other hand, G-CSF induced bone and generalised muscle pain are considered to be rare side effects during the neutrophil recovery phase.[1 2] Histamine has been suggested to be one of the chemical mediators which cause oedema in bone; the resultant increase in pressure leads to pain.[3] Gudi *et al* reported that histamine induced arthritis during chemotherapy combined with G-CSF administration.[4] It has also been reported that paclitaxel-induced arthralgia or myalgia is augmented by G-CSF.[5] Recently, pseudogout during systemic high dose chemotherapy with G-CSF administration[6 7] or reactivation of rheumatoid arthritis in Felty's syndrome treated with G-CSF have been reported.[8]

For this report we assessed the relationship between clinical course and laboratory findings. Polyarthralgia and myalgia with rising fever developed on the fifth consecutive day of subcutaneous administration of G-CSF. Peak concentrations of histamine in the serum showed on day 8, but the serum IL8 concentration was higher during the attack. G-CSF mediated acute synovitis accompanied by foreign body-type giant cell reaction was suggested to be a cause of the rising fever and raised levels of serum IL8.

On the basis of these findings, G-CSF mediated non-rheumatic synovitis with foreign body-type giant cell reaction is suspected to possess a new responsiveness to G-CSF during chemotherapy. Close observation of a greater numbers of cases will be necessary to determine which insidious joint diseases may be caused by G-CSF.

ACKNOWLEDGEMENT

This work was supported in part by grant in aid for science research No 12670421 from the Ministry of Education in Japan.

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Accepted 27 February 2002

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Severe skin reaction after leflunomide and etanercept in a patient with rheumatoid arthritis

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Ann Rheum Dis 2002;**61**:850–851

CASE HISTORY

A 32 year old Pakistani woman developed a symmetrical polyarthritis, with a high erythrocyte sedimentation rate, in 1991. Within a few months, erosions developed and her rheumatoid factor became positive. The antinuclear antibodies were negative. Between 1991 and 1999 she was treated with sulfasalazine, sodium aurothiomalate, azathioprine, methotrexate, D-penicillamine, and hydroxychloroquine sequentially, but each drug had to be stopped either because of intolerance or leucopenia.

Her disease remained active and deformities developed. Her condition was maintained with 7.5 mg oral prednisolone and non-steroidal anti-inflammatory drugs. In April 2000 leflunomide was added. Three daily doses of 100 mg leflunomide were followed by 20 mg a day maintenance dose. Ten days later, she developed a vesicular rash over the trunk and the proximal parts of the arms and legs (fig 1). Leflunomide was discontinued and cholestyramine was introduced for wash out. A skin biopsy showed focal epidermal necrosis with partial lichenoid changes. Direct immunofluorescence was negative. The antinuclear and anti-dsDNA antibodies remained negative, but the anti-Ro antibodies were positive. No other features suggested a diagnosis of lupus. The dose of prednisolone was raised to 20 mg a day and topical corticosteroids were used. The skin lesions healed within a month with residual pigmentation and the prednisolone dose was reduced to 7.5 mg a day. Six months later there was a minor flare up of the rash. A skin biopsy showed resolving lichenoid changes.

Her arthritis remained active, and in February 2001 etanercept was introduced in a dose of 25 mg subcutaneously twice a week. Treatment continued with 7.5 mg prednisolone. A vesicular erythematous rash started after the second injection of etanercept, which worsened and spread to affect the trunk and the arms and legs after the fourth injection (fig 2). The rash was much more aggressive than the previous one. Etanercept was discontinued; the prednisolone dose was raised to 30 mg a day. A skin biopsy again showed areas of central necrosis surrounded by a rim of perivascular inflammation and there was also an inflammatory infiltrate at the dermoepidermal junction with necrosis of the basal keratinocytes. Again the anti-Ro antibodies became positive and in a higher titre. The lesions took several months to settle leaving pigmented scars.

DISCUSSION

Leflunomide, an inhibitor of pyrimidine synthesis, has recently been introduced in the treatment of patients with

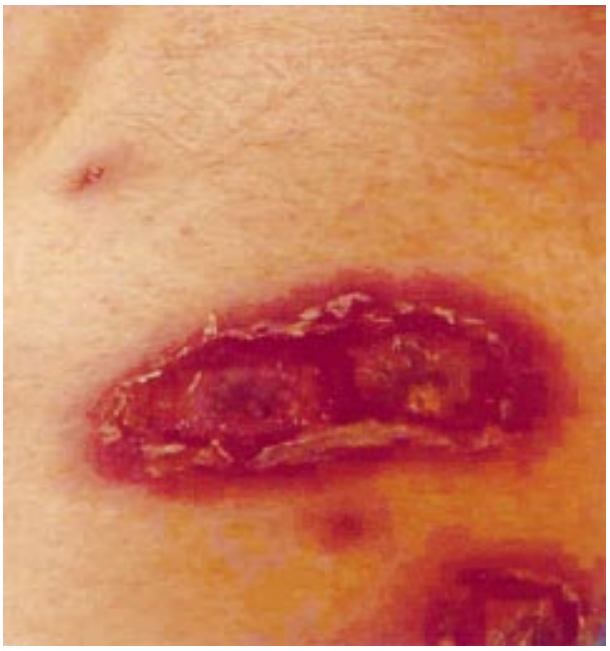

Figure 1 The leflunomide induced rash.

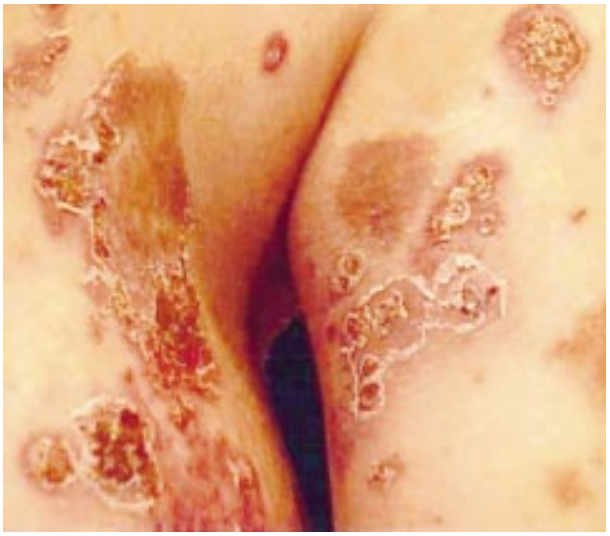

Figure 2 The etanercept induced rash.

rheumatoid arthritis (RA).[1] Skin side effects include dry skin, alopecia, eczema, rash, pruritus, and, rarely, Steven-Johnson syndrome and toxic epidermal necrolysis.[2]

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein that is used for the treatment of active RA if there is inadequate response to disease modifying antirheumatic drugs (DMARDs). A variety of skin rashes have been reported in controlled trials of etanercept in the treatment of RA. Most have been mild and only one reported case had a grade 3 rash (generalised symptomatic maculopapular or vesicular) (Wyeth Laboratories, unpublished data). The rash usually appears two to three weeks after the start of treatment.

Recently, three cases of acute discoid lupus and two cases of subacute cutaneous lupus erythematosus (SCLE) have been reported during treatment of patients with RA with etanercept.[3 4] One of the two patients reported with SCLE developed anti-Ro antibodies. About 15% of patients treated with etanercept develop anti-dsDNA antibodies and 11% develop antinuclear antibodies.[5–7]

Although our patient had positive anti-Ro antibodies, the blistering rash clinically and histologically was not in keeping with SCLE or other forms of lupus.

The initial leflunomide-induced rash (toxic epidermal necrosis) seen in our patient has been described previously.[2] The rash that developed after etanercept was a more severe form of a similar drug induced reaction. Clinically and histologically the etanercept-induced rash was in keeping with erythema multiforme It took several months of treatment with moderate doses of prednisolone for the rash to settle. Erythema multiforme has been associated with drugs such as sulphonamides, antimalarial drugs, penicillin, and salicylates, infections, lymphomas, and systemic lupus erythematosus. Our patient did not have any features to suggest any concurrent infections, lymphoma, or lupus.

Our patient developed toxic epidermal necrosis after leflunomide and erythema multiforme after etanercept. Both skin reactions, which are often drug related, share a similar pathogenesis, which is also suggested by the appearance of anti-Ro antibodies. Our case highlights that serious skin reaction to more than one DMARD including etanercept can occur in susceptible patients. What factor or immune phenotype determines this outcome is not clear. However, it poses a serious problem in the management of certain patients with RA.

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Accepted 4 April 2002

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