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BRIEF REPORT

Diagnostic and Therapeutic Challenges in Disseminated *Mycobacterium colombiense* Infection Caused by Interferon-γ Neutralizing Autoantibodies

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Adult-onset immunodeficiency due to interferon-γ-neutralizing autoantibodies (nIFNγ-autoAbs) can remain underdiagnosed. We present a case of severe *Mycobacterium colombiense* infection with nIFNγ-autoAbs. To ensure early diagnosis, clinicians should have a high index of suspicion in patients of Asian descent with opportunistic infections and perform QuantiFERON-TB assay for disease screening.

Keywords. adult-onset immunodeficiency syndrome; interferon-γ-neutralizing autoantibodies; *Mycobacterium colombiense*; QuantiFERON-TB assay.

Disseminated nontuberculous mycobacterial (NTM) disease is known to occur in severely immunocompromised patients, primarily with advanced human immunodeficiency virus (HIV) infection. The incidence of HIV-related disseminated NTM disease has decreased owing to the introduction of antiretroviral therapy and chemoprophylaxis [1]. However, drug-related NTM disease, especially due to tumor necrosis factor-alpha inhibitors, has been reported in recent years [2, 3].

Interferon-γ (IFN-γ)/interleukin-12 is a crucial pathway to control intracellular pathogens, including mycobacteria [4]. Interferon-γ-neutralizing autoantibodies (nIFNγ-autoAbs) can block this pathway and causes adult-onset immunodeficiency, which mimics advanced HIV infection. Since it was first described in 2004, nIFNγ-autoAbs has been reported to be associated with severe opportunistic infections, predominantly disseminated NTM infections, especially in patients of East/Southeast Asian origin [5, 6]. Early diagnosis of nIFNγ-autoAbs is important for appropriate clinical management; however, it is often delayed by failure to detect nIFNγ-autoAbs, which is challenging in the clinical settings. QuantiFERON-TB assay, which detects IFN-γ release, is widely used for diagnosis of *Mycobacterium tuberculosis* infections. This assay is thought to be useful for screening the presence of nIFNγ-autoAbs [7]. Furthermore, treatment of nIFNγ-autoAbs-related disseminated NTM diseases is challenging because a standard treatment duration and secondary prophylaxis strategies remain unestablished, and relapse after treatment interruption is known to occur frequently [5, 8]. In this study, we report a case of newly diagnosed nIFNγ-autoAbs that developed severe *Mycobacterium colombiense* infection and successfully recovered from the infection.

CASE PRESENTATION

A 70-year-old Japanese man with hypertension presented with a 2-month history of enlarging left cervical mass and neck and shoulder pain for past 1 week. Physical and ultrasonic examination showed an elastic hard cervical mass (39 × 12 × 23 mm), involving an abscess with multiple inflamed lymph nodes. Computed tomography and magnetic resonance imaging showed alveolar opacity in the left lung (Figure 1*A*),

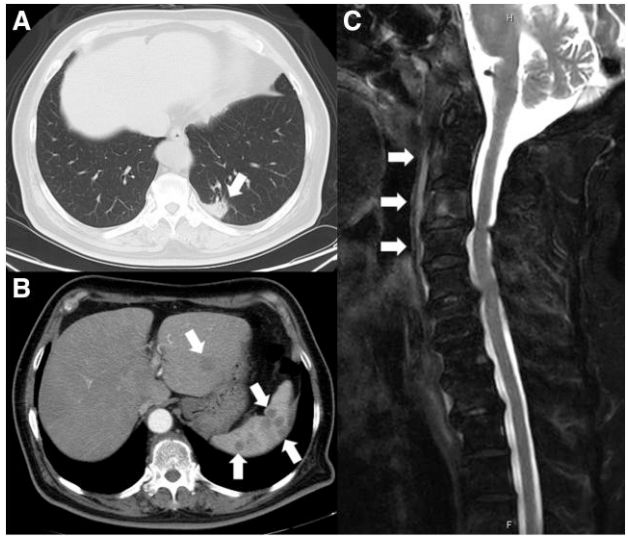

Figure 1. Image findings of interferon-γ neutralizing autoantibodies-related disseminated *Mycobacterium colombiense* infection. Contrast-enhanced computed tomography shows alveolar opacity in the left lung (*A*) and multiple masses in the liver and spleen (*B*). Magnetic resonance imaging (T2 STIR scan) shows prevertebral space infection around the second to fourth cervical spine vertebrae (*C*).

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osteomyelitis of the clavicles (sternal end), manubrium, and third cervical spine vertebra. No mycobacteria were detected in acid-fast bacilli smears and cultures of 3 sputum specimens, and polymerase chain reaction (PCR) assays of sputum for *M tuberculosis* complex and *M avium-intracellulare* complex (MAC) were negative by COBAS TaqMan MTB/MAI (Roche Diagnostics, Tokyo, Japan). A smear of a surgical biopsy specimen of a cervical lymph node was negative for acid-fast bacilli, but histopathology of the tissue revealed epithelioid granulomas. Polymerase chain reaction using the tissue was initially positive for *M intracellulare* by COBAS TaqMan MAI (Roche). After 4 weeks of mycobacterial culture of the tissue, 10 yellowish, smooth colonies were isolated on Ogawa medium (Kyokuto Pharmaceutical Industrial Co., Tokyo, Japan). Eventually, *M colombiense* was identified from the colony by matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS) using a MALDI Biotyper (Bruker Daltonics, Kanagawa, Japan) with Mycobacteria Library v5.0 (Bruker Daltonics). Clarithromycin, ethambutol, and rifampicin were administered as treatment for NTM infection. The minimum inhibitory concentration of drugs was 0.06 μg/mL for clarithromycin, 4 μg/mL for ethambutol, ≤0.03 μg/mL for rifampicin, 1 μg/mL for levofloxacin, and 1 μg/mL for amikacin. Two weeks after the initiation of treatment, the patient was admitted to our hospital with newly developed fever and headache and exacerbated neck and shoulder pain. Physical examination revealed a body temperature of 37.6°C, sternoclavicular joint inflammation (Figure 2*A*), pustules on the left hand (Figure 2*B*), and cellulitis of right foot (Figure 2*C*). Laboratory examination showed a total leukocyte count of 14 660/μL and C-reactive protein level of 79.5 mg/L. Image findings showed worsening of osteomyelitis of the clavicles and manubrium and revealed multiple masses in the liver and spleen (Figure 1*B*) and a newly developed prevertebral space infection around second to fourth cervical spine vertebrae (Figure 1*C*). No organisms, including mycobacteria, *Nocardia* sp, or fungus, were isolated from skin and liver tissue biopsies and specimens of blood and bone marrow fluid. Histopathologically, no cancer cells, granulomas, or acid-fast bacilli were identified in the tissue, and infiltration of inflammatory cells were observed, particularly in the skin fat tissue and the hepatic periportal zone. In addition, the HIV antigen/antibody was negative, and the positive control of QuantiFERON-TB Gold Plus (QIAGEN, Hilden, Germany) was undetectable under the absolute lymphocyte count of 3759/μL. Therefore, we investigated nIFNγ-autoAbs in the research laboratory at the Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan. Using methods described in previous reports [8, 9], the nIFNγ-autoAbs titer, quantified by enzyme-linked immunosorbent assay, was 186.4 Elisa Unit and the STAT1-phosphorylation index was 0. The combination of a >2-fold increase in the nIFNγ-autoAbs titer and a low (<0.3-fold) STAT1-phosphorylation index to healthy subjects is consistent with the presence of nIFNγ-autoAbs [8]. Four months after treatment initiation, the anti-NTM therapy was changed to azithromycin, levofloxacin, and rifampicin, owing to side effects such as eosinophilia (absolute eosinophilic counts of 8447/μL) and skin rashes. Prednisolone 0.5 mg/kg per day was initiated and gradually tapered because eosinophilic infiltration into perivascular and fat tissue was observed in skin tissue biopsy. The patient's symptoms gradually improved, starting 1.5 to 2 months after the initiation of treatment, and the progressive radiographic legions improved, starting 7 months after the initiation of treatment. Finally, all the identified lesions, including the lymphadenitis, subcutaneous abscess, pustules, osteomyelitis, prevertebral space infection, and masses in the liver and spleen, fully resolved clinically and radiographically after 3 years of anti-NTM therapy. Following the definition previously reported

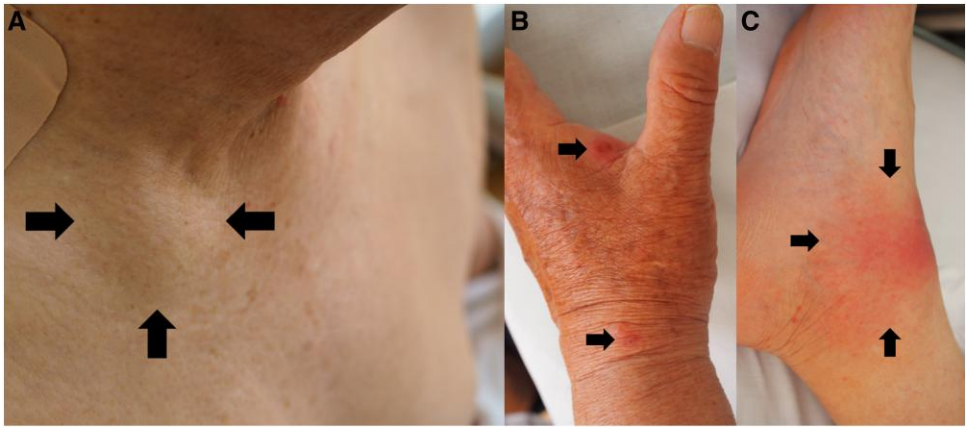

Figure 2. External symptoms of interferon-γ-neutralizing autoantibodies-related disseminated *Mycobacterium colombiense* infection. Sternoclavicular joint inflammation (*A*), pustules on the left hand (*B*), and right foot cellulitis (*C*) are observed.

(any site of NTM infection with reactive skin disease) [10, 11], and its clinical course after initiation of treatment, we clinically diagnosed the patient with the probable disseminated NTM disease caused by nIFNγ-autoAbs.

Patient Consent Statement

Written consent for publication was obtained from the patient.

DISCUSSION

We have described the successful diagnosis of a case of severe NTM infection with nIFNγ-autoAbs. In this study, we discuss the diagnostic tips of nIFNγ-autoAbs and the treatment course of nIFNγ-autoAbs-related disseminated NTM infection.

First, the lessons from this case can help clinicians to diagnose nIFNγ-autoAbs. Adult-onset immunodeficiency with nIFNγ-autoAbs has been reported predominantly in populations of East and Southeast Asia [5, 6]. A review of 111 patients reported that 95% of patients were of Asian descent [5]. The variation in prevalence by region is thought to be related to the relatively high prevalence of genetic human leukocyte antigen (HLA)-polymorphism (HLA-DRB1*16:02/DQB1*05:02) in these populations [12]. The nIFNγ-autoAbs causes late onset acquired immune deficiency [13], including in older adults—the mean age of onset has been reported as 52 years [5]—which mimics advanced HIV infection or idiopathic $CD4^+$ lymphocytopenia [14]. Nontuberculous mycobacterial infections (53%–96%) are the most frequently identified opportunistic infections, followed by herpes zoster (7%–21%) and salmonellosis (4%–20%) [6, 15], and thus the presence of these infections can be a key indicator that suggests a predisposing host factor (cell-mediated immune defect). Among NTM infections with nIFNγ-autoAbs, the most common sites of infection are the lymph nodes (82%) and bones/joints (82%), followed by the lungs (64%) [16]. This condition is often initially misdiagnosed as tuberculosis or malignancy [17]. Therefore, the diagnosis of disseminated NTM infection with nIFNγ-autoAbs is often delayed, as in our case, which required 2 months from symptom onset to diagnosis. For screening nIFNγ-autoAbs in clinical settings, the QuantiFERON-TB assay, which measures IFN-γ levels, is a practical method in patients with no evidence of common immunodeficiency. The presence of nIFNγ-autoAbs results in extremely low or no response of the positive control (mitogen tube) [7]. However, a negative mitogen result is nonspecific and can result from lymphocytopenia, which is sometimes observed in patients with acute illness or sepsis, and does not necessarily indicate that an immunodeficiency is present. Thus, to achieve early diagnosis of nIFNγ-autoAbs, clinicians should consider nIFNγ-autoAbs in the differential diagnosis in HIV-negative patients of Asian descent especially with disseminated NTM disease, and they should use the QuantiFERON-TB assay wisely for disease screening.

Second, the treatment of disseminated NTM infection with nIFNγ-autoAbs is often challenging, although the mortality rate (7%–8%) is lower than that of HIV infection (29%–54%) [5, 17]. This is because relapse is common in nIFNγ-autoAbs-related disseminated NTM infection after treatment discontinuation, and it has been reported to occur in 64% of patients [15], 1 month to 2.5 years after the treatment discontinuation [5]. The immune reconstitution inflammatory syndrome-like phenomenon, observed in our patient, is not fully understood, but it has been previously reported in a patient with disseminated tuberculosis with nIFNγ-autoAbs [18]. Therefore, to ensure a favorable outcome, precise long-term management is crucial, both during anti-NTM therapy and after treatment discontinuation. In refractory or recurrent cases, rituximab (or alternately, cyclophosphamide) should be considered as immunomodulatory therapy for nIFNγ-autoAbs [17].

Third, this case provides a knowledge base for identifying *Mycobacterium* spp. *Mycobacterium avium-intracellulare* complex comprises 12 species, according to genomic distance-based taxonomy [19]. Species-level identification of infrequent MAC members is generally difficult using a commercial PCR assay [20], as seen in our case. The MALDI-TOF MS has recently become accepted as a rapid and reliable alternative of sequencing housekeeping genes, including 16S rRNA, internal transcribed spacer-1 region, *hsp65*, and *rpoB*, with a species-level agreement of 92%–98% [21, 22]. However, the accuracy of identification depends on the score value, version of the library, and manufacturer. A limitation of our report is that we did not conduct sequencing such as 16S rRNA to confirm our *M colombiense* strain.

CONCLUSIONS

In conclusion, we present a rare case of successfully treated severe *M colombiense* infection with newly diagnosed nIFNγ-autoAbs. This case allows us to understand the diagnosis of nIFNγ-autoAbs and its challenging treatment course. To ensure appropriate management and favorable outcomes, accurate diagnosis of nIFNγ-autoAbs is warranted, particularly in HIV-negative patients of Asian descent with opportunistic infections, especially disseminated NTM infection. To screen for nIFNγ-autoAbs, smart use of QuantiFERON-TB assay is crucial.

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