CASE REPORT

Late-onset methotrexate-induced pneumonitis with neutrophilia in bronchoalveolar lavage fluid

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SUMMARY

A 61-year-old woman being treated with methotrexate (MTX) 8–10 mg/week and prednisolone 2.5 mg/day for rheumatoid arthritis presented with a 1-week history of increasing fever and dry cough. The patient deteriorated with administration of antibiotics. Chest CT scan showed bilateral diffuse ground-glass opacities. Analysis of bronchoalveolar lavage fluid (BALF) revealed marked neutrophilia (65.2% of total cells). The specimen from transbronchial lung biopsy showed a non-specific interstitial pneumonia pattern. Following withdrawal of the MTX, her pulmonary infiltration, clinical symptoms and laboratory findings gradually improved. Therefore, she was diagnosed as having MTX-induced pneumonitis. Lymphocytosis in BALF has been identified as a characteristic of MTX-induced pneumonitis, particularly in late onset of this disease. However, the BALF in our patient was neutrophilic. Although neutrophilia in BALF of patients with drug-induced pneumonitis is usually associated with poor outcome, rare cases of good outcome do exist.

BACKGROUND

Pneumonitis is a serious but rare complication of low-dose methotrexate (MTX) therapy for rheumatoid arthritis. Reports of MTX-induced pneumonitis are usually associated with an increase in the proportion of lymphocytes in the bronchoalveolar lavage fluid (BALF), but the role of inflammatory cells in MTX-induced pneumonitis remains obscure.¹ Our report is crucial to the understanding of this perplexing disorder because our patient presented with neutrophilia in her BALF.

CASE PRESENTATION

A 61-year-old woman, a housewife who had never smoked, presented with a 1-week history of increasing fever and dry cough. She was diagnosed as having bronchitis at another hospital. The patient had deteriorated with administration of antibiotics over 4 days. She was then admitted to our hospital because of dyspnoea on exertion and abnormal lung shadows. She was being treated at the time with MTX 8–10 mg/week and prednisolone 2.5 mg/day for rheumatoid arthritis that had begun 3.5 years before admission. Her vital signs on admission were as follows: temperature 37.4°C, blood pressure 116/74 mm Hg, pulse 96 bpm with regular rhythm and oxygen saturation 92% on pulse oximetry. An inspiratory squawk in the bilateral lungs was detected on auscultation, and heart sounds indicated a regular rhythm with no murmur.

INVESTIGATIONS

The C reactive protein level was elevated at 11.9 mg/dL. Anti-HIV-antibodies were negative. KL-6 and surfactant protein-D, markers of interstitial lung disease, were within normal limits, and at 7.3 pg/mL, her β -D-glucan level was not elevated. Chest CT scan revealed bilateral diffuse ground-glass opacities (figure 1). Bronchoalveolar lavage was performed using a total volume of 150 mL of sterile saline solution (61.3% recovery). BALF analysis revealed marked neutrophilia (65.2%), and other cells included lymphocytes (9.6%), eosinophils (0.8%) and macrophages (24.4%), with the total cell count elevated to 290/ μ L. The alveolar CD4 to CD8 T-cell ratio was high (3.99). *Pneumocystis jiroveci* PCR results were negative and no microorganisms were cultured in the BALF. The specimens from a transbronchial lung biopsy (TBLB) predominantly revealed interstitial inflammation with infiltration of lymphocytes and some plasma cells, alveolar septal thickening and intra-alveolar organisation, which indicated the presence of a non-specific interstitial pneumonia pattern (figure 2).

DIFFERENTIAL DIAGNOSIS

Radiological evidence of bilateral diffuse ground-glass opacities indicated possible MTX-induced

Figure 1 Chest high-resolution CT on admission revealed bilateral diffuse ground-glass opacities without swelling of hilar or mediastinal lymph nodes.

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Figure 2 Histological findings from the lung biopsy specimen predominantly showed interstitial inflammation with infiltration of lymphocytes and some plasma cells, alveolar septal thickening and intra-alveolar organisation (A: H&E stain, $\times 80$; B: Masson trichrome stain, $\times 80$).

pneumonitis or *Pneumocystis* pneumonia (PCP). However, PCP was thought to be unlikely because the patient's β -D-glucan level was not elevated and the *P. jiroveci* PCR results were negative. Moreover, although neutrophilia in BALF usually indicates a disorder associated with bacterial infection, other differential diagnoses such as bacterial pneumonia were dismissed on the basis of the clinical findings.

TREATMENT

After bronchoscopy, the MTX was withdrawn, and the patient was maintained on prednisolone (2.5 mg/day) during follow-up.

OUTCOME AND FOLLOW-UP

Subsequent to the withdrawal of the MTX, the patient's pulmonary infiltration, clinical symptoms and laboratory findings gradually improved, and she was discharged from our hospital on the 16th hospital day.

DISCUSSION

MTX-induced pneumonitis may be life-threatening, leading to death in about 10% of cases. Clinical features, that is, fever, cough and dyspnoea as well as radiological findings such as diffuse interstitial pneumonitis are non-specific.² Subacute occurrence of diffuse interstitial pneumonitis in patients receiving MTX for various underlying diseases should initially suggest a pulmonary infection. The findings in our patient were compatible with MTX-induced pneumonitis because antibiotics for bacterial infection were not effective, and her condition and the radiological abnormality of diffuse ground-glass opacities in her lungs improved within a few weeks after discontinuation of the MTX. PCP was excluded on the basis of the BALF examination and the lack of an elevated β -D-glucan level.

Schnabel *et al*³ reported that MTX-induced pneumonitis is associated with lymphocytic alveolitis with a preferential increase in CD4+ T cells, which usually results in lymphocytosis in BALF. Other researchers have reported similar findings,^{1 4 5} but the neutrophilia in the BALF of our patient contrasted with these reports. Generally, neutrophilia in the BALF of patients with drug-induced pneumonitis is due to a cytotoxic reaction and, therefore, the clinical course is thought to lead to a poor outcome.⁶ Moreover, Chikura *et al*⁷ recently reported that the immunological responses in MTX-induced pneumonitis vary with the degree of exposure to MTX. Early-onset MTX-induced pneumonitis (<6 months) is associated with neutrophilia, lung fibrosis and high mortality, whereas late-onset MTX-induced pneumonitis (>6 months) is associated with

lymphocytosis and low mortality. Neutrophils can cause lung injury by releasing gelatinases and collagenases, resulting in tissue damage and lung fibrosis.⁸ Our patient had neutrophilia despite having late-onset MTX-induced pneumonitis. Moreover, unlike the patients in these previous reports, despite the neutrophilia in her BALF, our patient experienced improvement and a good outcome following MTX withdrawal without an increase in her prednisolone dose. On the other hand, Chiba *et al*⁹ reported that a case of bronchiolitis obliterans organising pneumonia with neutrophilia in BALF was a favourable outcome. The reason for few neutrophils in the TBLB specimen in spite of neutrophilia in BALF is unclear; we thought that perhaps the TBLB may not have been sufficient for the definitive pathological diagnosis due to the amount and site of the biopsies. Neutrophilia can sometimes be seen in the analysis of BALF from patients with late-onset MTX-induced pneumonitis and cases of good outcome do exist. Therefore, further analysis focusing on pulmonary disease with neutrophilia in BALF is warranted and will be necessary.

Learning points

- ▶ Immunological responses in methotrexate (MTX)-induced pneumonitis vary with the degree of exposure to MTX.
- ▶ Neutrophilia is sometimes seen in the analysis of bronchoalveolar lavage fluid (BALF) from patients with MTX-induced pneumonitis. Clinicians should keep MTX-induced pneumonitis in mind as a differential diagnosis in these patients, even if BALF analysis shows neutrophilia.
- ▶ Although neutrophilia in BALF of patients with drug-induced pneumonitis is usually associated with a poor outcome, rare instances of good outcome do exist.

Contributors HY was the primary author of the manuscript. MT and KK were the senior authors, and MY was the author who performed clinical analyses reported herein.

Competing interests None.

Patient consent Obtained.

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