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CASE REPORT

A Fatal Case of Relapsing Pneumonia Caused by *Legionella pneumophila* in a Patient with Rheumatoid Arthritis After Two Injections of Adalimumab

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Abstract: We present a rare fatal case of relapsing pneumonia caused by *Legionella pneumophila* in a patient with rheumatoid arthritis after only two injections of adalimumab. A 78-year-old Japanese woman with a 14-year history of rheumatoid arthritis was prescribed adalimumab because her disease activity remained high. However, 8 days after her second injection of adalimumab, she was admitted to our hospital and diagnosed with pneumonia caused by *L. pneumophila*. Following intravenous antibiotic therapy, she recovered completely from pneumonia and was discharged on day 10, but pneumonia relapsed, resulting in death 79 days after the first episode of pneumonia. *L. pneumophila* can lead to recurrence of pneumonia that can ultimately prove fatal, similar to the present case. A review of the pertinent literature is also presented.

Keywords: adalimumab, fatal infection, *Legionella pneumophila*, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is an obstinate, systemic inflammatory disease which has a negative impact on the quality of life.[1] Anti-tumor necrosis factor (TNF) therapy has proved to be beneficial to RA patients because it can suppress inflammation and joint damage;[2] therefore, the percentage of RA patients treated with ant-TNF agents is steadily increasing. Adalimumab (ADA), a fully human anti-TNF monoclonal antibody, exhibits excellent effectiveness in RA; however, its use has been reported to cause many adverse events in RA patients. TNF is an important cytokine involved in initiating a protective immune response; therefore, patients receiving this therapy may be at a high risk of infection.

Legionella pneumophila is a fastidious intracellular gram-negative bacillus that requires special microbiological culture media. Difficulty in isolation of this organism from cultures leads to its detection. The incubation period of *L. pneumophila* pneumonia is considered to be 2–10 days. Recently, however, it seems that the risk of *L. pneumophila* pneumonia may be increasing in RA patients receiving TNF antagonist therapy.[3]

We report a rare case of pneumonia caused by *L. pneumophila* in an RA patient after only two ADA injections. The patient had initially recovered from the infection but later died because of relapse.

This report suggests a possible association between the use of ADA and the incidence of pneumonia, which is a severe and often fatal infection.

Case Presentation

A seventy-eight-year-old Japanese woman with seropositive RA, diagnosed in 1998 based on the ACR 1987 criteria, underwent sulphasalazine (SASP) therapy before she visited our institute. In 2008 she was started on methotrexate (MTX) and low-dose prednisolone (PSL) therapies.

Despite administration of low-dose therapies of MTX (6 mg/week), SASP (500 mg/day), and PSL (2.5 mg/day), because of her age and history of drug intolerance, her RA disease activity remained high [tender joint count, 4/28, and swollen joint count, 11/28; patient global assessment score, 72 mm/100 mm; C-reactive protein (CRP), 2.55 mg/dL; erythrocyte sedimentation rate (ESR), 52 mm/hour; matrix metalloproteinase-3, 71.7 ng/mL; and disease activity score 28-ESR, 5.82].

The patient was elderly and had a long-term smoking habit. Furthermore, she had pulmonary emphysema and slight fibrosis in her bilateral lower lungs, and her sister had previously suffered from tuberculosis. However, the patient had no other lung diseases, including tuberculosis (negative result on the tuberculin test quanti-FERON), no medical history of any viral infection, was not a hepatitis B virus carrier, and showed normal serum KL-6 and beta-D-glucan levels (410 U/mL and <2.84 pg/mL, respectively). She had also not undergone any surgery. Therefore, we decided to include anti-TNF therapy along with her current therapy after giving isoniazid (INH) 300 mg/day for three months.

ADA at a dose of 40 mg was introduced in addition to MTX (6 mg/week), SASP (500 mg/day), PSL (2.5 mg/day), and folic acid (5 mg/week) in June 2011. She experienced excellent pain relief in her joints after her first subcutaneous ADA injection, with no immediate adverse effects; her second injection was therefore safely administered two weeks after her first injection.

Eight days after her second ADA injection, she had fever (38.6 °C), fatigue, and bloody sputum for two consecutive days; thereafter, she was admitted to our hospital. At that time, we first heard that she regularly visited a public bath and had continued to do so after ADA treatment.

On admission (day 0, 8 days after her second ADA injection), her body temperature was 38.6 °C and she was slightly tachycardic (96 beats/minute) with a blood pressure of 142/68 mmHg. Her heart sounds were normal, and she had neither chest pain nor visible rash. However, coarse crackles were audible in her right lower lung, and oxygen monitoring showed hypoxemia (SpO2, 92%). Her joints were not swollen, painful, or warm, so we did not consider this state as a flare of RA. On the other hand, laboratory data showed marked acute inflammation (CRP, 27.05 mg/dL; white blood cell count, 20,600/mm^3) and a positive urine *L. pneumophila* antigen test (Binax, Portland, OR, USA). However, her serum beta-D-glucan levels were normal (<3.30 pg/mL). In addition, her expectoration culture, collected two days later, was weakly positive for *Haemophilus influenzae* (BLNAR).

Chest X-ray showed a permeation shadow in her right lower lung, and chest computed tomography (CT) showed pleural thickening, light ground glass

opacities (GGOs) right under the pleura, and consolidation with an air bronchogram in the right S6, S9, and S10 segments without fibrotic change from her baseline lung (Fig. 1). Two blood cultures taken at day 0 revealed no sepsis.

The patient was clinically diagnosed with pneumonia caused by *L. pneumophila* affecting her originally fibrotic RA lungs.

She was then admitted and given intravenous pazufloxacin (PZFX) 1000 mg/day (after an initial administration of 2 g twice daily at days 0 and 1) for 10 consecutive days. She showed remarkable recovery after being injected with PZFX and was discharged on day 10. Of course, she was forbidden to visit any public bath.

After discharge from our hospital, we confirmed her seroconversion of *L. pneumophila* and complete healing of pneumonia on chest CT. MTX (6 mg/week) and PSL (5 mg/day) therapies were then restarted without ADA because of an increase in her RA disease activity at day 20. However, pneumonia relapsed at day 55 along with loss of appetite, fatigue, and coughing. Laboratory data showed acute inflammation (CRP, 13.09 mg/dL; white blood cell count, 10,500/mm^3), and her urine *L. pneumophila* antigen test (Binax) was again positive. In addition, both her serum KL-6 and beta-D-glucan levels were high (815 U/mL and 29.56 pg/mL, respectively) unlike before. Blood gas data showed severe hypoxemia (PO_2, 47.5 mmHg; PCO_2, 29.5 mmHg). Chest CT findings showed multifocal consolidation with GGO extending to the bilateral lower aggravated fibrotic lungs (Fig. 2A and B) unlike pneumocystis pneumonia (PCP), which mostly showed diffuse GGO of the bilateral lungs. Furthermore, neither DNA of *Pneumocystis jiroveci* from bronchoalveolar lavage fluid (BALF) nor serum *Cryptococcus* and *Aspergillus* antigens were positive. We could not detect any bacteria from her BALF culture. On the other hand, serum *Candida* antigen and culture of *Candida albicans* were positive. On the basis of these findings, we diagnosed a relapse of *L. pneumophila* pneumonia with deep mycosis (eg, *Candida* infection) and interstitial pneumonia (IP). The patient's lungs were previously affected by RA, but not PCP. Unfortunately, although we tried every possible treatment, the patient eventually died of aggravated IP on day 79 (KL-6, 5030 U/mL; beta-D-glucan, 8.05 pg/mL at day 72).

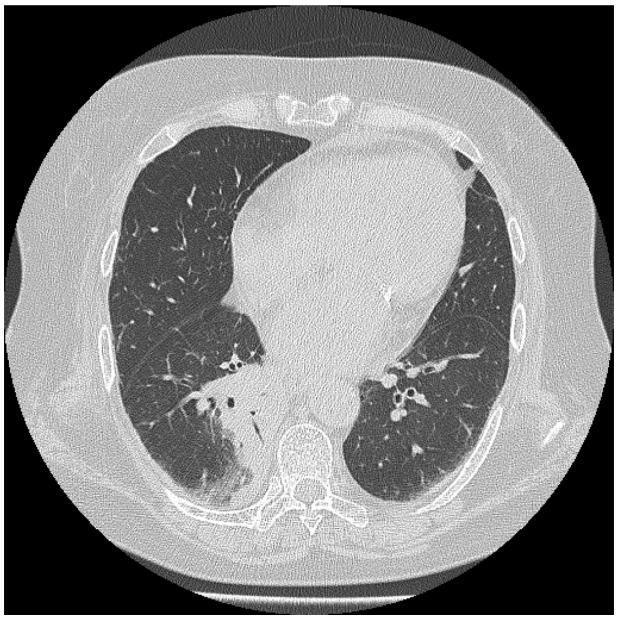

Figure 1. Day 0. Computed tomography of the chest. Air bronchogram showing consolidation and ground glass opacity (GGO) extending to the right S6, S9, and S10 segments of the lungs.

Discussion

ADA, a fully human anti-TNF monoclonal antibody, has been used in Japan since June 2008 for the treatment of RA and is administered at 40 mg once every 2 weeks or at 80 mg for cases of high disease activity which do not respond to 40 mg use. It is known to be very effective in decreasing inflammation, such as that in RA. However, it is also known that anti-TNF therapy may be a risk factor for a number of infections; in particular, ADA treatment is considered a risk factor for reactivation of latent tuberculosis.[4–6]

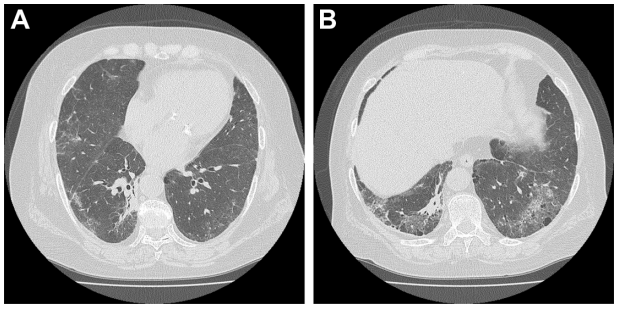

Figure 2. Day 55. (**A**) Computed tomography of the chest at the time of relapse. Same slice as shown in Figure 1. Consolidation appeared in the right S6 and S9 segments and GGO appeared in multiple affected segments. (**B**) Computed tomography of the chest. Lower slice of (**A**). Multifocal consolidation with GGO extending to both of the lower fibrotic lungs.

Anti-TNF agents including ADA are said to be risk factors for bacterial pneumonia.[7,8] In addition, RA disease severity in itself is known to be one of the strongest risk predictors of infection.[9] As mentioned above, patients treated with anti-TNF agents are generally believed to be at an increased risk of bacterial infections.[10] Conversely, another study found that the severity of serious infections was not increased in anti-TNF-treated patients compared with a disease-modifying antirheumatic drugs (DMARD)-treated cohort.[11] Considering the risks associated with the use of anti-TNF agents, we restrict their administration and occasionally exclude immunocompromised patients with co-morbidities, such as those with diabetes mellitus, heart disease, viral hepatitis, and lung disease, or elderly patients from these treatments. Our patient was a 78-year-old woman with RA, who had a long-term smoking habit and had bilateral fibrotic lungs; these were possibly be risk factors for *Legionella* infection in patient as well as other infections such as PCP.

Legionellosis presents as two types of diseases; one is Legionnaires' disease, the more severe form, and the other is Pontiac fever, the milder form, which shows minimal heat and muscular pain, and has a rapid complete recovery.[12] Legionellos is also often presents as pneumonia and is mainly caused by the *L. pneumophila* serogroup 1 (SG1), a ubiquitous, opportunistic, gram-negative intracellular pathogen.[3]

TNF induces differentiation of monocytes into macrophages, which are essential in the induction of granuloma, and is important for maintaining the integrity of granuloma.[13] In addition, TNF plays an important role in host resistance against infectious agents, especially those multiplying intracellularly.[14] Thus, treatment with TNF antagonists is associated with an increased risk of infection, particularly infections caused by intracellular microorganisms such as *L. pneumophila*. In contrast, in Japanese post-marketing surveillance with TNF antagonists for RA, both fatal and surviving cases of *Legionella* pneumonia were reported to be very rare (infliximab, 1 and 0 in 7522 cases; etanercept, 0 and 0 in 13894 cases; ADA, 3 and 2 in 3084 cases, respectively).

Legionella pneumonia tends to be a severe and fatal form of community-acquired pneumonia very similar to *Pneumococcal* pneumonia. Nowadays, however, *L. pneumophila* pneumonia is considered to be a curable disease if appropriate antimicrobial therapy is administered at an early stage.

Usually, legionellosis is considered to be caused by inhalation of aerosols containing *L. pneumophila* and bathing in hot springs and circulation-type bathtubs available in public bathing facilities that are infected with *L. pneumophila*. But further investigations showed that her case was an isolated infection and was not part of a mass outbreak, suggesting that *L. pneumophila* infection in our patient was more likely caused after ADA treatment.

Nowadays in Japan, both the introduction of the urinary *Legionella* antigen test and improvements in the 'Infectious Disease Law' have led to an increase in the number of reports of *L. pneumophila*. Accordingly, milder cases of *Legionella* pneumonia have been reported. In the past, many cases of legionellosis might have been overlooked, including milder cases of *Legionella* pneumonia or minor Pontiac fever.

Winthrop-University Hospital criteria are said to be very useful for discriminating fairly well between *L. pneumophila* pneumonia and bacteremic pneumococcal pneumonia, at the time of hospitalization, for community-acquired pneumonia.[15]

Chest CT findings of *Legionella* pneumonia are said to be bilateral or unilateral with single and multifocal consolidation and GGO,[16] while those of mild *Legionella* pneumonia are said to be bilateral, with multiple affected segments and peripheral lung consolidation with GGO.[17] *L. pneumophila* includes 16 types of serogroups, and only SG1 can be detected by the urine *L. pneumophila* antigen test (Binax). The percentage of *L. pneumophila* SG1 may be high in Japan, as it is in a lot of countries, but we are unable to detect all *L. pneumophila* by this antigen test. Urine *L. pneumophila* antigen test may be positive for a few weeks after treatment of *Legionella* pneumonia as seen in this case; however, we diagnosed this case as a recurrence of *L. pneumophila* pneumonia with deep mycosis (eg, *Candida* infection) and IP on the basis of data from serum, culture, BALF analysis, and CT scans, which showed multifocal consolidation with GGO extending to the lower parts of her fibrotic lungs bilaterally at recurrence (Fig. 2A and B).

The risk of *L. pneumophila* pneumonia is reported to increase in patients receiving TNF antagonists, with a relative risk of 16.5–21, compared with that

in the overall population in France.[3] The use of corticosteroids and MTX might also have played a role in the emergence of this infection, but the patient had been treated with these medications for a long time. Conversely, ADA had been introduced just 22 days before.

Legionella tends to colonize the respiratory tract of immune-compromised patients and causes severe health problems once their immune system is further affected.[18] In our case, because the patient did not visit any public bath after discharge from our hospital, it is possible that although she initially recovered from *L. pneumophila* pneumonia and was discharged from the hospital, the organism was still present in her respiratory tract, causing pneumonia to recur and ultimately prove fatal. In such cases, it is important to prevent tuberculosis by INH, PCP by trimethoprim—sulfamethoxazole, and pneumococcal pneumonia by vaccination, in all immune-compromised RA patients before the first treatment with anti-TNF agents; additionally, it is important to carefully monitor RA patients who have been given anti-TNF agents in the past, not only in the early phase when they are first given TNF inhibitors, but also afterwards, especially after they have recovered from infections such as that described in our case.

Conclusions

To our knowledge, this is the first reported fatality triggered by relapsing pneumonia caused by *L. pneumophila* with deep mycosis and IP in an RA patient treated with ADA. The patient eventually died of aggravated IP following a relapse of pneumonia caused by *L. pneumophila*. To avoid exacerbation of a patient's illness and to prevent fatality due to severe infection, it is important for us to be aware of the fact that the use of TNF-inhibitors can lead to infections such as that described here. Because a delay in controlling some infections worsens the patient's RA disease activity during that period, it is important to control any infection rapidly and completely. Recently, RA treatment has been rapidly and aggressively adopted based on the concept of "treat-to-target"; therefore, we need both to accumulate evidence from case studies to promote safe and effective treatments for RA, and to avoid therapeutic errors, which will result in the maximum possible survival of patients.

Consent

Written informed consent was obtained from the patient's family for publication of this case report and any accompanying data.

Author Contributions

MH analyzed and interpreted the patient data, and was a major contributor in writing this manuscript. All of the other authors read and approved the final manuscript.

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Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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