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CASE REPORT

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Methotrexate pneumonia lacking dyspnea and radiographic interstitial patterns during treatment for early rheumatoid arthritis: bronchoalveolar lavage and transbronchial lung biopsy in a differential diagnosis

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Abstract Methotrexate (MTX) pneumonia is an unpredictable and sometimes life-threatening adverse effect occurring in the treatment of rheumatoid arthritis (RA). We present a case of MTX pneumonia lacking severe respiratory symptoms and typical radiographic findings. A 66-year-old man with early RA presented with intermittent fever and nonproductive cough during the MTX therapy, but neither hypoxemia nor dyspnea was a complaint. His chest X-ray films revealed multiple bilateral consolidations, but interstitial infiltrates were not observed. High-resolution computed tomography showed no ground-glass opacities. In contrast, the histological findings of transbronchial lung biopsy (TBLB) samples were characterized by the interstitial infiltration of mononuclear cells and hyperplasia of type II alveolar cells, which are the main features of drug-induced interstitial inflammation. Special stains for microorganisms were negative for the TBLB samples. Although cultures of bronchoalveolar lavage (BAL) fluids were slightly positive for *Haemophilus influenzae*, intensive antibiotic therapy was ineffective. A discontinuation of MTX followed by steroid therapy induced the patient's dramatic recovery. A new treatment with tacrolimus was started for RA. We would like to emphasize that the histological examinations and microbiological studies using BAL and TBLB are useful for the exclusion of other causes and the diagnosis of MTX pneumonia, especially in a case without typical respiratory symptoms and radiographic patterns.

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Introduction

Methotrexate (MTX) is often used as the first-line disease-modifying antirheumatic drug (DMARD) for patients with early progressive rheumatoid arthritis (RA) who are at the risk of the development of joint destruction. When compared with other DMARDs, MTX is proved to be more effective over long periods and truly disease modifying in terms of slower radiographic progression and better survival benefits.[1] Currently, MTX is considered an anchor drug, since it can be used in combination with biological agents.[2,3] Several randomized controlled trials showed that in comparison to monotherapy, the combination therapy of MTX with tumor necrosis factor (TNF)-blocking agents conveys greater clinical and radiographic efficacy in both established and early RA.[2] Methotrexate is generally well tolerated and has a better toxicity profile than other DMARDs. However, the development of toxicity is a major reason for the withdrawal of MTX. Methotrexate pneumonia is the most common encountered form of MTX-induced lung toxicity, and it sometimes becomes life threatening.[4–7] It is difficult to predict which patients receiving MTX will develop MTX pneumonia. Rheumatoid arthritis is the most frequent underlying disease in patients having it, possibly reflecting a high susceptibility of RA patients to MTX. This complication occurred in 0.5%–7.25% of RA patients receiving low-dose MTX.[4–6,8]

The most common complaints are dyspnea, dry cough, and fever. Crackles are frequently audible. Hypoxia and tachypnea are always reported abnormalities in laboratory findings. A chest radiograph usually shows diffuse interstitial infiltrates or mixed interstitial and alveolar patterns. High-resolution computed tomography (HR-CT) reveals ground-glass patchy opacities, interstitial infiltrates, septal lines, or widespread consolidation.[4–6,9,10] Because these clinical findings are nonspecific, a definite diagnosis of MTX

pneumonia is difficult. No widely accepted definition of MTX pneumonia is available in the literature. The most frequently used diagnostic criteria include the use of MTX prior to the onset of pulmonary symptoms, an exclusion of infection and other pulmonary diseases, a high index of suspicion based on clinical features, lung pathology consistent with drug-induced lung toxicity, new or evolving pulmonary infiltrates on chest radiographs, and the evidence of improvement upon the discontinuation of MTX or after steroid therapy.[6,8,11]

Here we report MTX pneumonia lacking severe respiratory symptoms and typical interstitial patterns on chest radiographs in a patient with early progressive RA during MTX monotherapy. Because of a rapid exclusion of infectious pneumonia and an early diagnosis of MTX pneumonia, this patient was successfully treated with the cessation of MTX use and the introduction of steroid therapy. Knowledge and understanding about the atypical type of MTX pneumonia is therefore important in the management of RA patients under MTX treatment.

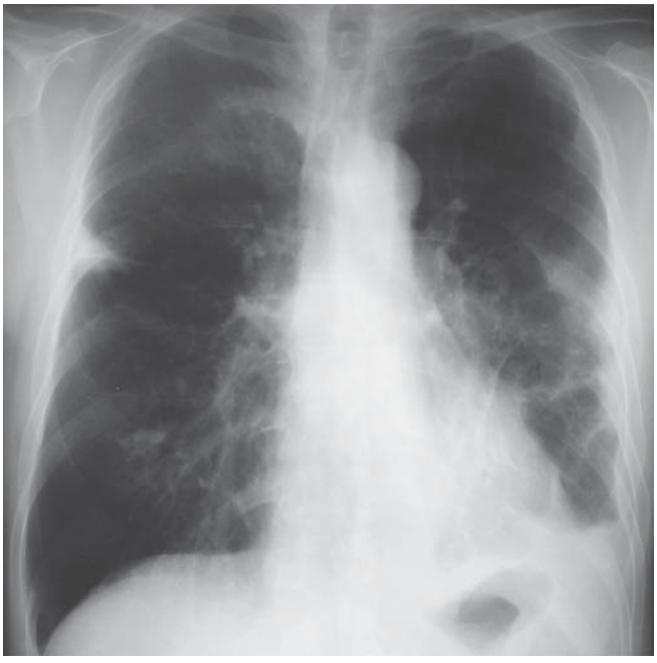

Fig. 1. Chest X-ray film on admission. Multiple bilateral consolidations are seen. Interstitial infiltrates were not observed

Case report

A 66-year-old man, whose symptoms 8 months earlier had been diagnosed as RA, had received low-dose MTX for 5 months. He had no evidence of pre-existing pulmonary involvement. Despite an early initiation of MTX therapy (8 mg/week), his disease had been uncontrolled and was getting worse. Two months earlier, he had complained of common cold-like symptoms such as nonproductive cough and general fatigue, but neither hypoxemia nor fever was found. A serum C-reactive protein (CRP) value was 2.3 mg/dl, and the numbers of swollen and tender joints were 5 and 6, respectively. The visual analog scale (VAS) for pain was 65, and the disease activity score for 28 joints (DAS28-CRP) was 5.0. Symptomatic therapy was done, but respiratory symptoms were continued. At a regular medical check for RA, the serum CRP level was elevated to 17.1 mg/dl. The numbers of swollen and tender joints were 6 and 8, respectively, and the VAS for pain was 64. These data indicated dissociation between the serum CRP value and rheumatoid activity. Chest X-ray films showed multiple consolidations on both sides of the lung (Fig. 1). On the other hand, oxygen saturation obtained by pulse oximetry (SpO_2) was 96% at rest, and no decrease was seen after motion. Tachypnea was not present. No crackles were audible on lung fields. Raynaud's phenomenon did not occur spontaneously or in response to cold stress.

To learn the cause of radiographic abnormalities, the patient entered our hospital. On admission, he presented with cough, general fatigue, and a high grade of fever (38.9°C), but he did not complain of dyspnea. Laboratory data are summarized in Table 1. The white blood cell count was slightly elevated (10400/μl). Serum levels of CRP and the erythrocyte sedimentation rate (ESR) were also increased to 18.2 mg/dl and 71 mm/h, respectively. The serum levels of interstitial pneumonia markers, lactate dehydrogenase, KL-6, and SP-D, were all within normal ranges. High-resolution CT showed multiple patchy air-space consolidations on both lung fields, but no ground-glass opacities were observed (Fig. 2). A small amount of pleural effusion was found. An analysis of bronchoalveolar lavage (BAL) fluids was as follows: total cells, 5×10^5/ml; alveolar macrophages, 85%; lymphocytes, 0.5%; neutrophils, 11%; eosinophils, 3.5%; and CD4/CD8 ratio, 3.2. In microorganism cultures of BAL fluids, a very small number of *Haemophilus influenzae* was detected. Because the bacterial infection was suspected, ciprofloxacin, meropenem, and minocycline, which are effective for the isolated bacteria, were intravenously administered for 7 days. In spite of the intensive antibiotic treatment, the clinical condition, laboratory data, and radiographic abnormalities did not improve. The histology of transbronchial lung biopsy (TBLB) samples showed a moderate degree of cellular interstitial infiltration with plasma cells, partly with foamy macrophages, and hyperplasia of type II alveolar cells. No evidence of microorganisms was obtained (Fig. 3). These findings were compatible with nonspecific interstitial pneumonia group I or II. A pathological pattern of bronchiolitis obliterans with organizing pneumonia (BOOP) was not observed. Considering the invalidity of antibiotic therapy and the histological findings of TBLB samples, we excluded a possibility of infectious pneumonia and suspected MTX pneumonia. Methotrexate was discontinued, and steroid pulse therapy was started (intravenous injection of methylprednisolone, 1 g daily for 3 days), followed by 60 mg/day oral administration of prednisolone. Fourteen days after the introduction of steroid therapy, the clinical symptoms, radiographic abnormalities, and laboratory data were remarkably improved. High-resolution CT findings are shown in Fig. 4. These ob-

Table 1. Laboratory data on admission

Hematology		**Serology**	
WBC (/μl)	10490	CRP (mg/dl)	18.2
Neut (%)	80.9	ESR (mm/h)	71
Lym (%)	6.0	IgG (mg/dl)	2300
Mo (%)	7.1	IgA (mg/dl)	459
Eo (%)	5.8	IgM (mg/dl)	73
Ba (%)	0.2	C-ANCA	Negative
RBC (/μl)	360×10^4	P-ANCA	Negative
Hb (/dl)	10.2	RF (IU/ml)	171
Ht (%)	32.9	ANA	Negative
Plts (/μl)	60.8×10^4	β-D-Glucan (pg/ml)	7.3
		KL-6 (U/ml)	212
Biochemistry		SP-D (ng/ml)	71.9
TP (g/dl)	6.9	DLST for MTX	Positive (S.I. = 6.4)
Alb	No data		
Na (mEq/l)	139	**Bronchoalveolar lavage**	
K (mEq/l)	4.8	Appearance	Clear
Cl (mEq/l)	103	Total cell count (/ml)	50×10^4
BUN (mg/dl)	22.4	Lym (%)	0.5
Cr (mg/dl)	1.11	AMϕ (%)	85.0
Glu (mg/dl)	152	PMN (%)	11.0
T-Bil (mg/dl)	0.54	Eos (%)	3.5
GOT (U/l)	21	CD4/CD8 ratio	3.2
GPT (U/l)	19	Cytology	No evidence for malignancy
LDH (U/l)	188		

servations fulfilled the diagnostic criteria of MTX pneumonia proposed by Zisman et al.,[6] although he lacked the common clinical symptoms and typical radiographic findings. We reached the final diagnosis of MTX pneumonia.

After the clinical improvement, the oral administration of prednisolone was tapered off by 5 mg every week and finally reduced to 7.5 mg/day. At this time, the CRP level was 4.0 mg/dl and DAS28-CRP was 5.3. To avoid a recurrence of MTX pneumonia, we decided to start tacrolimus (1.5 mg/day) therapy. After 6 months, the patient accomplished a moderate response defined by European League Against Rheumatism (EULAR) criteria.[12] The CRP value was reduced to 2.3 mg/dl, and DAS-CRP was 4.0.

Discussion

During the course of RA treatment, we encountered a case of MTX pneumonia that lacked characteristic clinical manifestations and findings, namely, dyspnea, hypoxemia, interstitial patterns on chest radiographs, and ground-glass patchy opacities on HR-CT.[4,6,13] In contrast, TBLB samples showed interstitial infiltrates of mononuclear cells and hyperplasia of type II alveolar cells, which are the main histological features of drug-induced interstitial inflammation.[4,6,9] Bronchoalveolar lavage analysis also revealed an increase in the CD4/CD8 ratio, a finding characteristic of MTX pneumonia.[14,15] Primarily, the diagnosis of MTX pneumonia is thought to be a clinical diagnosis based on history, symptoms, physical examinations, and radiographic findings.[13] The lung biopsy and BAL analysis are not always required for the diagnosis of MTX pneumonia, since observations obtained with these examinations are not specific and can be seen in other forms of hypersensitivity pneumonia and a variety of inflammatory lung processes.[4,6] However, we would like to emphasize that for a nonsymptomatic case lacking typical radiographic findings, TBLB and BAL appear to be the appropriate approaches to the rapid diagnosis of MTX pneumonia.

Transbronchial lung biopsy and BAL analysis may be helpful in ruling out other possible diagnoses, especially an infectious etiology. Special stains for pathogenic microorganisms were negative for TBLB samples of this patient. Of note, the culture of BAL fluids revealed the presence of *Haemophilus influenzae*, but the intensive treatment with antibiotics failed to obtain any favorable effects on the clinical symptoms and radiographic findings. We therefore concluded that the bacterial infection was not the main cause of this pneumonia, though a possibility of its concomitant occurrence with MTX pneumonia was not entirely excluded. Besides pulmonary infections, the respiratory symptoms that develop in an RA patient receiving MTX therapy may indicate an RA-related lung disease (rheumatoid lung). The exclusion of this possibility is important for the final diagnosis of MTX pneumonia. In this report, the main finding on the chest X-ray film was bilateral multiple consolidation, which is reminiscent of rheumatoid lung. Cryptogenic organizing pneumonia (COP), also referred to as BOOP, is a clinicopathological syndrome of unknown etiology. Chest radiographs of BOOP/COP show bilateral patchy pneumonic consolidations, which occur more frequently in the periphery of the lung and in the lower lung zone.[16] The findings of our case were consistent with the radiological features of BOOP/COP. This syndrome is one of the pulmonary manifestations of RA,[17] but it is also observed in drug-induced toxicity such as MTX pneumonia.[4,18] In our case, however, the BOOP/COP pattern was not found in

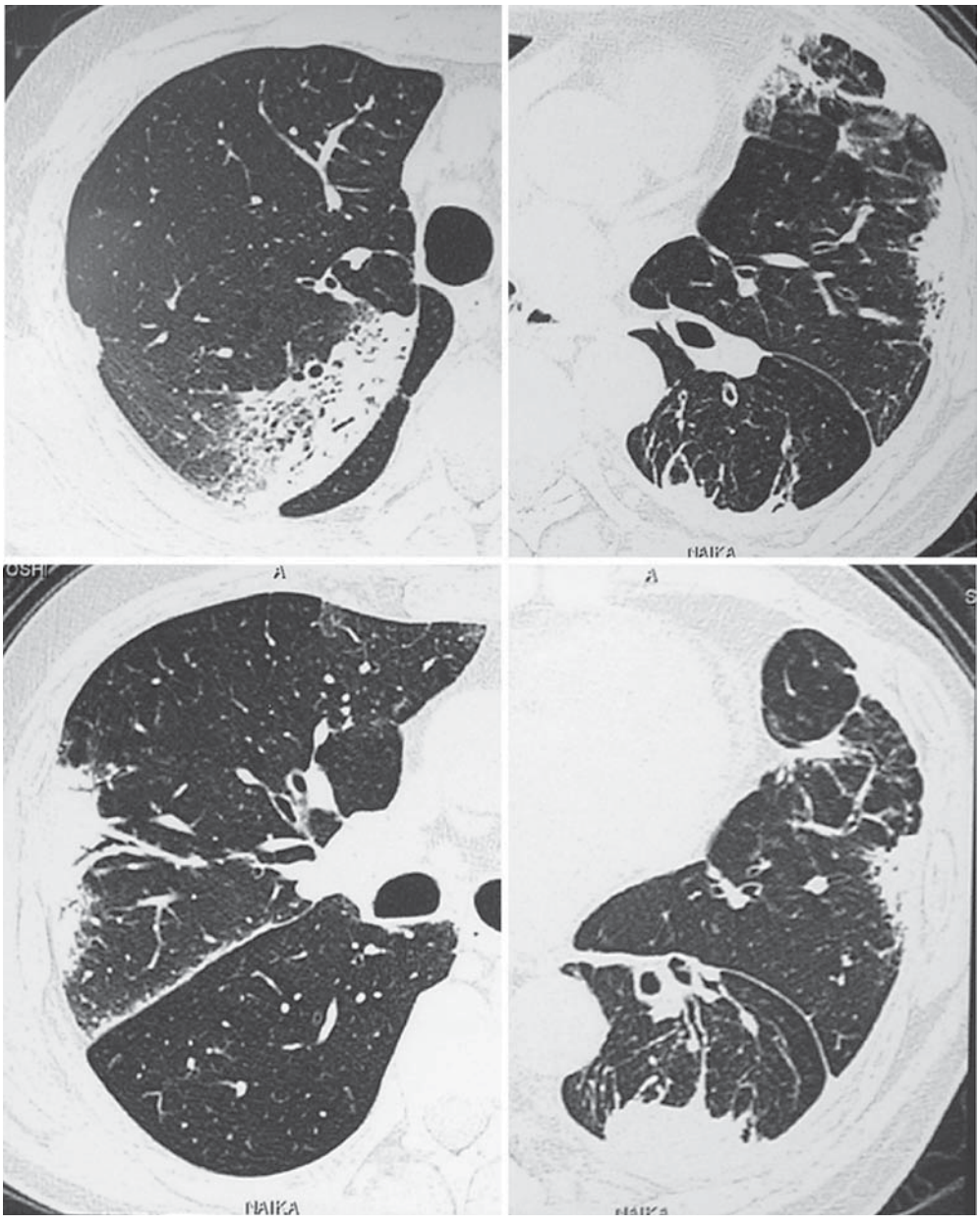

Fig. 2. High-resolution computed tomography (HR-CT) on admission. Multiple patchy consolidations are shown on both lung fields. No ground-glass opacities were present

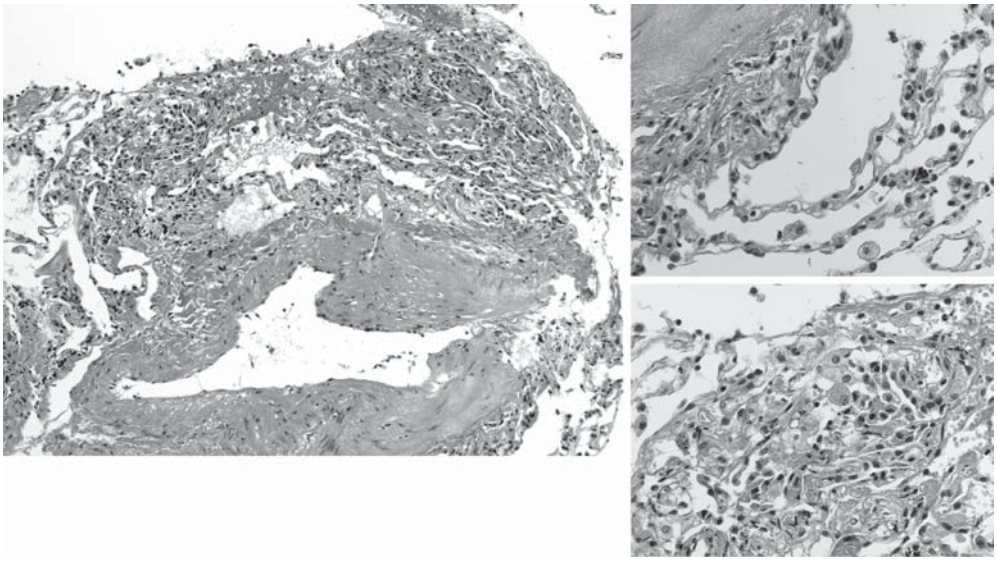

Fig. 3. Pathological findings obtained from transbronchial lung biopsy. Moderate cell infiltration with plasma cells and partly with foamy macrophages and hyperplasia of type II alveolar cells is observed. Pathological findings of BOOP/COP were not evident (H.E stain)

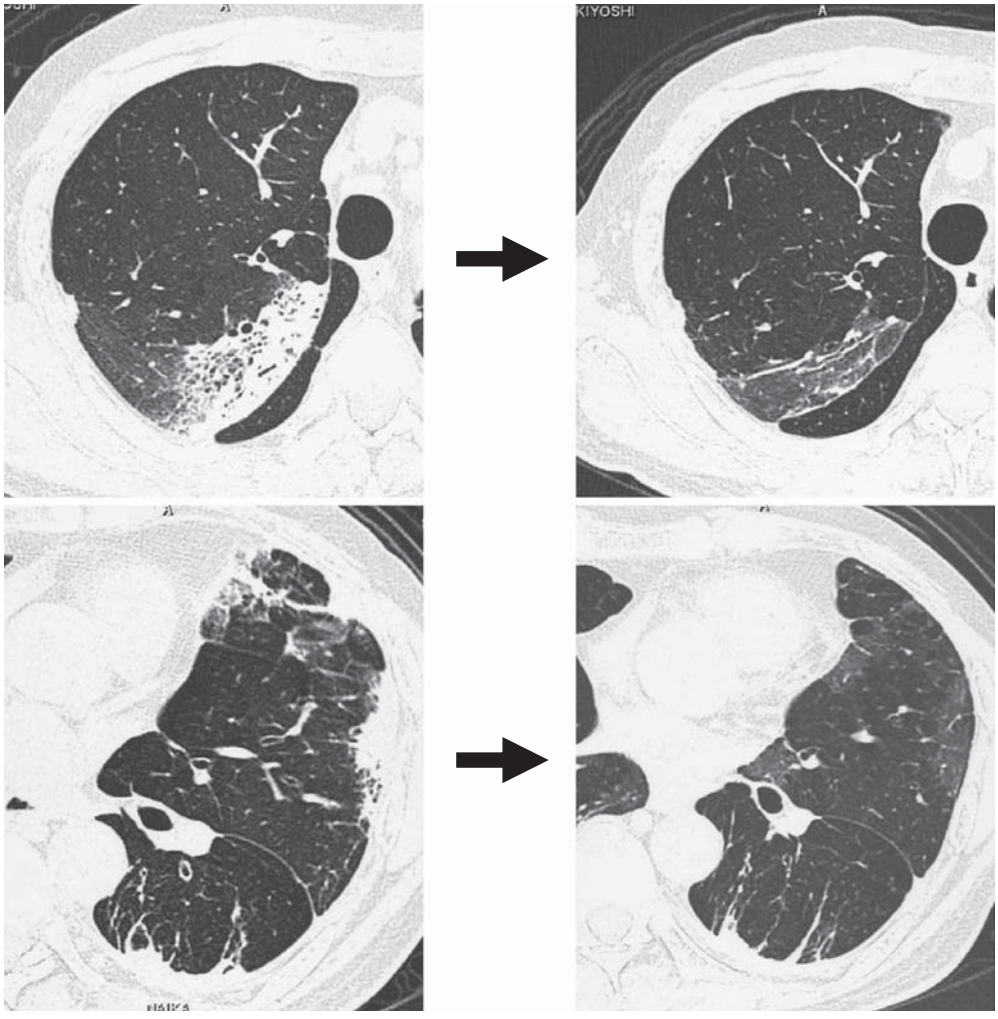

Fig. 4. Four weeks after the discontinuation of methotrexate and the start of steroid therapy, HR-CT findings were remarkably improved

the TBLB histology. The CD4/CD8 ratio was significantly increased in the case reported here. Schnabel et al.[14] showed that the increase in the CD4/CD8 ratio may assist in differentiating MTX pneumonia from rheumatoid lung. The CD4/CD8 ratio is usually decreased in a variety of inflammatory lung processes including RA,[14,15] and BAL analysis for BOOP/COP often reveals a decreased ratio of CD4/CD8.[19] There was no evidence suggesting that this patient had developed rheumatoid pulmonary involvement before the start of MTX therapy. Moreover, his clinical symptoms and radiological findings were dramatically improved by the discontinuation of MTX, but his RA was still uncontrolled. Considering these observations, we believe it reasonable to exclude the possibility that this is a case of rheumatoid lung.

Methotrexate pneumonia is far less predictable than hepatic and hematological toxicity.[5] Specific risk factors that predispose RA patients to MTX pneumonia have not been established.[20] Alarcon et al.[8] presented the following risk factors: older age (older than 60 years), rheumatoid pleuropulmonary involvement, previous use of DMARDs, hypoalbuminemia, and diabetes mellitus. Additional risk factors suggested by other investigators include higher doses of MTX,[21] daily rather than weekly administration of MTX,[22] pre-existing lung disease,[10] and concomitant use of medications that decrease the protein binding of MTX.[6] Since our case had none of these risk factors, except for the older age, we had not considered that he may belong to the high-risk group of MTX pneumonia. In contrast, several reports have suggested that RA itself may be involved in the development of MTX pneumonia,[4] because RA patients are generally prone to drug hypersensitivity. Those receiving MTX therapy should be informed of the potential risk of MTX pneumonia, even though they have no multiple risk factors and should be instructed to contact their rheumatologists if new respiratory symptoms, even subtle changes, develop during the MTX therapy.

The definitive and accurate diagnosis of MTX pneumonia is required for the determination of treatment strategies for RA when clinical improvement of this complication is achieved. Although there are reports of successful re-challenge without a recurrence of MTX-induced lung injury,[4,23] most authors recommend that patients not be rechallenged with MTX because of a potent risk of recurrence. Besides, some studies show that the relapse of MTX pneumonia is severe and often fatal.[4,24] In contrast, the resumption of MTX therapy is encouraged for rheumatoid lung cases, and with special care for host immune conditions this therapy

can be restarted for patients developing pulmonary infections. Tacrolimus is a newly approved immunosuppressant for RA treatment.[25] Since our case was finally diagnosed as MTX pneumonia, we avoided rechallenging with MTX and decided on a single use of tacrolimus.

In conclusion, the diagnosis appears to be underappreciated for a patient lacking dyspnea and hypoxemia if radiological studies alone are used. Once MTX pneumonia is suspected, the advice should be obtained from pulmonologists, and to differentiate from other causes of respiratory symptoms, we must consider the histological examinations and microbiological studies using BAL and TBLB specimens. The rapid improvement is achieved by an early diagnosis, a withdrawal of MTX, and an introduction of steroid therapy. Even for RA patients in the low risk group, we should be alert to the possibility of a development of MTX pneumonia.

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