Clinical Case Report

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Multidrug-resistance *Acinetobacter baumannii* pneumonia in a rheumatoid arthritis patient receiving tumor necrosis factor inhibitor

A case report

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Abstract

Introduction: Multidrug-resistant *Acinetobacter baumannii* (MDRAB) pneumonia with severe sepsis in a patient with rheumatoid arthritis (RA), who is predisposed after treatment with tumor necrosis factor inhibitor (TNFI), is a rare severe infection and can be successfully treated with prompt antibiotics.

Case presentation: A 75-year-old woman was diagnosed with RA >30 years previously. After inadequate treatment responses to conventional disease-modifying antirheumatic drugs (DMARDs), she developed progressive RA, including swollen joints in both hands, and had a high disease activity score of 4.96 when presenting at our rheumatology clinic. She had started taking the TNFI, golimumab (50 mg/month), 3 years before and developed a productive cough 4 weeks before this admission. One week after admission, she developed fever, dyspnea, hypoxemia, tachycardia, and increased serum C-reactive protein level.

Diagnosis: Chest plain film (CxR) and computed tomography of the chest showed hospital-acquired pneumonia; microbial examination of the sputum showed the presence of MDRAB.

Therapeutics: She was prescribed a full course of antibiotics with cefoperazone sulbactam.

Outcomes: CxR showed complete remission of pneumonia.

Conclusion: Biological DMARDs, such as TNFI, act as a double-edged sword: these drugs are used to treat autoimmune diseases, but they increase the risk of infection. The trend toward antibiotic resistance and persistent environmental survival of MDRAB is an emerging problem in countries with high rates of antibiotic abuse. TNFI may affect intestinal immunity by inducing dysbiosis, which affects T helper 17–mediated mucosal immunity and can contribute to *A baumannii* colonization and the development of MDRAB in frequently hospitalized patients.

Abbreviations: *AB* = *Acinetobacter baumannii*, bDMARD = biological disease-modifying antirheumatic drug, CRP = C-reactive protein, CxR = chest plain film, DAC28 = Disease Activity Score 28, DMARD = disease-modifying antirheumatic drug, IBD = inflammatory bowel disease, IL = interleukin, MDRAB = multidrug-resistance *Acinetobacter baumannii*, MTX = methotrexate, RA = rheumatoid arthritis, Th17 = T helper 17, TNFI = tumor necrosis factor inhibitor.

Keywords: disease-modifying antirheumatic drugs, multidrug-resistance *Acinetobacter baumannii*, rheumatoid arthritis, tumor necrosis factor inhibitor

1. Introduction

Rheumatoid arthritis (RA), a chronic inflammatory disease, is attributed to the actions of inflammatory cells and cytokines.[1,2] Patients with RA are often treated with biological disease-modifying antirheumatic drugs (bDMARDs), such as a tumor necrosis factor inhibitor (TNFI), which can decrease the risk of complications such as bone erosion and help to sustain joint function.[1] Nonetheless, bDMARDs may increase the risk of acquiring an infectious disease,[3] and TNFI slightly increases the risk of infectious diseases in patients with inflammatory bowel disease (IBD).[4] Therefore, TNFIs can act as a double-edged sword by successfully treating autoimmune diseases but at the same time increasing the risk of infection.[3]

Acinetobacter baumannii (*AB*), a gram-negative bacterium, is commonly present in the environment and can colonize the human intestinal tract[5] and cause extensive infections, such as pneumonia, because of the patient's immunosuppressed condition.[5] Lately, multidrug-resistant *AB* (MDRAB) has become an emerging problem in several hospitals and health settings because of its tendency to accumulate in hospital machinery, in which it

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can become resistance to antibiotics and difficulty in its eradication.[5] Here, we report an unusual case of MDRAB-induced pneumonia in a patient with RA receiving a TNFI.

2. Case presentation

A 75-year-old woman with RA had been receiving conventional treatment with DMARDs, including 7 years of methotrexate (MTX), 10 years of hydroxychloroquine and prednisolone before this admission. Three years before this admission, she started taking the TNFI, golimumab (50 mg/month) in addition to MTX, hydroxychloroquine and prednisolone, because of high disease activity, including swelling and deformity of the proximal interphalangeal joints, metacarpophalangeal joints, and wrist joints on both sides, and a Disease Activity Score 28 (DAC28) of 4.96. Four weeks before this admission, she had developed a productive cough without weight loss, afternoon fever, and altered bowel habits. She visited our emergency room because of hematochezia, dizziness, nausea, vomiting, and abdominal pain. Blood sampling revealed leukopenia (white blood count, 2200/μL; absolute neutrophil count, 770/μL) and thrombocytopenia (platelet count, 29,000/μL). A chest plain film (CxR) of the chest revealed infiltration into the left lower lung and peribronchial wall thickening in the right lung. Of note, MTX had been discontinued because of bone marrow suppression, and golimumab was stopped for infection of both lungs. She received piperacillin-tazobactam for complicated pneumonia immediately after admission.

One week after admission, the patient developed fever, dyspnea, hypoxemia, tachycardia, and increased serum C-reactive protein (CRP) level. CxR showed increased interstitial and alveolar opacity in both lungs, whereas chest contrast computed tomography revealed sparse progressive consolidation in both lung fields (Fig. 1). We administered meropenem trihydrate because of suspected hospital-acquired pneumonia complicated by severe sepsis. Because of *AB-A calcoaceticus* complex infection, which is resistant to multiple antibiotics, including penicillin, cephalosporins, aminoglycosides, and fluoroquinolones (i.e., MDRAB), was detected in microbial examination of the sputum, the patient received a full course of cefoperazone-sulbactam. A post-treatment CxR showed resolution of consolidation, and her fever had subsided. Finally, she was discharged 3 weeks after admission. This patient experienced recurrent high disease activity of RA after discharge, including swelling and tender joints, a high DAC28, and high serum CRP and erythrocyte sedimentation rate. Infectious diseases had been excluded at the follow-up at our rheumatology clinic. Because of the previous medical history of serious adverse effects such as stomatitis and bone marrow suppression, MTX is not suitable and has not been prescribed for her. Based on treatment guideline for RA, TNFI could be resumed after total recovery from infectious diseases. Thus, the patient received half dose of golimumab to prevent reinfection of MDRAB. We have monitored and collected this patient's sputum and fecal, which did not show *AB* colonization.

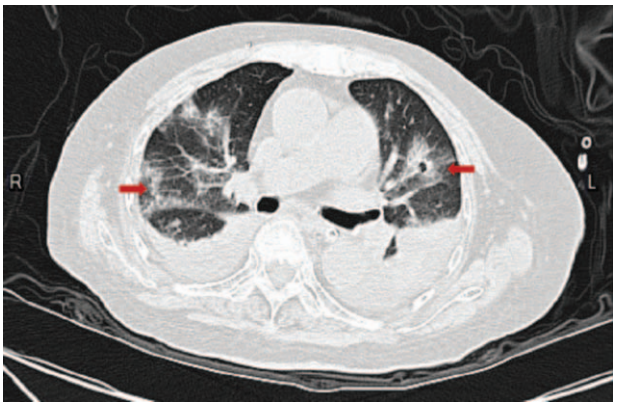

Figure 1. A high-resolution chest computed tomography scan revealed infiltration and air bronchograms in both lungs (arrow heads) and moderate pleural effusion with atelectasis of lower lobes of both lungs.

3. Discussion

RA is a chronic inflammatory disease that is characterized by joint inflammation and the devastation of cartilage and bone in multiple joints.[1,6] Inflammatory cells and cytokines, such as neutrophils, TNF-α, and interleukin-17, contribute to the synovitis and structural damage to joints.[2,7] An increased risk of infection has been reported in patients with RA.[8]

TNF-α is a 26 kDa homotrimeric transmembrane protein that appears on the surface of fibroblasts, macrophages, T lymphocytes, natural killer cells, and smooth muscle cells. TNF-α is involved in the pathogenesis of autoimmune diseases, such as RA, ankylosing spondylitis, and IBD.[3] The treatment of patients with RA aims at reducing the disease activity and preventing progressive joint damage.[1] bDMARDs can reduce disease activity and delay intra-articular structural damage, especially in patients with an inadequate response to conventional DMARDs.[6] Golimumab, a human anti-TNF-α immunoglobulin G1 monoclonal antibody, is widely prescribed for patients with RA.

TNFI therapy has beneficial effects on the immune system in the treatment of autoimmune diseases; however, TNF-α plays a major role in controlling infections by regulating the immune system.[8] Specifically, TNF-α released from macrophages plays an important role in the maintenance and formation of granulation tissue and in preventing invasion of intracellular organisms.[8] TNFIs affect cellular and humoral immunity, and may contribute to greater susceptibility to infection, such as invasive pneumococcal disease, granulomatous infection, new tuberculosis infection, chronic hepatitis B, varicella-zoster virus, reactivation of latent tuberculosis, and new onset of opportunistic infection by *Candida* or *Aspergillus*.[3] Old age, the presence of underlying disease in immunocompromised patients, or the combination of immunomodulatory therapy and biological therapy can impair innate immune function and increase the risk of opportunistic infections.[3] Before and during biological treatment, patients should be monitored regularly by assessment of complete blood count, biochemistry, C-reactive protein, hepatitis B, hepatitis C, tuberculosis, and CxR. Adherence to the hospital's standard infection-prevention measures can reduce the risk of acquiring hospital-acquired infections.[5]

AB is commonly found in the environment.[5]*AB* bacteremia has become a significant public health problem and accounts for one of the most common nosocomial pathogens in healthcare centers because of accidental spreading by health caregivers or environmental contamination by patients.[9]*AB* can colonize the human intestinal tract and cause extensive infection, including pneumonia, peritonitis, urinary tract infection, and bacteremia.[5] Because of its tendency to develop antibiotic resistance, persistent environmental survival, and difficult eradication, MDRAB is a significant nosocomial pathogen, that often requires treatment

with carbapenems.[5] MDRAB infection or colonization also increases the mortality rate.[5] Risk factors for MDRAB include cardiovascular disease, chronic obstructive lung disease, neurological impairment, and diabetes mellitus, and the risk is elevated in surgical patient groups receiving mechanical ventilation, previous antibiotic therapy, or with comorbidities, in particular multiple *Acinetobacter* isolates and neurological impairment.[5] A recent study reported that 88% of patients with MDRAB were infected during hospitalization and that the rest of the patients had recently visited a hospital before infection.[10] Frequent visits to the rheumatology clinic may have exposed our patient to MDRAB, which has become an emerging problem in hospitals, especially in countries with antibiotic abuse. Because of the tendency of *AB* to develop antibiotic resistance and difficult eradication, it is critical and very important to avoid *AB* colonization as much as possible. Clinicians and rheumatologists should emphasize the importance of adherence to the hospital's standard infection-prevention measures to all patients receiving TNFI and all immunosuppressants.

The chronic inflammation of RA results in pathogenic gut bacterial overgrowth or the lack of immunomodulatory commensal bacteria.[11] TNF-α agonists facilitate the regulation and eradication of intestinal pathogens and microbial-induced inflammation.[3] T helper 17 (Th17) cells in the gut mucosa help to regulate mucosal immunity and prevent *AB* colonization.[2] Thus, it is rational that TNFI may affect intestinal immunity by inducing dysbiosis, which affects Th17-mediated mucosal immunity and contributes to *AB* colonization and the development of MDRAB in this patient because she frequently visited the hospital and exposed to environmental *AB*.

In this case, it is reasonable that golimumab raised an additional impact on the development of MDRAB pneumonia. In the real-world practice, rheumatologists should not focus only on the therapeutic effects of bDMARDs but also be aware of possible adverse effects, such as serious infections, especially in countries with high rates of antibiotic abuse and drugs resistance. To our knowledge, this is the first case of MDRAB-induced pneumonia with severe sepsis in a patient with RA who was predisposed to infection because of TNFI treatment and was successfully treated with adequate antibiotics. We hypothesize that TNFI may affect intestinal immunity by inducing dysbiosis, which affects Th17-mediated mucosal immunity and contributes to *AB* colonization and the development of MDRAB in this patient. However, we still need more real-world data to prove the hypothesis. We have launched a prospective registry study to observe whether there is increased prevalence of *AB* colonization at gut in patients receiving TNFI or other biological agents.

This case shows that clinicians should be aware of the possibility of TNFI-related adverse effects, such as infectious disease, especially in patients exposed to a nosocomial infection environment and in countries with a high rate of antibiotic abuse.

Author contributions

All authors had contributed to the patient care and had access to the data and a role in writing this manuscript.

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