Mod Rheumatol (2002) 12:76–79

CASE REPORT

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Atypical mycobacteriosis in two patients with rheumatoid arthritis

Received: January 22, 2001 / Accepted: July 21, 2001

Abstract We report two cases of rheumatoid arthritis (RA) with atypical mycobacteriosis. Opportunistic infections are critical complications for rheumatic diseases. The use of steroids or immunosuppressants may increase the risk of opportunistic infections. However, these reports are rare in that they demonstrate atypical mycobacterial infections as complications of RA, even though no immunosuppressive agents were used. We discuss the characteristics of atypical mycobacterial infections of the lung in RA.

Key words Atypical mycobacteriosis · Rheumatoid arthritis (RA)

Introduction

A wide variety of microbes, ranging from common bacterial pathogens to exotic fungal and protozoan organisms, may cause pulmonary infections in patients with rheumatoid arthritis (RA).[1] Although less frequent than bacterial pneumonia, pulmonary infection with opportunistic pathogens is often associated with a poorer clinical outcome. The higher mortality rate of patients with opportunistic pneumonia is often directly related to a delay in diagnosis. Opportunistic pathogens that may cause pneumonia in patients with RA include mycobacteria, fungi, *Norcardia* spp., herpes zoster, cytomegalovirus, and *Pneumocystis carinii*.

It was estimated that 51.7 new cases of all forms of tuberculosis per 100000 inhabitants were found in 1997, and the incidence of tuberculosis in patients with systemic rheumatic diseases was about 2.5% in 1994.[2] Concerning atypical mycobacterial diseases, an estimated 1 case per 100000 inhabitants was found in Japan in 1971, and this rate increased to about 2.99 per 100000 by 1992. About 16% of all mycobacterial infections were atypical mycobacteriosis. The most common origin of atypical mycobacterial diseases is *Mycobacterium avium* complex (MAC) (80%), and the second is *Mycobacterium kansasii* (*M. kansasii*) (20%).

Although *M. kansasii* and *Mycobacterium chelonae* infections in patients with RA have been reported, few reports have demonstrated atypical mycobacterial infection occurring in patients with RA.[3–7] Almost all patients received corticosteroids with or without immunosuppressive drugs. We report here two cases of RA with atypical mycobacteriosis, even though no immunosuppressive agents were used.

Case reports

Case 1

A 70-year-old Japanese woman had been suffering from polyarthralgia without any medications for more than 20 years. She had had generalized edema since 1993. A chest X-ray and computed tomography (CT) in December 1994 showed nodular shadows with cavities and pericardial calcifications in both lung fields (Fig. 1). *M. avium* was detected in her sputum by DNA probing. She was diagnosed as having atypical mycobacterial infection and restrictive pericarditis. Antitubercular drugs, including rifampicin, were refused because of diarrhea. The lung shadows gradually extended. In May 1995, the polyarthralgia became more severe and morning stiffness developed. Her activity of daily living (ADL) became restricted. She was diagnosed as having RA with positive rheumatoid factor (166 IU/ml) and bone destruction of the wrist joints in June 1995. The activity of RA was well controlled with auranofin (6 mg/day) and indomethacin suppository (50 mg/day). However, she

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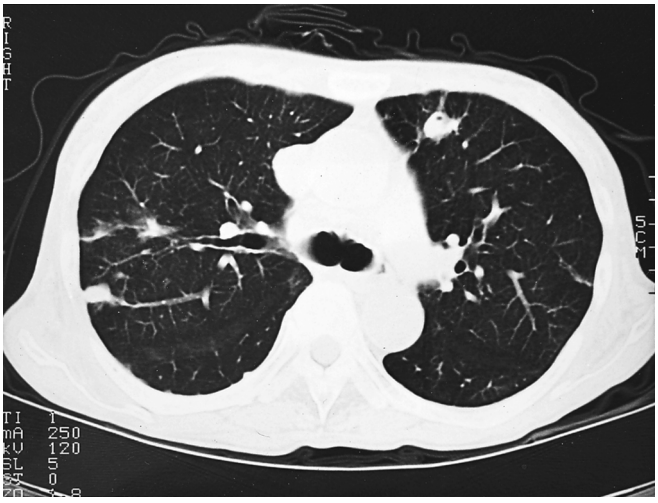

Fig. 1. Computed tomography (CT) shows nodular shadows partly with cavitic changes, bronchiectasia, and calcifications in both lung fields in December 1994

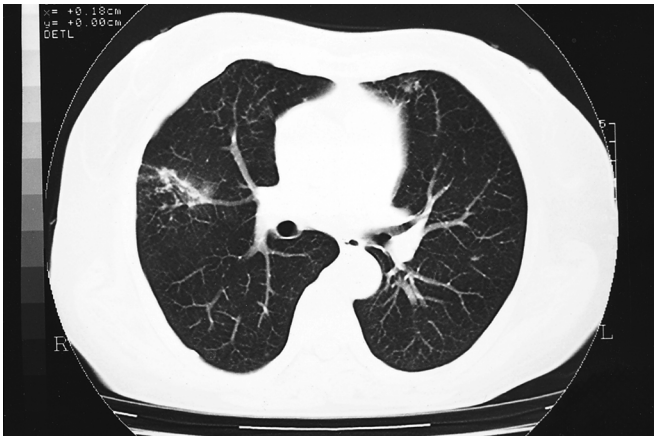

Fig. 2. CT shows small nodular shadows in middle of right lung fields. Small granular shadows developed in bilateral lung fields. Pleural thickness and calcification were also detected

suffered constrictive pericarditis in July 1995. She was admitted to our hospital for the treatment of atypical mycobacterium pneumonia and then underwent surgery for the constrictive pericarditis. The lung shadows improved after treatment with clarithromycin (400 mg/day) and levofloxacin (400 mg/day).

Case 2

A 65-year-old Japanese woman had, at the age of 30, been diagnosed as having RA because of polyarthralgia and joint swelling in both proximal interphalangeal (PIP) joints. She had been treated with non-steroidal antiinflammatory drugs (NSAIDs) for about 30 years. As she developed goiter in August 1986, she was introduced to our hospital. Since then, she has also been diagnosed with chronic thyroiditis, for which she has been receiving follow-up care as an outpatient at our hospital. Some disease-modifying antirheumatic drugs (DMARDs) had been used to treat her RA. However, she had allergic reactions against some of the DMARDs. Finally, her RA activity was well controlled with sulfasalazine (SSZ) and sulindac. In August 1997, a chest X-ray and CT showed small nodular shadows in the middle of the right lung field (Fig. 2). Small granular shadows had developed in the bilateral lung fields. Pleural thickening and calcification were also detected in October 1997. The next month, positive Ziehl–Neelsen staining of the bronchoalveolar lavage fluid (BALF) was detected. Furthermore, *M. avium* was detected by the polymerase chain reaction (PCR) products of the BALF, and she was diagnosed as having atypical mycobacterium infection of the lung. She was treated with isoniazide (0.4 g/day), rifampicin (0.45 g/day), streptomycin (1 g i.m., twice/week), ethambutol (0.75 g/day), and clarithromycin (800 mg/day). In December 1997, the lung shadows had decreased and *M. avium* could not be detected either in the culture or by the PCR products of the BALF.

Discussion

Two patients with RA and atypical mycobacterial infection of the lung were admitted to our hospital in recent years. These infections occurred after the onset of RA.

The risk factors for MAC are advanced age, underlying pulmonary disease, collagen-vascular disease, a possible genetic predilection, and an intake of immunosuppressive agents including corticosteroids. As shown in Table 1, RA patients with pulmonary MAC infection reported so far had predisposing pulmonary diseases. No other underlying pulmonary diseases were present in these patients. The patient of case 1 had the complication of constrictive pericarditis. Malignancies, diabetes mellitus, and liver diseases were not complications in our patients. They also did not have collagen-vascular diseases other than RA. No glucocorticoids or immunosuppressive agents were used in any of the patients before the diagnosis of atypical mycobacterial infection. Although several reports demonstrated that atypical mycobacterial infections occurred in RA patients, all those patients received either corticosteroids or cyclophosphamide.[6–7] In all cases, atypical *Mycobacterium* sp. infection occurred in a disseminated pattern. The frequency of opportunistic infections must be ascertained because the use of low-dose oral methotrexate is increasing. However, it was rare that MAC infections occurred in patients with RA who received neither corticosteroids nor immunosuppressants and further had no predisposing pulmonary diseases.

MAC infections are classified into tuberculosis-like type, bronchial type, and disseminated type. Recently, it was reported that MAC occurred in elderly women without predisposing bronchopulmonary illeness.[3] This type of MAC involved mainly the bronchial regions. In general, the respiratory symptoms of MAC are quite mild in comparison to tuberculosis and *M. kansasii* infection. Especially, almost all patients with the bronchial type of MAC do not have any symptoms. Our cases were found because of abnormal

Table 1. Characteristics of pulmonary atypical mycobacterial infections in rheumatoid arthritis (RA)

Source	Age/sex	Species of *Mycobacterium*	Respiratory symptoms	Predisposing pulmonary illness	Type of infection	CT findings	Years since onset of RA	Treatment for RA	Activity of RA
Murayama et al.[3]	69/F	MAC	None	Tuberculous pleurisy Gold-induced interstitial pneumonia	Bronchial type	Clusters of small nodules in subpleural regions of both lungs combined with bronchiectasia	20	Bucillamine Prednisolone 4 mg/day	Moderate
Case 1	70/F	MAC	None	None	Bronchial and tuberculosis-like mixed type	Nodules in subpleural regions of middle lobes combined with bronchiectasia and cavitation	20	Auranofine 6 mg/day Corticosteroid (−)	Quiescent
Case 2	65/F	MAC	None	None	Bronchial type	Clusters of small nodules in subpleural regions of middle lobes	30	Sulfasalazine 1000 mg/day Sulindac 300 mg/day Corticosteroid (−)	Quiescent
Watkin et al.[4]	51/M	*M. kansasii*	Dry cough	Pulmonary fibrosis	Tuberculosis-like type	Cavitation in upper lobe bilateral pulmonary infiltrate	6	Fenoprofen 600 mg/day Diclofenac 100 mg/day Corticosteroid (−)	Quiescent

MAC, *Mycobacterium avium* complex

shadows on chest X-rays. Characteristic CT findings of bronchial type are clusters of small nodules in the subpleural regions of the lung in combination with dilated changes of the bronchi.[3]

In general, atypical mycobacterial infections occur in immunocompromised hosts. RA is one of the risk factors in atypical *Mycobacterium* infections; this may be a result of disease-related, impaired cell-mediated immunity and antibody-producing capacity, or the reduced chemotactic responses of polymorphonuclear cells.[4] It has also been reported that CD4+ T cells and γ/δ T cells from MAC patients were defective in inducing anti-MAC activity.[8] T-cell-dependent growth inhibition and production of interferon-γ and macrophage colony-stimulating factor decreased in those patients.

Kubo et al.[9] reported that HLA-A26, DR6, and DQ-4 frequencies in patients with MAC were significantly increased compared with those of healthy Japanese control subjects. HLA-DQ4 was positive in the case 1 patient. Development of pulmonary MAC might be associated with HLA-DQ4 in the case 1 patient. However, there seemed to be no association between MAC and RA in disease susceptibility genes.

The recognition and treatment of MAC infections in RA patients are particularly difficult tasks for several reasons.[1] Clinical symptoms of MAC infection are quite mild. The clinical manifestations of infection may be indistinguishable from those of RA. Pulmonary involvement is one of the extraarticular manifestations of RA and includes pleuritis, parenchymal nodules, interstitial diseases, bronchiolitis obliterans organizing pneumonia (BOOP), and Caplan syndrome. Pulmonary diseases also may be observed as a toxic event consequent to treatment for RA. RA patients with interstitial pneumonia were commonly male and older and had significantly high levels of rheumatoid factor.[10] However, we have summarized here the characteristics of MAC infections in two patients with RA; bronchial involvements of MAC were observed in these elderly women without predisposing bronchopulmonary illness. Almost all their RA activities were quiescent, and they did not always receive corticosteroids and immunosuppressants. Furthermore, it is suggested that impaired immune mechanisms or a possible genetic predilection might be related to MAC infection in RA. It is necessary to accumulate further cases to define the characteristics of pulmonary MAC infections in RA, thus providing helpful information for treatments in the future.

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