

Rheumatoid Nodules Developing under Methotrexate Treatment for Rheumatoid Arthritis

Sir,

Rheumatoid nodules have been reported to occur in about 20% of patients with chronic rheumatoid polyarthritis (1, 2). In the recent literature, a correlation between treatment of rheumatoid arthritis with methotrexate and the development or worsening of rheumatoid nodules has been suggested (2–4).

We describe here the explosive deterioration of rheumatoid nodules during the course of methotrexate treatment for rheumatoid polyarthritis in a 63-year-old woman and discuss current aspects of possible pathogenetic mechanisms as well as therapeutic options for methotrexate-induced rheumatoid nodules.

CASE REPORT

A 63-year-old woman presented to our department with a 15-year history of chronic rheumatoid polyarthritis affecting her fingers, hand, elbow and knee joints. Ten years previously, she first developed a few firm nodules on her fingers and feet. Four years before presentation, systemic treatment with methotrexate, 10 mg weekly, and prednisolone, 5 mg every second day, was initiated. In the course of this treatment the nodules dramatically increased in size and volume. The rheumatic disease was persistently active and in February 1998 treatment with cyclophosphamide and prednisolone by intravenous pulses was started. During this treatment ulcerations and continuous draining of whitish material occurred. A further history revealed a thyroid gland resection in 1983 due to a cold nodule, followed by treatment with L-thyroxin 50 µg/day.

Clinical examination revealed multiple indolent flesh-coloured subcutaneous nodules in the patient's fingers, containing whitish material; some of them were superficially ulcerated (Fig. 1). In addition, she had finger joint deformities and firm immovable nodules on her heels and the borders of her feet.

Biopsy specimens were obtained from nodules on the fingers of the right hand and revealed areas of necrotic connective tissue surrounded by histiocytic proliferation, leading to the diagnosis of rheumatoid nodules.

Laboratory examination showed a positive rheumatoid factor of 410 kU/l (normal <15 kU/l) and anti-nuclear antibodies titre of 1:80. White and red blood cell counts, serum uric acid, creatinine, calcium, phosphate and liver function tests were within the normal range. TSH was 0.3 mU/l at the lower limit (normal 0.27–4.2 mU/l).

Radiological examination of both hands revealed definite destruction of the joints with subluxation, demineralization of the bones with

several punched-out radiolucencies and non-calcifying nodules projecting in the soft parts surrounding the joints.

DISCUSSION

Methotrexate, a common drug for the treatment of rheumatoid arthritis, has been used successfully, but various side-effects have been reported. Among patients with rheumatoid arthritis under methotrexate therapy, the ones whose joint symptoms are improving due to administration of methotrexate frequently develop subcutaneous nodules increasing in size and number (1–3, 5). Nevertheless, only in rare cases the severity or the localization of the nodules, e.g. vascular, pulmonary or cardiac manifestation, necessitated discontinuation of the drug (3). Cause and effect relationship between methotrexate treatment and the accelerated development of nodules is supported by the regression of the nodules after discontinuation of the drug (2, 6). Although the predominant anti-inflammatory action of methotrexate controls the chronic polyarthritis in almost all cases reported so far, it is unable to prevent the granulomatous reaction to tissue necrosis leading to rheumatoid nodules.

Rheumatoid nodules do not always require therapy. However, indications for therapeutic intervention include local pain, nerve compression, limited range of joint motion, nodule erosion and infection (7). In these cases surgery is the only effective regimen.

Interestingly, a previous study showed that agents inhibiting adenosine A1 receptors on the macrophages may be useful in the treatment of methotrexate-induced rheumatoid nodules. Perhaps methotrexate promotes this immunological reaction through the liberation of adenosine (3). The occupancy of adenosine A1 and A2 receptors may subsequently oppose effects on giant cell formation. DPCPX, a specific adenosine A1 receptor antagonist, was tested and proved to be able to completely reverse the pro-inflammatory A1-mediated side-effect of methotrexate in rheumatoid nodule formation (7). Moreover, DPCPX seemed to potentiate the A2-mediated anti-inflammatory effects of methotrexate on synovitis within the joints. However, these results are still preliminary and their clinical usefulness has to be proven. In our case, further worsening of the rheumatoid nodules was observed during cyclophosphamide treatment. This effect has not been reported previously and remains to be confirmed.

REFERENCES

1. Veys EM, de Keyser F. Rheumatoid nodules: differential diagnosis and immunohistological findings. *Ann Rheum Dis* 1993; 52: 625–626.
2. Segal R, Caspi D, Tishler M, Fishel B, Yaron M. Accelerated nodulosis and vasculitis during methotrexate therapy for rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 1182–1185.
3. Miehle W, Streibl H. Does methotrexate induce "Rheumatoid nodules"? *Fortschr Med* 1994; 112: 459–462.
4. Fuchs HA. Rheumatoid vasculitis with worsening nodulosis. *J Rheumatol* 1990; 17: 123–124.
5. Merrill JT, Shen C, Schreiber D, Coffey D, Zakharenko O,



Fig. 1. Firm, flesh-coloured nodules on the patient's fingers, containing a whitish material, showing partly superficial ulcerations and joint deformities.

- Fisher R, et al. Adenosine A1 receptor promotion of multi-nucleated giant cell formation by human monocytes. A mechanism for methotrexate-induced nodulosis in rheumatoid arthritis. *Arthritis Rheum* 1997; 40: 1308–1315.
6. Fürst DE, Kremer JM. Methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 305–314.
7. Arnold C. The management of rheumatoid nodules. *Am J Orthop* 1996; 25: 706–708.

Accepted February 10, 1999.

T.N.Y. Duong, U. Blume-Peytavi, S. Kregel, Ch. C. Zouboulis and C.E. Orfanos
Department of Dermatology, University Medical Centre Benjamin Franklin, The Free University of Berlin, Hindenburgdamm 30, D-12200 Berlin, Germany.

Cutaneous and Systemic Infection by *Gemella morbillorum*

Sir,

Gemella morbillorum is rarely associated with human infections. However, *G. morbillorum* normally remains unidentified because microbiology laboratories have difficulty in isolating this bacterial agent. We report here a case of cutaneous and systemic infection with *G. morbillorum* following hand trauma sustained by a man while fishing.

CASE REPORT

A previously healthy 24-year-old man, a builder, was admitted to our dermatology department for suspected erysipelas. He was an active fisherman and 5 days before, had repeatedly wounded the fingers of his left hand with a fishing-hook while he was on the river. In the evening of the same day, he developed a strong pain in his left arm, followed a few days later by an increasing cutaneous inflammation.

Clinical observation showed that his left arm and forearm appeared to have homogeneous erythema and oedema, with pain, remittent fever and 2 enlarged lymph nodes in the left armpit, which were about 2 cm in diameter, hard-elastic, moveable and painful.

Routine laboratory tests showed a neutrophilic-leukocytosis (19,400 WBC/mm³, 79.9% neutrophils) and an increase in non-specific inflammation indices (ESR 75 mm/h). The lymphocyte subpopulations and other routine tests were normal. The serology was positive for hepatitis C virus infection with normal transaminases and negative for HIV.

The patient was treated surgically with incision and drainage of an abscess in the left antecubital hollow. There was secretion of pus with a putrid smell.

While waiting for the culture results we began therapy with stearate erythromycin (2 g/day).

Eight days after hospitalization a basal left pleura-pneumonia became evident, probably produced by a secondary localization of septicaemic infection. Blood and broncho-alveolar lavage cultures were negative. The following day a massive haemorrhage occurred with rapid onset of anaemia as a consequence of the erosion of the left-humeral artery. He was treated urgently in surgery with ligation of the damaged arterial branch. Surgical cleansing of the large abscessual cavity, which had caused a large muscle-cutaneous ungluing of the arm from the armpit to the elbow, was carried out. The general condition and pulmonary status of the patient was worsening. On the advice of the pneumologist, therapy with teichoplanin (0.2 mg/kg/day i.m.) and tobramycin (3 mg/kg/day i.m.) was started. After 2 days the fever disappeared and there was a significant improvement in the pulmonary infection. Pus culture resulted positive for *G. morbillorum*, which was sensitive to these antibiotics. Due to the high frequency of

endocarditis caused by this microorganism we performed an echocardiogram, but it did not reveal vegetation.

DISCUSSION

To our best knowledge, this is the first case of cutaneous infection with *G. morbillorum*. In literature, cases are reported of septic arthritis, meningitis (1), pericarditis, sinusitis, peritonitis and, particularly, endocarditis (2). These infections are potentially severe, with the typical formation of abscesses, empyema (3) and septic shock (4). The drained pus has a characteristic putrid smell.

The danger of infection is high in surgery, especially in perianal and mouth surgery (5), diabetic patients, immunodeficiency, neoplasm, drug abuse and trauma. As occurred in our patient, we believe that particular attention must be paid to the possibilities of infection by parenteral inoculation, particularly if the patient takes part in fishing. We suggest that specific research be carried out because of the difficulty of identifying this rare pathogen in the microbiology laboratory.

REFERENCES

1. Debast SB, Koot R, Meis JFGM. Infections caused by *Gemella morbillorum*. *Lancet* 1993; 342: 560.
2. Omran Y, Wood CA. Endovascular infection and septic arthritis caused by *Gemella Morbillorum*. *Diagn Microbiol Infect Dis* 1993; 16: 131–134.
3. Da Costa CT, Porter C, Parry K, Morris A, Quoraishi AH. Empyema thoracis and lung abscess due to *Gemella Morbillorum*. *Eur J Clin Microbiol Infect Dis* 1996; 15: 75–77.
4. Vashistha S, Isenberg HD, Sood SK. *Gemella Morbillorum* as a cause of septic shock. *Clin Infect Dis* 1996; 22: 11084–11086.
5. Terada H, Miyahara K, Sohara H, Sonoda M, Uonomachi H, Sanada J, et al. Infective endocarditis caused by an indigenous bacterium (*Gemella morbillorum*). *Intern Med* 1994; 33: 628–631.

Accepted March 20, 1999.

P. Rosina¹, S. Cunego¹, G. Meloni¹, F. Favari² and A. Leoni¹
¹Department of Dermatology, University of Verona, Piazzale Stefani 1, 37126, Verona, Italy (E-mail: prosina@yahoo.com) and ²Department of Microbiology, Azienda Ospedaliera, Verona, Italy.