LETTERS

Severe septicaemia in a patient with polychondritis and Sweet's syndrome after initiation of treatment with infliximab

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RD Sweet first described an acute febrile neutrophilic dermatosis in 1964 characterised by acute onset, fever, leucocytosis, and erythematous plaques.[1] Skin biopsy specimens show infiltrates consisting of mononuclear cells and neutrophils with leucocytoclasis, but without signs of vasculitis. Sweet's syndrome is frequently associated with solid malignancies or haemoproliferative disorders, but associations with chronic autoimmune connective tissue disorders have also been reported.[2] The aetiology of Sweet's syndrome is unknown, but evidence suggests that an immunological reaction of unknown specificity is the underlying mechanism.

CASE REPORT

A 51 year old white man with relapsing polychondritis (first diagnosed in 1997) was admitted to our hospital in June 2001 with a five week history of general malaise, fever, recurrent arthritis, and complaints of morning stiffness. Besides autoimmune polychondritis, he had insulin dependent diabetes mellitus that was diagnosed in 1989.

On admission, he presented with multiple small to medium, sharply demarked, raised erythematous plaques on both forearms and lower legs, multiple acne-like pustules on the face, neck, and chest, two abscesses on both thighs, and paronychia of several fingers. Microbiological examinations of the abscesses showed that they were sterile, and no bacterial or viral DNA was found in the acne-like lesions. *Staphylococcus aureus* was isolated from the finger paronychia. Laboratory testing showed a white blood cell count of 3.1×10^9/l with 40% lymphocytes and 46% neutrophils, a C reactive protein of 0.21 g/l and maximally raised erythrocyte sedimentation rate. Surgical wound debridement was performed on the fingers and, because of immunosuppressive treatment (glucocorticoids, methotrexate, and azathioprine), systemic antibiotic treatment was started even in the absence of detectable systemic infection. Several days after admission, the patient developed an arthritis flare. Multiple skin biopsy samples were taken and showed typical features of Sweet's syndrome without signs of bacterial or viral infection.

As the patient had developed Sweet's syndrome while receiving immunosuppression and the underlying immunological activity of his polychondritis appeared to be insufficiently controlled, azathioprine was stopped and, in the absence of detectable infections, infliximab was used in an attempt to suppress the continuous (auto)immune reactivity.

Infliximab was given at 3 mg/kg body weight. Arthritis and morning stiffness rapidly resolved. The skin lesions disappeared and no new skin lesions developed. However, 14 days after the application, the patient developed fever of up to 40°C and new erythematous plaques, similar in appearance and location to the original plaques (fig 1). As at first admission, an infection was ruled out by intensive clinical, laboratory, microbiological, and radiological tests. Consequently, a higher dose of glucocorticoids (80 mg) and a second application of infliximab (3 mg/kg body weight) were given. The erythematous rash rapidly resolved and the patient was discharged from the hospital in apparently good health.

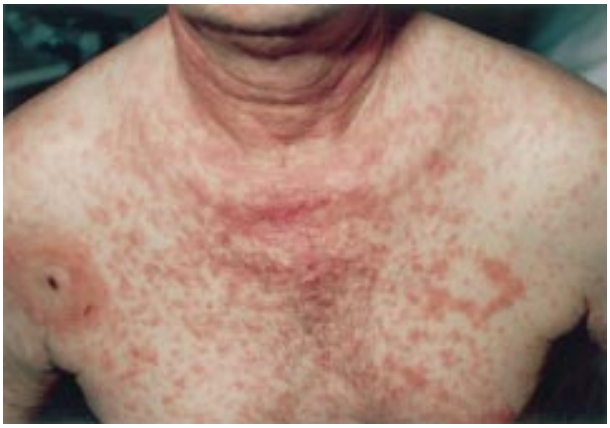

Figure 1 Manifestation of Sweet's syndrome in a patient with relapsing polychondritis.

Eleven days after the second treatment with infliximab, the patient presented with myalgias, subfebrile temperatures, and general malaise. A parasternal abscess with connection into the mediastinum and new multiple pulmonal round formations were detected by computed tomography scan. Subsequently, the patient developed multiple abscesses on the right elbow and both feet. Penicillin resistant *Staphylococcus aureus* was isolated from the parasternal abscess. Despite systemic antibiotic treatment and surgical incisions, the patient deteriorated, developed pneumonia and rapidly met the criteria of septicaemia with acute renal and respiratory failure. Despite continuous aggressive wide range antibiotic and antimycotic treatment and maximum intensive care, he died of multiorgan failure as a consequence of progressive septicaemia. Shortly before his death, 11 weeks after the second infusion of infliximab, the typical Sweet's syndrome skin lesions reappeared.

DISCUSSION

Neutralising tumour necrosis factor α (TNFα) has been employed as a powerful anti-inflammatory principle in patients with rheumatoid arthritis and other rheumatic diseases such as Still's disease or giant cell arteritis.[3–5] After several immunosuppressive drugs alone or in combination had failed to control immunological activity in our patient, infliximab was used and the clinical symptoms rapidly improved, leading to complete resolution of the arthritis, morning stiffness, and skin lesions. However, the case of our

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]

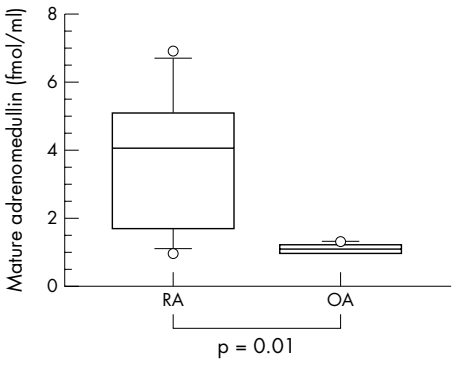

Figure 1 The concentration of mature AM was higher in patients with RA than in those with OA (p=0.01). Synovial fluids were obtained from nine patients with RA and six patients with OA.

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).