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CASE REPORT

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Rapidly aggravated *Mycobacterium avium* infection in a patient with rheumatoid arthritis treated with infliximab

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Abstract Infliximab was introduced along with methotrexate 8 mg/week to a female patient with intractable rheumatoid arthritis. Although a dramatic improvement of her arthritic symptoms was achieved immediately, a small nodular shadow developed in the right middle field of her lung, visible on chest X-ray at the third injection. Because the nodular shadow rapidly increased its size in a week, transbronchial fiberoptic examination was performed and lavage fluid was obtained. The polymerase chain reaction was positive for *Mycobacterium avium* and the bacterial growth in culture confirmed the diagnosis. Although tuberculosis is a well-known adverse reaction to infliximab, development of nontuberculous mycobacteriosis is quite rare and no such report has so far been published in the context of infliximab usage. We should be alert to the fact that nontuberculous mycobacteriosis of slow progression in a usual clinical setting progresses quite rapidly, thus treatment should not be delayed, especially in patients on infliximab.

Key words Infliximab · *Mycobacterium avium* complex (MAC) · Tuberculosis

Introduction

Infliximab, a mouse–human chimeric monoclonal antibody against tumor necrosis factor α, was recently approved in Japan for treatment of rheumatoid arthritis (RA). Although the efficacy of infliximab for abatement of joint inflammation is well established, many precautions are proclaimed as to its side effects.[1] These include: lowered resistance to infectious agents inducing sepsis, pneumonia, and opportunistic infections; infusion reactions; and delayed hypersensitivity. The number of patients with tuberculosis has increased rapidly since infliximab was introduced for treatment of patients with RA in Western countries.[2] Tuberculosis induced by infliximab infusion could be much more serious in Japan, because prevalence of tuberculosis in the general population is approximately four times higher than that in most European countries and the United States.

On the other hand, nontuberculous mycobacterial infection such as *Mycobacterium avium* complex (MAC) is much more indolent and patients with this infection sometimes receive no treatment when the symptoms are trivial.[3] However, patients who are immunocompromised by virtue of acquired immunodeficiency syndrome, lymphatic malignancies, or immunosuppressive drugs have a greater tendency to develop a disseminated form of nontuberculous mycobacterial infection.[4] Here, we report a case of RA in a female patient who developed a rapidly progressing MAC infection in the lung as early as 6 weeks after initiation of infliximab treatment.

Case report

A 67-year-old Japanese woman developed RA in 1959 and she had been treated with traditional disease-modifying antirheumatic drugs since then: gold sodium thiomalate 25 mg every other week, lobenzarit 240 mg/day, bucillamine 200 mg/day, and sulfasalazine 1000 mg/day. Although predonisolone had been used intermittently, the information on the precise amount and duration was not available. However, the arthritic activity had scarcely abated and both her knees were replaced by artificial joints at the age of 61 and 63 years. She was referred to our hospital because of the poor control of the arthritis. At the time of referral, she had 10 painful and 15 swollen joints and her serum C-reactive protein (CRP) was 4.4 mg/dl. She had been treated

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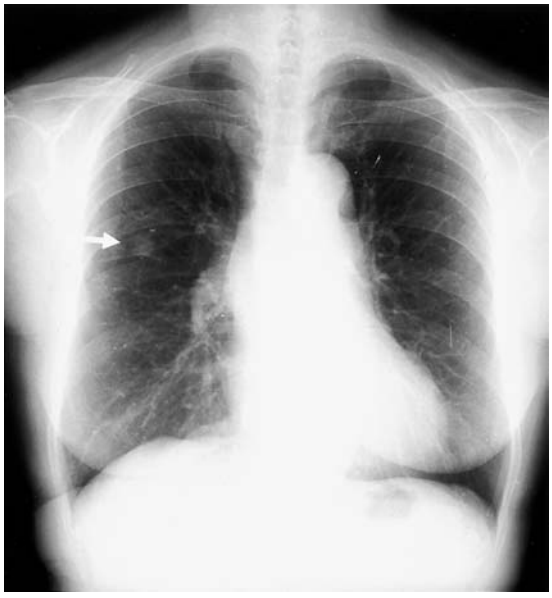

Fig. 1. Chest X-ray on November 6. A small nodular shadow (*arrow*) developed in the patient's right middle field at the third injection

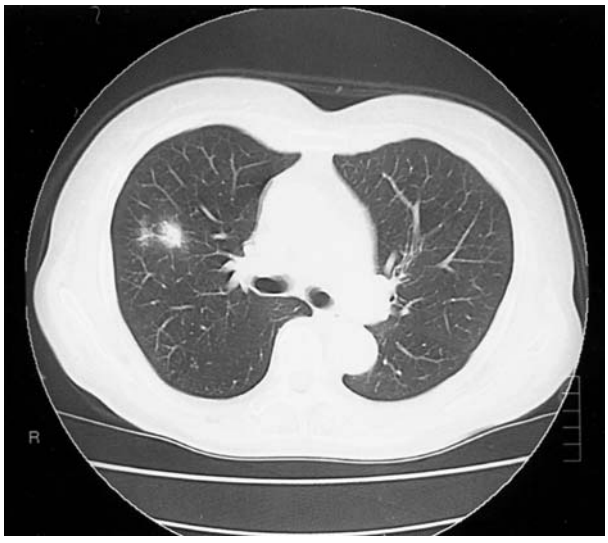

Fig. 2. Computed tomography taken on the same day shows small nodular shadow in the right upper lobe

with sulfasalazine 1000 mg/day and gold sodium thiomalate 25 mg every other week as well as prednisolone 5 mg/day. Gold sodium thiomalate was replaced by methotrexate 8 mg/week without any beneficial effects. Methotrexate 8 mg/week is the maximal amount allowed in Japan. On September 25, 2003, her serum CRP became 5.2 mg/dl and the numbers of painful and swollen joints were 13 and 20, respectively. Serum levels of IgG and RAPA were 1557 mg/dl and 1:320, respectively. Because her chest X-ray did not show any abnormal shadow including old or active tuberculous changes, the patient was placed on infliximab in addition to methotrexate 8 mg/day and sulfasalazine. Her serum CRP became 1.2 mg/dl in 2 weeks and ACR 20 was achieved in 4 weeks. At 6 weeks, however, soon after the third infusion, a small nodular shadow appeared suddenly in her right upper lobe and the computed tomography (CT) scan taken on the same day confirmed such a lesion (Figs. 1 and 2). She was immediately referred to a pneumologist at this time. The nodular lesion increased its size to a large extent within a week (Fig. 3) and transbronchial lavage fluid was obtained immediately. The polymerase chain reaction was positive for MAC and the bacterial culture confirmed the diagnosis of nontuberculous mycobacteriosis of MAC. Although she was asymptomatic, infliximab was immediately withdrawn and she was started on methotrexate 8 mg/week and bucillamine 200 mg/day. Because the addition of sulfasalazine to methotrexate had not been so effective, bucillamine was chosen this time as an adjunctive therapy of methotrexate. However, her arthritic symptoms aggravated rapidly thereafter.

On November 26, she was prescribed, for treatment of MAC, clarithromycin 600 mg/day, with a favorable outcome (Fig. 4). Although an abnormal shadow due to MAC infection almost disappeared on her plain chest X-ray by January 6, 2004, the residual shadow was still apparent on the CT scan examined on January 13, 2004.

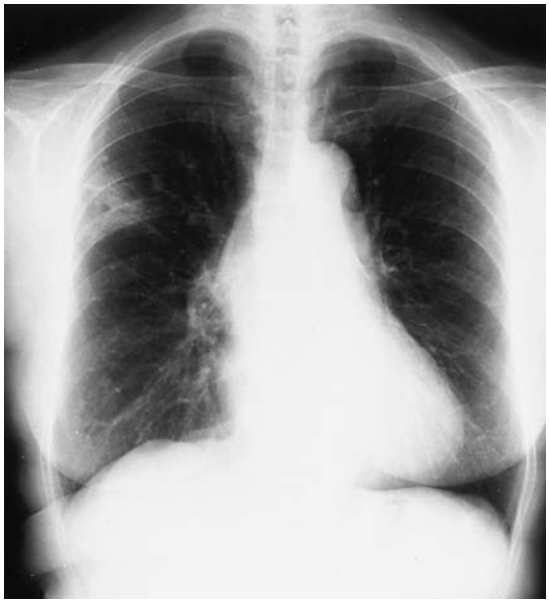

Fig. 3. Chest X-ray at 1 week after the third injection. The nodular shadow rapidly increased in size

During the treatment of MAC infection, a new massive abnormal shadow suddenly developed in her right lower lung field on January 6 (Fig. 4). Faropenem sodium 600 mg/day was started immediately and the shadow became barely discernible within 4 weeks. Although the offending microorganism was not identified, it was considered to be caused by bacteria.

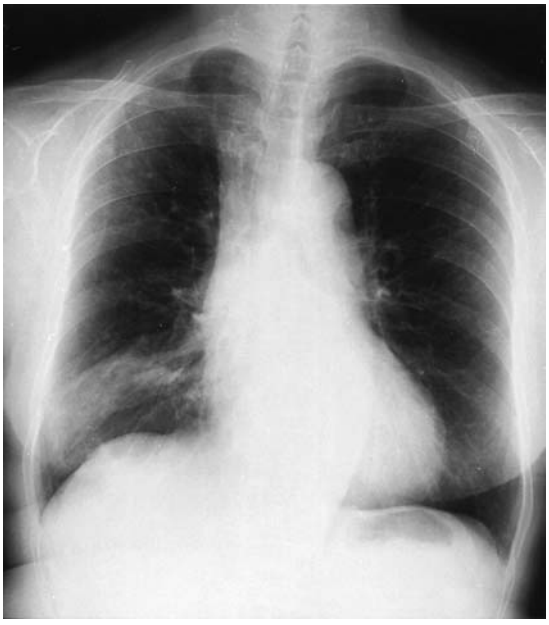

Fig. 4. Chest X-ray on January 6. Although an abnormal shadow due to *Mycobacterium avium* complex (MAC) infection in the right middle field almost disappeared, a massive new abnormal shadow suddenly developed in the right lower lung field. Antibiotic agent treatment was started and the shadow became barely discernible after 4 weeks

Discussion

Infliximab was approved on July 17, 2003 by the Japanese government for the treatment of RA, contingent upon registration and complete follow-up of all the patients being treated by this biological agent. A major concern for the use of infliximab is a prospective increase of the incidence of infection, in particular, tuberculosis.[2] The prevalence of tuberculosis in the general population of the United States was 5.8 per 100000 persons in the year 2000. In contrast, its prevalence in Japan was 31.0 per 100000 persons and even higher in the elderly.

As anticipated, the incidence of tuberculosis in the United States increased enormously after the introduction of infliximab as one of the treatment regimens for RA. However, according to reports from European countries,[5,6] proper precautions have successfully decreased its incidence and Japan is now following the lessons.

Nontuberculous mycobacteria such as *M. avium* or *Mycobacterium intracellulare* are much less pathogenic, and these are clinically important only to the patients with chronic lung diseases or who are profoundly immunocompromised, such as those with acquired immunodeficiency syndrome (AIDS). In the latter case, even disseminated forms of nontuberculous mycobacteriosis were reported.[4]

In the present case, the patient did not have any history of chronic lung disease and her chest X-ray was normal when infliximab was started. Because infliximab-induced tuberculosis occurs most frequently around the third injection,[2] pulmonary tuberculosis was the likeliest probability for this patient. However, the polymerase chain reaction and culture of the bronchoalveolar lavage fluids confirmed the diagnosis of MAC infection. Aggravation of the lung shadow by MAC infection in such a short period of time is quite unusual, and the level of immunosuppression by infliximab could equal that of AIDS in this sense.

Bacterial pneumonia occurred 2 months after infliximab-withdrawal. The estimated half-life of infliximab is 8–9.5 days, and the serum concentration of infliximab appears to be sustained longer when the drug is administered in combination with methotrexate.[1] Eight weeks after the last infliximab infusion of 3 mg/kg with methotrexate, the serum concentration of infliximab is approximately 2 mg/l[1] and this is still within the effective and, therefore, dangerous range.

Tumor necrosis factor α is produced by activated macrophages and natural killer cells, and is an important immune modulator for controlling mycobacterial infection. It is now generally accepted that the reservoir for most human MAC infection is environmental, especially natural waters, and its development in the presence of immune deficiency seems to be mainly the result of a new infection with this ubiquitous microorganism rather than the reactivation of a previously acquired infection.[7]

We learned several lessons from the present case. First, usually indolent MAC infection could aggravate very quickly and meticulous follow-up is necessary during infliximab treatment. Secondly, the time of the third injection is an important window even in MAC infection, just like *M. tuberculosis*. Lastly, immunosuppression induced by infliximab could have lasted for a long time.

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