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CASE REPORT

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Development of interstitial pneumonia in a rheumatoid arthritis patient treated with infliximab, an anti-tumor necrosis factor α-neutralizing antibody

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Abstract Infliximab, an anti-tumor necrosis factor (TNF)-α antibody, was introduced to a 66-year-old woman with methotrexate (MTX)-resistant rheumatoid arthritis (RA). Although the TNF-blocking therapy was successful, she developed noninfectious interstitial pneumonia (IP) after a second infusion of infliximab. In most cases reported previously, infliximab-associated noninfectious IP occurred after a second or third infusion of infliximab, and this type of IP was more fatal in comparison with cases associated with MTX treatment alone. Keeping a sharp lookout on IP development during this period is crucial to the success of infliximab treatment. After MTX discontinuation and steroid pulse therapy, our patient made a dramatic recovery from IP.

Key words Infliximab · Interstitial pneumonia (IP) · Methotrexate (MTX) · Rheumatoid arthritis (RA) · Tumor necrosis factor (TNF)

Introduction

Tumor necrosis factor alpha (TNFα) plays a central role in initiating a cascade of cytokines and growth factors that make up numerous immune responses. There is evidence in many cases to show that an overproduction of TNFα causes serious chronic synovitis and joint destruction in rheumatoid arthritis (RA). Accumulated data from recent clinical trials have shown that TNF inhibitors have significant efficacy for the treatment of RA patients.[1–4] Although TNF-blocking therapy is recognized to be safe and well tolerated, several data that emerged following Food and Drug Administration (FDA) approval have alerted clinicians to increased severe adverse effects such as opportunistic infections.[5] Infliximab, a human/mouse chimeric monoclonal antibody against human TNFα, is most commonly used as the TNF inhibitor for RA therapy in combination with methotrexate (MTX), which is one of the disease-modifying antirheumatic drugs (DMARDs). Data from postmarketing surveillance (PMS) for infliximab in Japan (PMS report in Japanese by the Japan College of Rheumatology [JCR], http://www.ryumachi-jp.com) warned us of a high incidence of two types of pneumonia, namely, *Pneumocystis jiroveci* pneumonia (PCP) and noninfectious interstitial pneumonia (IP). These complications are sometimes fatal to RA patients; however, only a few reports on infliximab-associated IP have so far been published.[6–9]

In this study, we describe noninfectious IP occurring in an RA patient treated with infliximab. Based on clinical, radiological, and laboratory data, we diagnosed this case as MTX pneumonia. Through careful assessment of previous reports, we noticed that infliximab-associated noninfectious IP occurs especially after a second or third infusion of infliximab. Furthermore, it was frequently vicious, and its mortality was higher compared with that of IP in RA patients treated with only MTX. We also discuss a possible role of TNFα in the pathogenesis of infliximab-associated IP.

Case report

A 66-year-old woman, afflicted for 5 years with seropositive, anticyclic citrullinated peptide antibody-positive RA, undertook an operation in our hospital of tendon transfer for extensor tendon rupture in her left hand and of arthroplasty for a deformity of her left foot. She made favorable progress after the operation. During hospitalization, she started to receive infliximab therapy because her disease had been uncontrolled despite 8 mg/week MTX treatment

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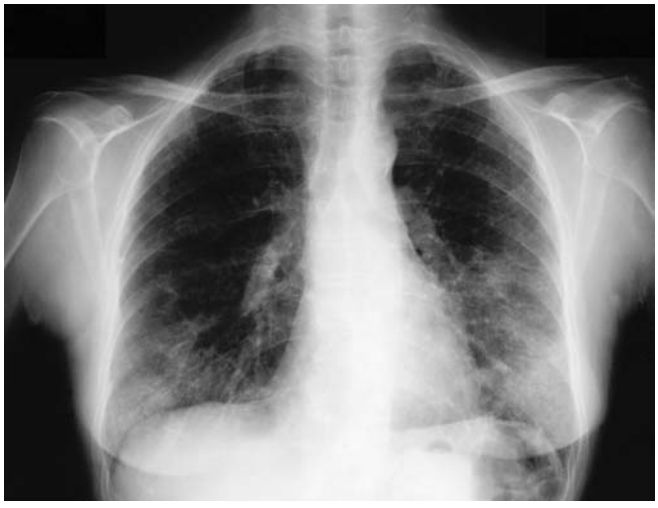

Fig. 1. Chest X-ray when the oxygen saturation suddenly dropped. Ground-glass opacity is shown at the bilateral lower lobes

and 5 mg/day prednisone for more than 2 years. Fifteen months prior to the initiation of infliximab, she had developed systemic eruption because of leflunomide, which is also used as the DMARD. A first infusion of infliximab (3 mg/kg) was given, and a second infusion of the same dosage was administered 2 weeks later. The infliximab therapy was successful; namely, the disease activity score for 28 joints (DAS28) decreased from 6.4 to 1.9 after the second infusion, and the values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 12 mm/h and below 0.05 mg/dl, respectively.

Thirty-seven days after the initial infusion of infliximab, the patient complained of a low-grade fever and headache. These symptoms were improved by an administration of epinastine hydrochloride, a histamine blocker. We thought of these symptoms as delayed-type infusion reactions. She complained of similar symptoms again 2 days later; however, she was able to walk around in a hospital ward. The oxygen saturation data on the nursing notes showed no changes during this period, and physical examinations were within the normal range. Forty days after the initiation of infliximab therapy, oxygen saturation suddenly dropped to 91% at rest. In spite of a low level of oxygenation, she did not complain of dyspnea or dry cough, and no crackles or wheeze were detected by auscultation. A chest radiograph showed ground-glass opacity at the bilateral lower lobes (Fig. 1). The serum levels of CRP and lactate dehydrogenase (LDH) were increased to 6.51 mg/dl and 336 U/ml, respectively. Her arterial blood gas measurement in room air yielded pH 7.454, PaO_2 59.9 mmHg, and $PaCO_2$ 35.4 mmHg. A high-resolution chest-computed tomographic (HRCT) scan demonstrated diffuse bilateral ground-glass opacity with reticular opacity and septal thickening (Fig. 2A). An analysis of bronchoalveolar lavage (BAL) fluids was as follows: total cells, 4×10^4/ml; alveolar macrophages, 61%; neutrophils, 18%; lymphocytes, 16%; eosinophils, 1%; CD3 positive cells, 95.7%; CD4 positive cells, 74.1%; CD8 positive cells, 18.7%; CD4/CD8 ratio, 4. Bacterial cultures of specimens from venous blood and sputum revealed negative results. Data from polymerase chain reactions (PCRs) for *Pneumocystis jiroveci*, *Mycobacterium tuberculosis*, and *Mycobacterium avium* were also negative. Cytomegalovirus (CMV) pp65 antigen (C7-HRP) was not detected by immunocytochemistry. β-D-Glucan, a component of fungus cell walls, was 30 pg/ml (normal value <20 pg/ml) in serum of the patient. Serum levels of IP markers, KL-6 (583 U/ml), SP-A (119 ng/ml), and SP-D (240 ng/ml) were elevated. The numbers of white blood cells and lymphocytes were 6310/μl and 1562/μl, respectively. The serum IgG count was 1260 mg/dl (the normal range, 600–2000 mg/dl).

Methotrexate was discontinued, and steroid pulse therapy was started (intravenous injection of methylprednisolone sodium succinate 1 g daily for 3 days), followed by 25 mg/day oral administration of prednisolone. The low oxygenation and the elevation of serum CRP and LDH levels were both improved after 3 days from the onset of IP. HRCT findings were also improved (Fig. 2B). These observations with our case met the criteria of MTX pneumonia.[10] Furthermore, the BAL analysis showed an increased CD4/CD8 ratio, a finding characteristic of MTX pneumonia. Although the serum level of β-D-glucan was weakly positive in our patient reported here, the data from PCR for *Pneumocystis jiroveci* were negative, and she responded to steroid pulse therapy without the use of trimethoprim-sulfamethoxazole. A risk of reactivation of lymphotropic herpesviruses, especially CMV, has been found to induce severe viral pneumonia in patients under immunosuppressive conditions, such as organ transplantation and human immunodeficiency virus infection.[11] Although infliximab therapy is also considered as a model of immunosuppression, the immune condition of our patient was maintained within the normal range, both at cellular and humoral levels. Data from immunocytochemistry for CMV were negative when she developed IP. Torre-Cisneros et al. also reported that infliximab therapy does not activate a replication of lymphotropic herpesviruses in patients with refractory RA.[11] Besides, it is unlikely that this case is RA-associated IP, because her RA has been well controlled throughout infliximab therapy. Taking these data into consideration, we reached the final diagnosis of noninfectious IP, namely, MTX pneumonia.

After the improvement of clinical symptoms, radiographic findings, and laboratory data, the oral administration of prednisolone was tapered off by 5 mg every week and finally reduced to 10 mg/day. The patient was discharged 20 days after the onset of IP.

Discussion

Recently, a high incidence of noninfectious IP has been noticed during infliximab therapy for RA. The data of PMS for infliximab in Japan showed that of 4000 RA patients treated with infliximab, there were 19 cases of noninfectious IP (http://www.ryumachi-jp.com). Furthermore, IP associated with infliximab therapy is also relatively common in

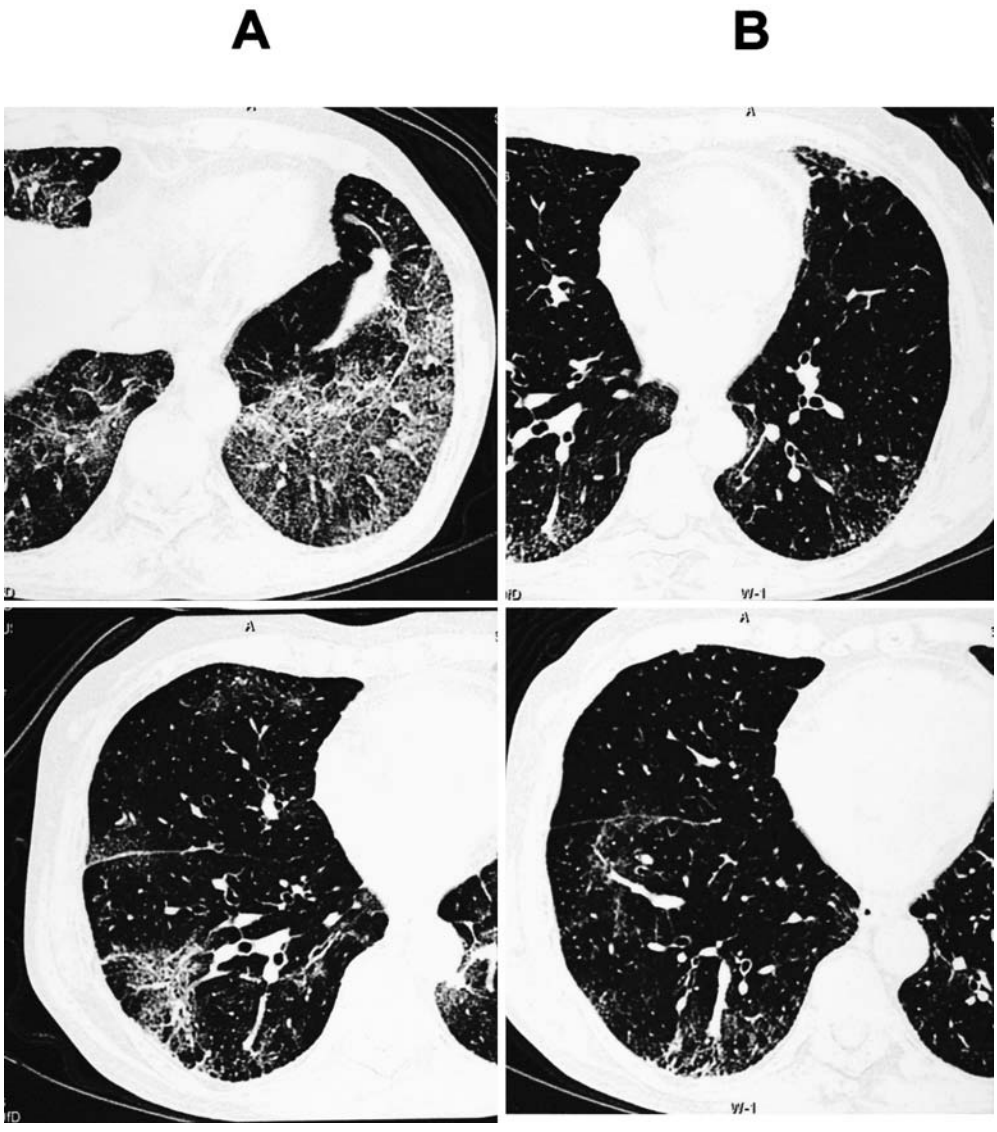

Fig. 2. **A** High-resolution computed tomography scan taken on the day the oxygen saturation suddenly dropped. Diffuse bilateral ground-glass opacity with reticular opacity and septal thickening are seen. **B** After the treatment for methotrexate pneumonia, these patterns disappeared. Preexistent rheumatoid interstitial changes remained in dorsal lesions

Western countries. In Japan, infliximab therapy for RA is carried out only in combination with MTX. Before the initiation of infliximab therapy, most RA patients had already received MTX treatment, and it is well known that MTX-treated RA patients often develop noninfectious IP, i.e., MTX pneumonia. Based on the English-language literature since 1966, Zisman et al. showed that MTX pneumonia had occurred in 0.5%–7.25% of RA patients receiving low-dose MTX, and collectively, there had been 108 events reported among 3677 patients (3%).[10] However, they mentioned that these figures possibly overestimate the true incidence because of reporting bias, and their informal survey on 1000 RA patients suggested that MTX pneumonia occurs in less than 1%. The true incidence of MTX pneumonia may remain uncertain. Whether the introduction of infliximab may influence the incidence of MTX pneumonia in RA patients also remains an unanswered question. Methotrexate pneumonia is reported to occur with a high incidence, especially within the first 32 weeks of MTX treatment.[12] Our patient had received the single MTX treatment for 30 months, but she had no symptoms of IP for this period. Immediately after the second infusion of infliximab, however, she developed noninfectious IP. It is possible that the introduction of infliximab therapy might trigger the development of noninfectious IP in RA patients who have already received MTX treatment. Besides MTX, the start of infliximab therapy has been reported to induce noninfectious IP in patients treated with leflunomide and azathiopurine.[6,9] This is also indicative of the collaborative role of infliximab in the occurrence of drug-induced IP. There is further evidence to suggest that the TNFα-blocking agents may contribute to the induction of drug-induced IP. Etanercept, a type-II TNF receptor/immunoglobulin hybrid protein, is also used as a blocker of TNFα activities. Like infliximab, etanercept therapy is also found to frequently induce noninfectious IP in RA patients,[5] and many of these patients have received DMARDs. Cannon et al. reported that the incidences of IP associated with infliximab and etanercept were 33.42 and 24.8 per 100000 patient years of drug exposure, respectively.[5] Kuroki et al., using a TNFα-deficient mouse model,

Table 1. Summary of eight cases of infliximab-associated interstitial pneumonia reported from Western countries

Case	Age (years)	Sex	No. of infliximab infusions	Combination	Outcome	First author[Ref.]
1	84	F	2	Leflunomid	Home oxygen therapy	Chatterjee[6]
2	72	F	3	MTX	Fatal	Courtney[7]
3	64	F	3	MTX, cyclosporine	Improved	Kramer[8]
4	63	F	3	MTX	Improved	Kramer[8]
5	80	F	3	MTX, sulfasalazine, HCQ	Improved	Kramer[8]
6	67	F	3	Azathiopurine	Fatal	Ostor[9]
7	60	F	2	Azathiopurine	Fatal	Ostor[9]
8	75	F	2	Azathiopurine	Fatal	Ostor[9]

All patients received infliximab therapy for rheumatoid arthritis. In all cases, the dose of infliximab was 3 mg/kg
MTX, methotrexate; HCQ, hydroxychloroquine

presented evidence to prove that endogenous TNFα plays a pivotal role in the suppression of bleomycin-induced pneumonia.[13] They suggested that TNFα induces apoptosis in inflammatory cells and thereby regulates a cascade of drug-induced inflammatory reactions in lung.[13] In consideration of these data, it may safely be supposed that the TNFα-blocking agents provide a favorable environment for the induction and/or progression of drug-induced IP through the modulation of the immune system.

As mentioned above, the occurrence of infliximab-associated IP is relatively high in Japan and Western countries; however, little attention has been given to its clinical features. By a careful survey of PMS data for infliximab in Japan (http://www.ryumachi-jp.com), we found two intriguing features of this type of IP. Table 1 summarizes eight cases of IP associated with infliximab therapy for RA. To the best of our knowledge, these comprise all cases previously reported in Western countries.[6–8] The first feature is that its onset is more aggressive and its mortality higher compared with IP occurring in RA patients treated with MTX alone. The PMS report in Japan showed that of 4000 RA patients treated with infliximab, 19 cases developed noninfectious IP, and two died of it (http://www.ryumachi-jp.com). In Western countries, four cases out of eight were fatal (Table 1). Our patient reported here also showed the sudden onset of noninfectious IP and its rapid progression. Her oxygen saturation suddenly dropped, although she had not yet presented any typical symptoms of IP, such as dyspnea and dry cough. On the same day, a chest X-ray had already revealed typical ground-glass opacity at the bilateral lower lobes. In the case of IP associated with a single use of MTX, it is known to take more than several weeks from the presentation of clinical symptoms of IP to the development of typical findings on chest X-ray films.[10] The concomitant use of MTX with infliximab seems to make this complication more vicious. The second feature is that most cases of noninfectious IP occur particularly after the second or third infusion of infliximab. The PMS data in Japan indicated that the median interval from the start of infliximab treatment to the IP occurrence and the median number of infusions were 62.9 days (range 40–77 days) and 2.8 times (range 2–4 times), respectively (http://www.ryumachi-jp.com). The literature from Western countries also shows that all cases develop noninfectious IP after the second or third infusion of infliximab (Table 1). Our patient developed IP after the second infusion (40 days after the start of infliximab treatment). In consideration of these findings, rheumatologists should be on the lookout for IP occurrence, especially after the second and third infusions of infliximab. Since the mortality of infliximab-associated IP is high, proper monitoring and early diagnosis are critical for a satisfactory prognosis of RA patients. Besides these clinical features, we noticed that RA patients of relatively advanced ages often suffer from noninfectious IP associated with infliximab therapy (Table 1). A similar tendency is shown by the PMS data in Japan (http://www.ryumachi-jp.com). Therefore, the introduction of infliximab into aged individuals should be done with special caution.

Alarcon et al. presented the following risk factors of MTX pneumonia: older age, diabetes, rheumatoid pleuropulmonary involvement, hypoalbuminemia, and a previous use of DMARDs.[12] In particular, the last two have larger attributions to the development of MTX pneumonia. Our case had all of these factors except diabetes. We have learned by experience that most RA patients carry at least one of these risk factors. In this respect, RA patients belong to the risk group of MTX pneumonia. As mentioned above, the introduction of infliximab often triggers drug-induced IP such as MTX pneumonia in RA patients who have already been treated with DMARDs. Therefore, we should be alert to the possibility of the development of noninfectious IP when we introduce infliximab therapy to RA patients who have received MTX treatment.

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