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CASE REPORT

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Nontuberculous Mycobacterium-associated immune reconstitution inflammatory syndrome in a non-HIV immunosuppressed patient

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Abstract

A 69-year-old woman with rheumatoid arthritis, using immunosuppressants, including etanercept—a tumour necrosis factor (TNF)-α antagonist—was referred to our hospital with fever and fatigue. Chest computed tomography revealed cavities in the left upper lobe. As *Mycobacterium intracellulare* infection was diagnosed, all immunosuppressants were discontinued, and treatment with anti-nontuberculous Mycobacterium drugs was initiated. However, her condition worsened paradoxically. We diagnosed immune reconstitution inflammatory syndrome (IRIS) resulting from the discontinuation of the TNF-α antagonist. Her condition improved with prednisolone treatment. IRIS is generally observed during HIV treatment, but a good understanding of immunosuppressant-related non-HIV IRIS is needed.

KEYWORDS
immune reconstitution inflammatory syndrome, nontuberculous Mycobacterium, paradoxical reactions, tumour necrosis factor-α antagonists

INTRODUCTION

In immune reconstitution inflammatory syndrome (IRIS), excessive inflammatory response occurs during recovery from immunosuppression. IRIS was originally reported in HIV-positive patients receiving antiretroviral therapy (ART) and well recognized primarily in the field of haematology. However, cases of non-HIV IRIS are less common. Recently, cases involving tuberculosis-associated non-HIV IRIS due to discontinuation of biologic drugs have been described.[1] However, reports are limited on non-tuberculous Mycobacterium (NTM)-associated IRIS among non-HIV patients.[2] Therefore, information regarding NTM-associated IRIS is scarce, and the condition might have been misdiagnosed as an uncontrollable infectious condition in the past. Here, we report a case of NTM-associated non-HIV IRIS.

CASE REPORT

A 69-year-old woman using etanercept, a tumour necrosis factor (TNF)-α antagonist (50 mg/week), methotrexate (4 mg/week) and methylprednisolone (2 mg/day) for rheumatoid arthritis (RA) was referred to our hospital on presenting with fever and fatigue. Chest radiography and computed tomography (CT) revealed cavities and pulmonary consolidations in the left upper lobe, without evidence of hypoxaemia (Figures 1 and 2A). Her white blood cell count was normal, lymphocyte count was 600/μl and C-reactive protein (CRP) level was 3.7 mg/dl She was positive for anti-*Mycobacterium avium* complex antibody (concentration 2.7 U/ml). She had been taking methotrexate and methylprednisolone for RA treatment for 12 years, and etanercept was prescribed concurrently in the recent 8 years. Since then, the types and doses of these therapeutic agents

had not been changed. She had a possible history of NTM infection because previous chest CT scans had showed nodular and granular shadows with bronchiectasis, and *Mycobacterium intracellulare* was detected in the sputum examined at another hospital 3 years ago. Her previous doctor discontinued etanercept 1 week before she presented to our hospital, suspecting infections because of her complains of fatigue and loss of appetite. Then, we discontinued methotrexate and methylprednisolone. *Mycobacterium intracellulare* infection was confirmed by polymerase chain reaction using two different sputum specimens. Clarithromycin, rifampicin and ethambutol were initiated for NTM infection on day 3 from admission. However, fatigue and slight fever persisted. Streptomycin was initiated on day 11 from admission as the anti-NTM treatment was possibly insufficient, although we did not perform drug susceptibility testing for any of these anti-NTM drugs. However, CRP levels continued to increase, eventually reaching 22.3 mg/dl on day 14 from admission (Figure 2). CT revealed exacerbation of the pulmonary consolidation

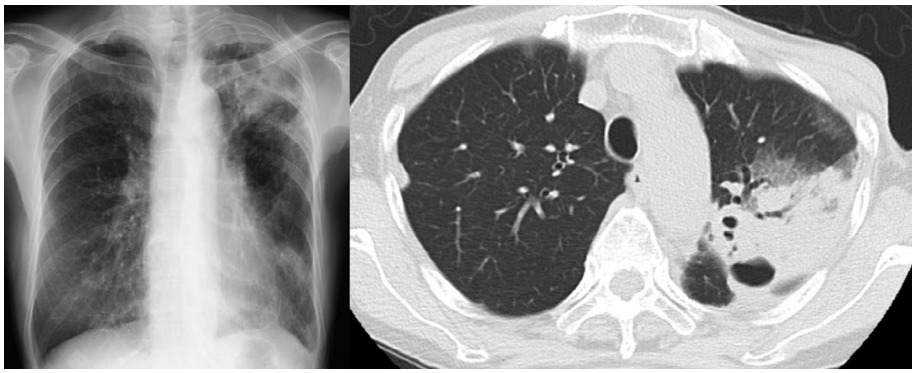

FIGURE 1 (A) Chest radiography and (B) computed tomography on admission showing cavities and consolidations in the left upper lobe

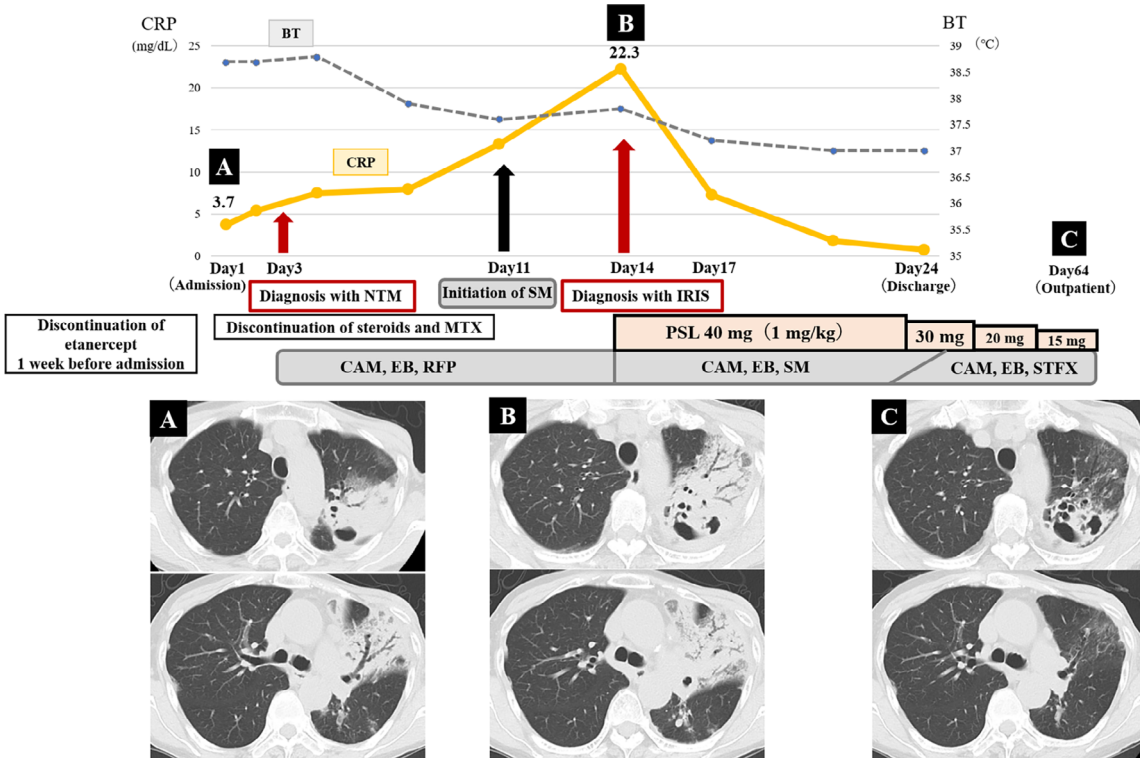

FIGURE 2 Timelines for diagnosis and treatment of IRIS. (A) CT on admission. Despite administration of anti-NTM drugs, CRP level continued to increase. (B) On day 14, CRP level increased to 22.3 mg/dl, and CT showed exacerbation of the pulmonary consolidation. We diagnosed NTM-associated IRIS and started prednisolone. Then, the patient's symptom of fatigue improved and CRP level decreased. (C) CT performed approximately 50 days after prednisolone initiation (during outpatient treatment), showing improvement in consolidation. BT, body temperature; CAM, clarithromycin; CRP, C-reactive protein; CT, computed tomography; EB, ethambutol; IRIS, immune reconstitution inflammatory syndrome; MTX, methotrexate; NTM, nontuberculous Mycobacterium; PSL, prednisolone; RFP, rifampicin; SM, streptomycin; STFX, sitafloxacin

(Figure 2B). We diagnosed NTM-associated IRIS. Prednisolone (40 mg: 1 mg/kg) was initiated, and rifampicin was discontinued as it lowers the level of prednisolone in the blood. The fever resolved next day, CRP levels decreased from 22.3 to 7.22 mg/dl on day 17 from admission and the pulmonary consolidation gradually improved. On day 24 from admission, the patient was discharged from the hospital, and she underwent outpatient treatment for NTM infection with clarithromycin, ethambutol and sitafloxacin instead of streptomycin due to a drug-related complication (dizziness). The prednisolone dose was tapered, and chest CT approximately 50 days after prednisolone initiation (day 64 from admission day) revealed that the consolidations had almost disappeared after treatment with 15 mg of prednisolone (Figure 2C). Two months after starting steroids, the prednisolone dose was reduced to 10 mg. Although swelling and tenderness in both shoulders and hand joints caused by RA were observed, the Disease Activity Score for RA indicated medium disease activity, and the subjective symptoms were the same as those when she was hospitalized. Treatment with other immunosuppressants was not re-commenced. Three months after initiating anti-NTM treatment, sputum continued to be positive for *M. intracellulare*. As the patient had cavities in the lungs and treatment for RA might be resumed, we had planned long-term NTM treatment. When the prednisolone dose was reduced to 5 mg, the symptoms for RA worsened, and salazosulfapyridine (500 mg) was added. Her treatment with the rheumatologist and the pulmonologist in the outpatient department is ongoing.

DISCUSSION

Here, we describe a case of NTM-associated IRIS from the discontinuation of a TNF-α antagonist. IRIS was originally reported in HIV patients receiving ART. During ART, the HIV load significantly decreases, and the number of CD4+ T cells begins to increase, causing overreaction against a pathogenic insult. In recent years, IRIS was reported even in non-HIV patients,[1] especially in solid organ transplant recipients and those who discontinue TNF-α antagonists or steroids. The mechanism of action is presumed to be a balance between proinflammatory responses, mainly regulated by macrophages and natural killer cells, and anti-inflammatory responses, regulated by Th2 cells and regulatory T cells[3,4]; however, certain conditions/drugs such as immunosuppressants including TNF-α antagonists cause disruption, and recovery from immunosuppression elicits stronger proinflammatory responses.[3]

Although the criteria for IRIS diagnosis in non-HIV patients are not established, potential criteria were proposed by a research group investigating non-HIV IRIS.[5] The pathology, which is the primary determinant of the presence of IRIS, is not worsening infection, but an inflammatory overreaction. In this case, determining the main reason of the patient's worsening condition was important because she showed widespread consolidation in the lungs and delayed treatment could have led to deterioration of the respiratory condition. However, the diagnosis of IRIS was difficult to determine because her condition deteriorated during the acute phase of NTM treatment. Takazono et al.[2] reported a patient with relapsing polychondritis treated with tacrolimus, which caused non-HIV IRIS associated with *M. intracellulare*. The patient was diagnosed with IRIS after 9 months of starting NTM treatment. In non-HIV IRIS, the median time to develop IRIS after the discontinuation of a TNF-α antagonist is reportedly 6.5 weeks (shortest, 4 days; longest, 24 weeks) for tuberculosis.[1] These differences may depend on the patient's immune status, pathogenic organism, the type of medication or lesions when IRIS occurs.[3,5] In the present case, although some clinical findings, such as markedly high fever (38.7°C), improved with NTM treatment, fever with temperature of 37.5–38°C persisted. Thereafter, pulmonary consolidation worsened on chest radiography, and CRP level continued to increase. Therefore, we considered the possibility of poor response to NTM treatment or combined infections to be high and struggled to diagnose IRIS. However, this patient showed rapid and remarkable response to steroids. Although determining the actual cause was difficult until response to steroids was confirmed, IRIS was highly likely in this case because NTM infection generally tends to show slow response and needs long-term treatment. Etanercept is a once-weekly drug with a half-life of about 4 days. In our case, IRIS could have occurred early in the course of TNF-α antagonist discontinuation and NTM treatment.

Steroids are used to treat and prevent IRIS from ART and are beneficial for non-HIV patients as well. For non-HIV IRIS patients who abruptly discontinue TNF-α antagonists, re-administration of TNF-α antagonists may be useful.[3,5] More information on the risk and frequency of IRIS needs to be accumulated to clarify not only the treatment but also the prevention of IRIS, such as whether TNF-α antagonists and other immunosuppressants should be continued or discontinued during treatment of infections.

There is a limitation to the approach used for this patient. The possibility that her symptoms were due to secondary organizing pneumonia (OP) associated with RA remains. However, we cannot distinguish between IRIS and OP at this time. Furthermore, her RA status was controlled despite discontinuation of immunosuppressants. Another research group is currently trying to clarify the manifestations of non-HIV IRIS and explore its biomarkers.[5] Extensive data are required for establishing a definitive diagnosis of IRIS.

In conclusion, the patient developed NTM-associated IRIS after discontinuation of a TNF-α antagonist. Clinicians should therefore be cognizant of the potential of IRIS developing not only in HIV-positive patients, but also in patients withdrawn from immunosuppressants. It is possible that cases of IRIS may have been misdiagnosed as intractable infectious diseases in the past. Presently, in patients with any history of immunosuppressant use exhibiting paradoxical worsening despite corresponding treatment, IRIS may be considered.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Misato Kobayashi: writing, review and editing of the original draft of the manuscript. Yukari Tsubata: supervision, review and editing of the original draft of the manuscript. Yohei Shiratsuki, Takamasa Hotta and Megumi Hamaguchi: review and editing of the original draft of the manuscript. Takeshi Isobe: supervision, review and editing of the original draft of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Yukari Tsubata, upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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