patient dramatically underlines the risk of infectious complications after neutralising TNFα[6] that might be particularly important in patients with a compromised immune system as a consequence of immunosuppressive drugs and/or diseases favouring infectious diseases, such as diabetes, as was the case here. The unfortunate course of our patient should alert rheumatologists to employ reagents that neutralise TNFα with extreme caution in patients who are more susceptible to infections because of accompanying diseases and/or concomitant immunosuppressive treatment.

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Adrenomedullin in synovial fluids from patients with rheumatoid arthritis inhibits interleukin 6 production from synoviocytes

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Adrenomedullin (AM) is a hypotensive peptide found in human pheochromocytoma tissue, which comprises 52 amino acids with an intramolecular disulphide bond.[1 2] The ring structure and amidated C-terminus of AM are critical for its receptor binding and hypotensive activity. The mature AM is synthesised as glycine extended AM followed by C-terminal amidation to assume a biologically active form in tissues. AM has a vasorelaxant effect, antagonising the vasospastic effect of endothelin-1 (ET-1). Recently, proinflammatory cytokines, such as tumour necrosis factors α (TNFα) and interleukin-1 (IL1), were found to stimulate production and secretion of AM from vascular endothelial cells and vascular smooth muscle cells in vitro, suggesting that AM interacts with the immune system.[3] However, AM reduces the production of TNFα from macrophages stimulated with lipopolysaccharide. In addition, AM shows an anti-inflammatory effect that reduces the production of the IL8 family by macrophages.[4] We recently reported that the concentration of AM is raised in plasma from patients with systemic sclerosis complicated by pulmonary hypertension.[5]

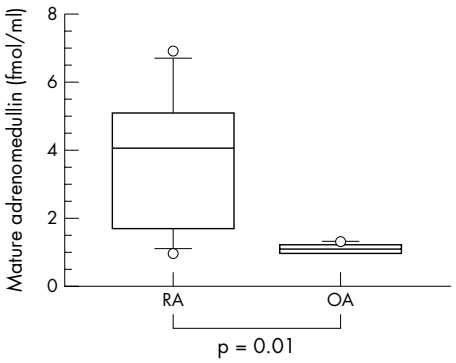

Figure 1 The concentration of mature AM was higher in patients with RA than in those with OA (p=0.01). Synovial fluids were obtained from nine patients with RA and six patients with OA.

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown cause. Inflammatory cells and cytokines such as IL1, IL6, TNFα, and IL17 are responsible, at least in part, for the pathological immune response in RA.[6] Thus, we suggested that AM may play a part in the pathogenesis of RA.

Synovial fluids were obtained from nine patients with RA,[7] and from six patients with osteoarthritis (OA). The concentrations of total and mature AM were measured by immunoradiometric assay. The level of ET-1 was measured by radioimmune assay. For the immunohistochemical studies, synovial tissue was obtained from the knees of three patients with RA and three with OA and stained using antihuman AM antibody and antihuman ET-1 antibody.

To explore the effect of AM on the production of IL6 from RA synoviocytes, the synovial cells obtained from three patients with RA were cultured for eight days and AM was added at various concentrations for three days. The level of IL6 in the supernatant was measured by an enzyme immunoassay.

The concentration of total AM in synovial fluid (mean (SD); pg/ml) was significantly higher in patients with RA (31.4 (14.7) pg/ml) than in patients with OA (5.5 (1.7) pg/ml (p=0.001) (web extra fig W1). The levels of mature AM were also higher in patients with RA (3.7 (2.1) fmol/l) than in patients with OA (1.1 (0.2) fmol/l) (p=0.01) (fig 1). There was no significant difference between the level of ET-1 in synovial fluids from patients with RA and OA (data not shown).

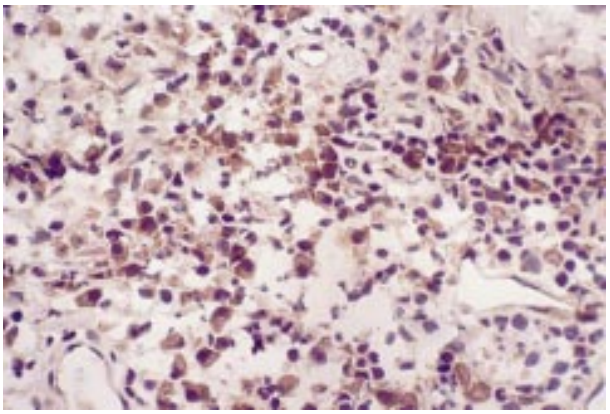

Figure 2 Immunohistochemical staining using anti-AM antibody. AM was positive in endothelial cells in the RA synovium. Original magnification ×200.

AM and ET-1 were positive around the perivascular and endothelial cells in the synovial tissue from patients with RA (fig 2, web extra fig W2). In contrast, the synovial tissue from patients with OA was negative. AM reduced constitutive production of IL6 from RA synoviocytes dose dependently. A high concentration of AM ($\geq 10^{-8}$ mmol/l) significantly reduced constitutive production of IL6 compared with a low concentration of AM ($\leq 10^{-9}$ mmol/l) ($p=0.0029$). TNFα dose dependently induced production of IL6 from RA synoviocytes (data not shown). AM did not reduce IL6 production induced by TNFα (data not shown).

Our study showed that the concentration of total and mature AM in synovial fluids was significantly higher in patients with RA than in patients with OA. In addition, by immunohistochemical staining, AM and ET-1 were shown to be positive around the perivascular area, the endothelial cells, and synoviocytes in RA synovial tissue. We have reported that osteoclasts are present in synovial tissues from patients with RA and that IL6 and soluble IL6 receptors in synovial fluids may participate in osteoclast formation.[8] Thus, IL6 is responsible for joint destruction in the presence of soluble IL6 receptor through osteoclastogenesis. In this study we showed that AM reduced constitutive production of IL6 from RA synoviocytes dose dependently. Thus, our results suggest that AM in patients with RA inhibits both synovitis and osteoclastogenesis through the inhibition of IL6 production.

Additional figures can be found on the website at www.annrheumdis.com

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Abnormal IgA levels in patients with rheumatoid arthritis

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The dominant antibody at mucous membranes and in exocrine secretions is IgA. It has been implicated in the pathogenesis of rheumatoid arthritis (RA), possibly due to immune complex formation.[1 2] If IgA is important in RA pathogenesis one might predict that patients with abnormal levels would have different characteristics from the "normal" IgA population. Limited work published on patients with high IgA levels has suggested that there is an increase in erythrocyte sedimentation rate (ESR), microscopic haematuria, and both distal interphalangeal joint involvement and unilateral sacroiliitis, even though patients fulfil the American College of Rheumatology (ACR) criteria for RA and have no other evidence of spondyloarthropathy.[3]

Primary selective IgA deficiency is the most common hypogammaglobulinaemia in the general population, with a prevalence of around 1:500.[4] It is associated with increased risk of autoimmune disease[5] and, possibly, with RA.[6] Primary IgA deficiency may result from impaired switching from class IgM to IgA.[7] Secondary IgA deficiency may be caused by drugs such as D-penicillamine, sulfasalazine, and gold. The few descriptions of primary IgA deficiency and RA have been single case studies and a longitudinal study is needed to determine if these cases represent a subgroup.

METHODS AND RESULTS

Serum immunoglobulins were measured in 352 patients (aged 18–75) attending a rheumatology outpatient department over a six year period. All patients fulfilled the ACR criteria for diagnosis of RA.[8] Patients with selective hypergammaglobulinaemia (>240 IU/ml) or primary selective IgA deficiency (<50 IU/ml) were identified as the two study cohorts. These