

MATTERS ARISING

Severe, disseminated, life threatening herpes zoster infection in a patient with rheumatoid arthritis treated with methotrexate

It was interesting to read the paper by van der Veen and colleagues on the frequency and type of infections in patients with rheumatoid arthritis (RA) treated with methotrexate.¹ Their experience concurs with that of Antonelli *et al*² who concluded that herpes varicella zoster infection in patients with RA receiving methotrexate therapy appears to be self limiting and benign. I wish to report a case of severe and systemic herpes zoster infection in a patient with RA receiving methotrexate.

In April 1994, a 26 year old white woman presented to her general practitioner with a characteristic (but non-pruritic) chicken pox rash. She was receiving methotrexate 20 mg weekly (Fridays), folic acid 20 mg weekly (Tuesdays) and hydroxychloroquine 200 mg daily for RA. Her RA had started when she was aged 16, and it had either temporarily or partially responded to ketoprofen, myocrisin injections and sulphasalazine in the past. Methotrexate was commenced at 7.5 mg weekly in February 1993. This was effective in suppressing her RA until August 1993 when she experienced a flare up; this was treated with an intramuscular dose of triamcinolone acetonide 80 mg, steroid injections to her elbows, and an increased dose of methotrexate (15 mg weekly). In September 1993, her RA was still troublesome and her methotrexate dosage was increased further to 20 mg weekly. When she was still no better in November 1993, hydroxychloroquine was added to the regimen at 400 mg daily in the first month, followed by a maintenance dose of 200 mg daily. Approximately six weeks later, her arthritis went into remission.

One week after she consulted her doctor, the patient's rash had become so generalised and severe that she was admitted to Timaru Hospital. Her mucous membranes (eyes, mouth, and vagina) were also ulcerated (figure). She also had systemic features: general malaise, pyrexia, tachycardia; her blood pressure was always normal. Her full blood count (including a white cell count of $7.9 \times 10^9/l$ and differential count) and liver function tests were normal a week before she developed herpes varicella zoster infection. Three days after admission, her white cell count was $23.6 \times 10^9/l$ with atypical lymphocytes, characteristic of a viral illness. Her liver function tests were also mildly deranged in a hepatic pattern and her albumin decreased to 26 mg/l. Five days after admission, she was mildly dyspnoeic and her chest radiographs, which were normal on admission, had developed features consistent with pulmonary alveolitis. Her alveolitis was probably secondary to disseminated varicella infection, although we were mindful of methotrexate induced pneumonitis.



The tongue with candida infection (obscuring the ulcers) and crops of varicella vesicles in different stages.

Regular medication with Maxitrol eye drops was started by an ophthalmologist two days before her admission to hospital: all her antirheumatic medications were stopped on admission. She began receiving intravenous hydrocortisone and broadspectrum antibiotics on day 3 of her inpatient treatment. She was also given a course of oral acyclovir although it was later in the course of her infection than was ideal. Supportive therapy including oxygen, analgesia, chlorhexidine and difflam mouth washes, nystatin pastilles, and hypnotics were also given.

Stevens-Johnson Syndrome was considered as a differential diagnosis and attempts were made to confirm the diagnosis of disseminated varicella acutely by electron microscopy of the vesicle fluid and skin scrapings, but it was not possible to identify any varicella virus. Fortunately, the patient's condition gradually improved from day 7 of her admission, and she was able to go home on day 16. At the time of her discharge, the diagnosis of disseminated varicella was confirmed by isolation of the virus on culture of the vesicle fluid and by demonstration of an increase in her varicella serology from a titre of 1/8 to 1/256. Her white cell count, liver function tests and chest radiographs were all normal two weeks after her discharge. When reviewed in the clinic five months later, she was left with some scarring of her skin and ketoprofen alone was sufficient to control her RA symptoms.

Although the patient has made a good recovery, her episode of herpes varicella zoster infection was not benign but life-threatening. There are two reports^{3,4} of disseminated zoster in patients with RA receiving methotrexate, but neither indicates any systemic or other organ involvement beyond the skin. Both reports suggest the acute illnesses in these patients were brief. One of these patients developed disseminated herpes varicella zoster after beginning steroids while receiving chronic low dose methotrexate.⁴ The patient reported now was also taking another immunomodulating drug, hydroxychloroquine.

Review of the management of this patient suggests zoster specific immune globulin could have been used had she presented within 96 hours of her contact with a relative who had chicken pox, to reduce the severity

of her varicella infection. Had there been a more confident diagnosis of varicella pneumonitis, intravenous rather than oral acyclovir should have been used.

D W T CHING
Department of Medicine,
Timaru Hospital,
Queen Street, Private Bag,
Timaru, New Zealand

- 1 van der Veen M J, van der Heide A, Kruije A A, Bijlsma J W J. Infection rate and use of antibiotics in patients with rheumatoid arthritis treated with methotrexate. *Ann Rheum Dis* 1994; 53: 224-8.
- 2 Antonelli M A S, Moreland L W, Brick J E. Herpes zoster in patients with rheumatoid arthritis treated with weekly, low-dose methotrexate. *Am J Med* 1991; 90: 295-8.
- 3 Groff G D, Shenberger K N, Wilke W S, Taylor T H. Low dose oral methotrexate in rheumatoid arthritis: an uncontrolled trial and review of the literature. *Semin Arthritis Rheum* 1983; 12: 333-47.
- 4 Anderson D J, Janoff E N. Herpes zoster in a patient on methotrexate given prednisone to prevent post-herpetic neuralgia [letter]. *Ann Intern Med* 1987; 107: 783.

LETTER TO THE EDITOR

Secondary acute myeloid leukaemia with 7q-complicating azathioprine treatment for rheumatoid arthritis

Cytotoxic agents are used increasingly in autoimmune disorders, with resulting improvement in the control and long term prognosis of these diseases. However, there is evidence that their prolonged use may be associated with increased risks of solid tumours, lymphoproliferative disorders and leukaemia.^{1,2} Use of alkylating agents, advanced age, long duration of therapy and high cumulative doses are associated risk factors.²⁻⁴