NK activity and C reactive protein.[11]

Such a reduction in NK activity could be either evidence of an inflammatory reaction leading to hyperproduction of prostaglandins (that decrease NK activity) or, alternatively, a pathogenetic factor contributing to persistence of bacterial antigens according to the current hypothesis of the aetiology of the disease.

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Changing the class of NSAID in cases of hepatotoxicity

SIR, Hepatic side effects with non-steroidal anti-inflammatory drugs (NSAIDs), especially with diclofenac, are rare. Subclinical biochemical abnormalities, however, such as increases in transaminases, serum alkaline phosphatase and glutamyl transferase levels, and acute hepatitis, have been reported.[1–3] When NSAIDs are stopped disturbances generally resolve. The problem then is to determine whether another NSAID can be given and which one to choose.

A man of 44 with ankylosing spondylitis had been taking diclofenac (200 mg/day) for two months. On investigation his sedimentation rate was 100 mm/h, white cell count $9{\cdot}1\times10^9$/l, eosinophils $8{\cdot}1\times10^8$/l, IgE 563 mg/l (normal <350), serum alanine aminotransferase 9 IU/l (normal <30), serum aspartate aminotransferase 16 IU/l (normal <45), serum glutamyl transferase 82 IU/l (normal <50), serum alkaline phosphatase 144 IU/l (normal <90), 5′-nucleotidase 7 IU/l (normal <5), total serum bilirubin 5 μmol/l, prothrombin 75%, amylase 20 IU/l (normal <70). Hepatitis B surface antigen, anti-hepatitis B core antibodies, hepatitis A IgM, cytomegalovirus antibodies, antinuclear and antimitochondrial antibodies were absent. Ultrasonography, tomodensitometry, and cholecystography were normal. Treatment with diclofenac was stopped. Serum liver function tests, IgE concentration, and eosinophils returned to normal in 10 days. Treatment with ketoprofen (150 mg/day) was started. Three months later biochemical liver tests were normal. Diclofenac was the most likely cause of the hepatic abnormalities according to imputability criteria[4] as the patient had no history of hepatic disease and was not alcoholic, there was no sign of a viral hepatitis or of biliary tract obstruction, diclofenac was the only drug given, disturbances of serum liver function tests normalised after diclofenac was withdrawn. High levels of eosinophils and IgE suggest an immunoallergic mechanism.

Similar cases of patients developing abnormalities of serum liver function tests without clinical symptoms have also been reported,[5] and it is advisable to stop the drug. If NSAIDs are still required the same drug should be avoided as illustrated by a case of relapsing hepatitis in a patient rechallenged with diclofenac.[3] NSAIDs of the same chemical class should also not be given, as demonstrated by a case of cross hepatoxicity between two propionic acid derivatives: naproxen and fenoprofen.[6] We suggest an NSAID of another chemical class be used. Further studies are necessary to confirm our hypothesis that changing to an NSAID of a different chemical class resolves the disturbances of hepatic toxicity and does not produce new features of liver damage.

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