CASE REPORTS

Nocardia asteroides pneumonia complicating low dose methotrexate treatment of refractory rheumatoid arthritis

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Abstract

Low dose methotrexate is used increasingly often in the treatment of rheumatoid arthritis. Severe complications due to toxicity of the lung or bone marrow occur infrequently. This report describes a 71 year old woman with longstanding rheumatoid arthritis who developed pleuritis, a pulmonary infiltrate, and pancytopenia during treatment with low dose methotrexate. Fatal respiratory insufficiency followed, and cultures from the lung after death showed *Nocardia asteroides*.

Low dose methotrexate is often used in refractory rheumatoid arthritis.¹⁻⁴ Clinical benefit has been shown in patients receiving 7.5-25 mg methotrexate weekly.^{2,3} Serious side effects due to low dose methotrexate have been reported in patients with rheumatoid arthritis and psoriatic arthropathy. Its use is considered safe, however, as severe complications occur infrequently. Complications due to haematological or pulmonary toxicity have been reported to occur in less than 5% of patients treated with low dose methotrexate.⁴

We report a case of *Nocardia asteroides* pneumonia in a patient with longstanding refractory rheumatoid arthritis, who was receiving low dose methotrexate weekly.

Case report

A 71 year old woman with a 34 year history of classical seropositive rheumatoid arthritis, who was previously unresponsive to gold, was maintained with naproxen (500 mg/day) and prednisone (10 mg/day). Because of a flare up of her arthritis methotrexate (7.5 mg/week) was started nine months before admission and naproxen was discontinued. Serial complete blood cell counts, hepatic enzyme test results, and renal function remained normal during that period. Further treatment consisted of paracetamol (1-2 g/day), digoxin (0.125 mg/day), frusemide (40 mg/day), triamterene (50 mg/day), famotidine (40 mg/day), and vitamin B.

She was admitted to hospital because of progressive dyspnoea and chest pain. On admission she was afebrile with a pulse rate of 140/min and a blood pressure of 190/90 mmHg. The patient was tired and pale with tachypnoea. The heart was enlarged without any murmurs. On auscultation both lungs had reduced breathing sounds with a pleural rub at the base of the left lung. Musculoskeletal examination showed severe and generalised joint deformities typical of longstanding rheumatoid arthritis, but no active arthritis.

Laboratory findings were as follows: erythrocyte sedimentation rate 120 mm/h; haemoglobin 118 g/l; packed cell volume 0.37; white blood cell count $1.2 \times 10^9/l$ with 66% neutrophils, 8% bands, 19% lymphocytes, and 7% monocytes; platelet count $40 \times 10^9/l$; urea 9.1 mmol/l; creatinine 108 $\mu\text{mol/l}$; bilirubin 11 $\mu\text{mol/l}$; alkaline phosphatase 130 U/l; serum aspartate aminotransferase 31 U/l; serum alanine aminotransferase 29 U/l; lactic dehydrogenase 434 U/l (normal <320 U/l); albumin 22.1 g/l, arterial blood gas analysis: pH 7.50, PaO_2 63 mmHg, Paco_2 34 mmHg, bicarbonate 27 mmol/l.

An electrocardiogram showed sinus tachycardia at a rate of 140/min and high voltages, indicating left ventricular hypertrophy. Admission chest radiograph showed an enlarged cardiac silhouette and some pleural fluid at the left base. Lung scintigraphy showed small perfusion defects matched with ventilation. Echocardiography disclosed a large left ventricle with mitral valve insufficiency without vegetations. Methotrexate was discontinued, oxygen was given (2 litres/min), prednisone was increased to 25 mg/day, and she received cefpirome (fourth generation cephalosporin) intravenously. Her clinical condition improved and arterial PaO_2 rose to 80 mmHg. After six days white blood cell and platelet count became normal. Ten days after admission she developed fever (39°C) and a productive cough. *Klebsiella* was cultured from her sputum. Repeated chest radiographs showed no changes. She was treated with ceftriaxone. She remained feverish and her general condition worsened. A chest radiograph showed progression of pleural fluid and an infiltrate at the left base (fig 1). She was treated with oxygen, diuretics, and antibiotics, without showing improvement. It was her repeated request not to be resuscitated and that no

Figure 1 Chest radiograph showing an enlarged cardiac silhouette, pleural fluid, and an infiltrate at the left base.

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Figure 2 Histology of the pleura showing multiple small abscesses.

Figure 3 Gram stain of *Nocardia asteroides* showing Gram positive bacteria growing with branching filaments.

mechanical ventilation be started. Her clinical condition deteriorated and she died as a result of respiratory failure. Necropsy was permitted and showed pneumonia and pleuritis of the left lung (fig 2). Cultures from the lung obtained after death were positive for *N asteroides* (fig 3).

Discussion

Low dose methotrexate treatment for refractory rheumatoid arthritis is used increasingly often.¹⁻⁴ Infectious complications are rare, but there have been previous reports of opportunistic infections in patients receiving low dose methotrexate.⁵⁻⁷ Our patient developed a pulmonary infiltrate and pleuritis due to *N asteroides*.

On admission, the differential diagnosis from methotrexate pneumonitis was debated. The clinical picture of methotrexate pneumonitis is characterised by fever, non-productive cough, bibasilar rales on auscultation, hypoxaemia, and bilateral interstitial infiltrates.⁴ Our patient did

not show severe hypoxaemia on admission. Repeated chest radiographs showed a unilateral pleural effusion in the left lung. Furthermore, her condition showed some improvement during the first week when she was treated with antibiotics, and the white blood cell count became normal. In view of these findings the possibility of methotrexate pneumonitis was rejected, and we considered her to have an infectious pleuritis. After 10 days she developed a productive cough, and later on a chest radiograph showed an infiltrate at the left base. Despite repeated sputum cultures *N asteroides* was not cultured until after she died owing to respiratory failure.

Nocardia bacteria are well known opportunistic pathogens in the immunocompromised host.⁸⁻¹⁰ *Nocardia* spp are irregularly staining Gram positive and mostly acid fast aerobic bacteria, which grow with branching filaments. They can be grown on a variety of media, but up to three weeks is needed for growth and identification. *Nocardia* spp are widely distributed in nature but are not commensals.

The recovery of *Nocardia* spp from immune suppressed patients should be regarded as proof of active infection.⁸⁻¹⁰ *Nocardia* spp can cause local or systemic disease. The local form (mycetoma, wound infections) is mostly caused by *N brasiliensis*. *N asteroides* is responsible for the pulmonary or disseminated form most often encountered in the immunocompromised host. Clinical findings are non-specific and may vary widely from low grade fever, malaise, anorexia, weight loss, to cough and pleural pain. Disease progression can be acute, subacute, or chronic, usually with remissions and exacerbations. Dissemination especially to the central nervous system may occur, and correlates with mortality.¹¹ The drugs of choice against nocardia infections are the sulphonamides, though other compounds, such as trimethoprim-sulphamethoxazole and amikacin, have been used with variable results.⁸⁻⁹⁻¹²

Our patient developed *N asteroides* infection in the presence of pancytopenia owing to methotrexate bone marrow toxicity. Bone marrow failure due to low dose methotrexate has been associated with older age, pre-existing folate deficiency, low albumin, other concurrent drugs, such as sulphonamides and non-steroidal anti-inflammatory drugs, and impaired renal function.¹³ Methotrexate is predominantly excreted by the kidneys, through both glomerular filtration and active tubular secretion.¹⁴ Our patient developed pancytopenia in the absence of overt renal failure. The presence of cardiac failure, however, as indicated by cardiomegaly and mitral insufficiency, might have impaired the renal excretion of methotrexate. Also, the use of concomitant diuretics (frusemide and triamterene) might have inhibited renal excretion of methotrexate in our patient. In addition, increased free methotrexate, secondary to low serum albumin concentration, might have contributed to methotrexate toxicity. Folate deficiency was not detected. The older age of this patient might have been an independent risk factor, as suggested by Mackinnon.¹³

Other factors might have contributed to her

impaired immune status. She was receiving low dose prednisone as well, which has been associated with nocardia infection in immunocompromised patients.⁹ Furthermore, methotrexate has been shown to inhibit neutrophil chemotaxis.¹⁵

N brasiliensis infection in a patient treated with low dose methotrexate has been reported previously.⁷ To our knowledge this is the first report of systemic *N asteroides* infection complicating low dose methotrexate treatment. *Nocardia asteroides* pneumonia may be a lethal infectious complication, as shown in our patient. The diagnosis of *N asteroides* pneumonia may prove to be difficult. Repeated sputum cultures did not show *N asteroides* in our patient. Recovery rates from sputum are known to be unsatisfactory.⁹ Furthermore, the differential diagnosis from methotrexate pneumonitis is of extreme importance, as both conditions require such different treatment. For these reasons invasive techniques, such as bronchoscopy with brushing or biopsy or even open lung biopsy, should not be postponed for patients who develop a pulmonary infiltrate during methotrexate treatment.

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