Methotrexate, pneumonitis, and infection

Sir: In a recent issue of this journal Cook and Carroll\(^1\) reported on two patients with rheumatoid arthritis (RA) in whom it was possible to reintroduce methotrexate after a period of methotrexate related pneumonitis. At the time these cases occurred (in 1985 and 1986) opportunistic infections were not considered to be important in the treatment of RA with methotrexate, and their report made no mention of specific investigations in that direction. Nowadays it is agreed that opportunistic infections, especially *Pneumocystis carinii*, must be excluded in the evaluation of pneumonitis in patients treated with methotrexate for RA.\(^2\) In the cases presented this type of pneumonitis could not be fully excluded, especially not in the patients who were also treated with co-trimoxazole.

We report the case of a patient who had two episodes of methotrexate related pneumonitis, in which opportunistic infections could be sufficiently excluded. This case history further emphasises that caution is needed when re-introduction of methotrexate after an episode of pneumonitis is considered.

A 61 year old man had had erosive, rheumatoid factor positive RA since 1985, previously treated with hydroxychloroquine, sulphasalazine, aurothioglucone, and azathioprine. Chest radiography showed slight reticular changes in the basal segments in August 1987. On pulmonary function testing a restriction to total lung capacity 5-1 litres (normal 6-1) and an increased carbon monoxide diffusing capacity (carbon monoxide transfer factor) (0-95 mmol.min -1.kPa -1 ) (normal 1-40–1-60) were found. In November 1987 methotrexate 7-5 mg orally weekly, increasing to 15 mg weekly over two months, was started. Ten months later, at a cumulative methotrexate dose of 540 mg, dyspnoea on effort and a non-productive cough without fever developed, together with mouth ulcers. Chest radiography showed progression of reticular changes, and the carbon monoxide transfer factor had decreased to 0-79. In the absence of sputum production no cultures could be obtained. Methotrexate was stopped, and low dose prednisone treatment (7-5 mg daily) started. Two weeks later pulmonary complaints and mouth ulcers had disappeared. Control chest radiographs and pulmonary function testing returned to pretreatment values. p-Penicillamine was given for active RA but proved ineffective.

In October 1989 methotrexate, 7-5 mg orally weekly, increasing to 10 mg weekly over three months, was restarted, with a sufficient response of the RA. In April 1991 the methotrexate dosage was increased to 12-5 mg weekly by mouth. In May 1991 chest reactivation of RA. One week later, at a cumulative methotrexate dose of 600 mg in this second episode, acute dyspnoea with a non-productive cough without fever developed. There was no response to amoxycillin. Methotrexate was stopped immediately.

On admission pulmonary complaints had already improved. The respiratory rate was 24/min and bibasilar crackles were heard over the lungs. Skin lesions on both legs, suspected to be due to vasculitis, were seen. Laboratory data were as follows: erythrocyte sedimentation rate 95 mm/hour, white cell count 9-7 x 10\(^9\) /l, no eosinophilia, arterial blood gas tensions were: PaO\(_2\) 8-9 kPa, PaCO\(_2\) 5-0 kPa on room air. Extension of bilateral reticular changes on chest radiographs and deterioration of pulmonary restriction (total lung capacity 4-6 litres) were found. The carbon monoxide transfer factor had not changed. Microbiological evaluation, including bronchoalveolar lavage and open lung biopsy, remained negative. The lung biopsy specimen showed interstitial pneumonitis with lymphocytic infiltrate, bronchiolitis, and multinucleated giant cells, without signs of vasculitis. Light microscopy of skin lesions showed allergic vasculitis. The patient's pulmonary condition rapidly improved after discontinuation of methotrexate, but the RA flared. Azathioprine was given, resulting in gradual improvement of both polyarthritis and skin lesions. Pulmonary complaints did not recur.

In our opinion both episodes of pulmonary complaints in our patient can be attributed to methotrexate treatment. Microbiological causes, including opportunistic infections, were sufficiently excluded during the second episode. Pathology of the lung biopsy specimen, and the clinical course after discontinuation of methotrexate are compatible with methotrexate induced pneumonitis. The first episode was less extensive, and, in particular, microbiological causes were not fully excluded, but the response to methotrexate withdrawal, without antimicrobial treatment, showed a relationship with methotrexate treatment. As far as we know, no correlation between cumulative methotrexate dose and pneumonitis has been reported. In our patient the cumulative methotrexate dosage of each treatment period at the time pneumonitis developed was in the same range (540 mg and 600 mg respectively). From the report of Cook and Carroll\(^1\) it can be calculated that in at least one of their patients the cumulative methotrexate dose after reintroduction of the drug exceeded that of the first episode. In our patient reinstitution of methotrexate after methotrexate pneumonitis seemed to be successful, until the dose was increased to about 80% of that at which the first episode of pneumonitis had developed. Both patients reported by Cook and Carroll were rechallenged at doses clearly below the initial dose (50% in patient 1; 66% in patient 2).

The pathophysiology of methotrexate related pneumonitis remains unknown. Reports of the successful reintroduction of methotrexate seem not to be compatible with a hypersensitivity reaction that has often been suggested. Our case suggests that at least in some patients a direct toxicity with a threshold may be responsible for the development of methotrexate related pneumonitis. At present no risk factors for the development of methotrexate pneumonitis or a recidivism upon rechallenge are known. Whenever a rechallenge cannot be avoided because of the necessity of methotrexate at a much lower dose seems to be advisable.

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Sirs: We read with interest the article on the successful reintroduction of methotrexate after pneumonitis in two patients with rheumatoid arthritis.\(^3\) In this article two pathogenic descriptors were not sufficiently classified as having definite methotrexate pneumonitis and the second probable methotrexate pneumonitis, though the authors conceded that pulmonary infection might have been responsible in both cases.

We feel that in the first case also a pulmonary infection might have been responsible—namely, *Pneumocystis carinii* pneumonia. In our opinion this possibility was not sufficiently ruled out. Since 1983 there have been several reports on *P carinii* pneumonia complicating low dose methotrexate treatment. Methotrexate pneumonitis and *P carinii* pneumonia have the same clinical presentation and cause almost the same abnormalities on the chest radiograph.\(^4\) Furthermore, the course of the illness in the first patient is also suggestive of *P carinii* pneumonia because improvements only started after institution of co-trimoxazole (besides other antibiotics), an agent to which *P carinii* responds particularly well.

*P carinii* is infrequently present in sputum, and pathological detection lacks sensitivity and specificity. The most commonly used procedure to diagnose *P carinii* pneumonia is bronchoalveolar lavage, followed by Grocott staining.\(^5\) The severity of *P carinii* pneumonia justifies in our opinion this invasive procedure on every patient who is treated with low dose methotrexate and who presents with acute pulmonary disease. Thus we fully agree with Lang and colleagues who state that opportunistic infections like *P carinii* pneumonia should be considered and ruled out, before a definite diagnosis of methotrexate pneumonitis is made.\(^6\) In any case this limitation should be made in diagnostic criteria advocated by Searles and McKendry are used.\(^7\)

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Authors' Reply We thank Drs Stenger and Houthaan for prompting us to reconsider pulmonary infection and, in particular, *Pneumocystis carinii* infection in patient 1 in
our report.1 We agree that opportunistic infection was not ruled out and that the recovery after treatment with warfarin increases the likelihood of pneumocystis pneumonia. No sputum was obtained at any stage in the course of our patient's illness and bronchoalveolar lavage was not performed.

We note with interest the frequency with which leucopenia and perhaps lymphopenia has been present in reported cases of P carinii infection complicating methotrexate treatment in patients with psoriatic arthritis in fact responsive for the pneumonitis rather than hypersensitivity or some other form of drug toxicity, such as accumulation of methotrexate in pulmonary tissue.

Clearly, it is important to diagnose opportunistic infection not only in institute appropriate treatment also but because it may be possible to use methotrexate again if the evidence of leucopenia is not due to a drug reaction. Furthermore, titrating the dose of methotrexate against peripheral blood lymphocyte counts may allow the drug to be used more safely in the treatment of rheumatic diseases.

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Sneddon’s syndrome comprises about 0·26% of total cerebrovascular cases.1 Clearly, however, testing to detect antiphospholipid antibodies in Sneddon’s original patients was undertaken.1 However, pathogenesis of Sneddon’s syndrome remains unclear. Sneddon1 speculated that skin biopsies in future cases would show endarteritis obliterans in dermal arteries. It was thought that intravascular pathology of a similar nature was responsible for cerebrovascular accidents.1 There is no histological evidence of SLE or other systemic disorders in most reported cases of classical Sneddon’s syndrome.2-4 None of these studies, however, included specific tests for antiphospholipid antibodies or lupus anticoagulant.

A recent study of 10 cases of cerebrovascular disease, in association with livedo reticularis in six cases, showed seven had SLE.5 Five were positive for the Venereal Disease Research Laboratory (VDRL) test, and were positive for lupus anticoagulant. All had cutaneous vascular disease in the form of digital gangrene, cutaneous ulcer, and superficial thrombophlebitis; two had pulmonary embolism. The latter is of interest as there is little doubt that these cases belong to the category of ‘primary’ APS, with or without SLE.

A case of Sneddon’s syndrome in association with deep vein thrombosis and pulmonary embolism is presented here; repeated search for antiphospholipid antibodies and lupus anticoagulant proved negative.

In October 1990 a 45 year old man presented with a history of recurrent attacks of left sided hemiparesis (MRC grade 4) and hemianesthesia. He had had deep vein thrombosis and pulmonary embolism in 1971. A chronic ulcer appeared on the front of his right leg in 1974. Apart from neurological signs he had left deep vein thrombosis, left sided pleural rub, and a chronic ‘venous’ ulcer on the front of his right leg with surrounding pigmentation. Additionally, he had acro-erythrocytosis of his toes and both dorsalis pedis pulsations were absent. No skin rash or nodules were present. He was in sinus rhythm and normotensive, with no heart murmur or carotid bruit. His haematological status was normal.

Laboratory investigations showed an erythrocyte sedimentation rate of 70 mm/h (normal <10), plasma viscosity 2·08 mPa.s at 25°C (normal ±0·05), C reactive protein 16 mg/l (normal <5), antithrombin III, protein C, and antithrombin III levels; lupus anticoagulant, IgG and IgM antiphospholipid antibodies (concurrent laboratory—Hammersmith Hospital, London); VDRL tests, antineutrophil cytoplasmic antibody, cryoglobulins, rheumatoid factor latex test, direct Coombs test, hepatitis B surface antibody, and protein S and phospholipid test, and urine microscopy. A duplex scan of the carotid arteries, a two dimensional echocardiogram, and the electrocardiogram were all normal.

About two weeks after his initial presentation the patient developed generalised livedo reticularis. Eighteen months later he still has left sided hemiparesis (MRC grade 4) and hemianesthesia. His skin rash persists. Multiple biopsy specimens of affected skin show essentially normal histology. The patient’s most recent erythrocyte sedimentation rate is normal, but his antinuclear factor remains positive with a low titer of 1:10 (homogeneous pattern). Double stranded DNA antibody is, however, negative. Repeat testing for antiphospholipid antibodies failed to show any abnormalities. In view of his proclivity to recurrent thromboembolism, long term anticoagulation treatment with warfarin has been continued. This case further illustrates that Sneddon’s syndrome may also exist as a distinct entity whose pathogenesis remains to be elucidated.

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Anticardiolipin antibodies and renovascular hypertension

Sir: Two cases of renovascular hypertension associated with antiphospholipid syndrome have been reported recently.1,2 We report a case of renovascular hypertension, without angiographic appearance of thrombus, associated with laboratory features found in primary antiphospholipid syndrome.

A 50 year old woman was admitted to our clinic with hypertension of 14 years duration; of 14 a positive Venereal Disease Research Laboratory (VDRL) test with negative fluorescent treponemal antibody (FTA) and fluorescent treponemal haemagglutination fixation antibody (TPHA) absorption was detected. She had had only one pregnancy at the age of 21 with a normal delivery. Since the age of 22 she had been using an intrauterine device. At 29 she began to complain of frequent headaches,
Authors' reply

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