Severe Disseminated *Mycobacterium avium* Infection in a Patient with a Positive Serum Autoantibody to Interferon-γ

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**Abstract**

We herein report a case of disseminated *Mycobacterium avium* infection that involved both optic nerves, the conjunctiva, the right lower lung, and multiple skin lesions, including a thoracic nodule. The patient was a 65-year-old man without any significant medical history. The pathogen was detected in the patient’s eye discharge, sputum, bronchial lavage fluid, and thoracic nodule. Anti-mycobacterial chemotherapy, including clarithromycin, rifampicin, and ethambutol, was administered, and the thoracic nodule was resected. An autoantibody to interferon-γ was detected in the patient’s serum. Bilateral swelling of his optic nerves and facial dermatitis improved after initiating anti-mycobacterial chemotherapy.

**Key words:** disseminated non-tuberculous mycobacteriosis, autoantibody to interferon-γ, *Mycobacterium avium*

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**Introduction**

Among the recently reported cases of disseminated non-tuberculous mycobacterial (NTM) infections in Asian patients without acquired immune deficiency syndrome (AIDS), a number of patients were positive for serum anti-interferon-γ (IFN-γ) neutralizing antibody (i.e., the autoantibody to IFN-γ) (1-3). Some cases have been reported from Japan (4-9). IFN-γ is important for anti-mycobacterial host immunity, including the formation of lung granulomas. Additionally, IFN-γ enhances the macrophage’s killing activity against mycobacteria. Patients with autoantibodies to IFN-γ were first described by Hoflich et al. in 2004 (1), followed by Doffinger et al. (2) in 2004. Most of these patients were Asian, non-HIV-infected individuals who were positive for specific human leukocyte antigens (HLAs) such as DRB1*16:02 and DQB1*05:02 (10). Some patients also develop recurrent NTM infections refractory to anti-mycobacterial chemotherapies (3, 11, 12). In one report, 2 of 16 patients with autoantibodies to IFN-γ died of disseminated NTM infections (1, 2, 13), and 2 of 16 had septicemia (13). In addition, NTM infections complicated by a pelvic abscess (3), tracheal (14) and bronchial (8) obstructions due to granuloma formation, pericarditis (2), osteomyelitis and spondylitis (13), and multifocal osteosclerosis (8) have been reported.

In the current report, we describe a case of disseminated *Mycobacterium avium* infection involving both optic nerves, the right conjunctiva, the right lower lung, and multiple skin lesions, including a thoracic nodule, in a Japanese man with a serum autoantibody to IFN-γ. The patient’s symptoms improved after receiving anti-mycobacterial chemotherapy with clarithromycin (CAM), rifampicin (RFP), and ethambutol (EB) and undergoing resection of the thoracic nodule. Written informed consent was obtained from the patient for the...
Cytic anemia and decreased total protein and albumin levels were detected. Normo-his right lower lung.

On chest auscultation, the breath sounds were weak in his right lateral area. Aside from these lymph nodes, a thumb-sized, painless subcutaneous mass was present on his right lateral neck. A physical examination on admission showed a blood pressure of 117/63 mmHg, pulse rate of 65 beats per min, and body temperature of 35.8°C. Both conjunctivae were moderately anemic without icterus. Viscous discharge was present in both eyes. Erythema was found on his right cheek, anterior and posterior chest, and both lower legs. On his right cheek, painless erythema with scabs was observed. Purulent discharge was observed while gently pressing the cheek, anterior and posterior chest, and both lower legs. On chest computed tomography, the right inferior lobar bronchus was completely occluded by a tumor-like lesion (1 cm x 1 cm in size), resulting in complete atelectasis of his right lower lung (Fig. 2a). Bronchoscopy showed that the tumor-like lesion completely occluded the right lower bronchus (Fig. 2b). An ultrasound analysis indicated that his left cervical mass was a subcutaneous abscess. Brain magnetic resonance imaging (MRI) showed swelling in the retrobulbar part of both optic nerves (Fig. 4c).

Bacterial cultures of the patient’s sputum on admission did not indicate any significant common bacteria. However, on Ziehl-Neelsen staining, 2+ for acid-fast bacilli (AFB) were observed in his sputum. A polymerase chain reaction (PCR) analysis showed that the bacilli were M. avium. Lavage fluid from the right lower bronchus also showed 3+ for AFB. In addition to the respiratory specimens, AFB was also detected in the eye discharge (1+), purulent discharge from the right cheek (2+), and a biopsy specimen from a mass-like lesion of the right lower bronchus and the chest nodule (3+) by Ziehl-Neelsen staining (Fig. 1b). All of these AFB were confirmed to be M. avium by PCR.

A biopsy of the tumor-like region in the right lower bron-
Table 1. Laboratory Data on Admission.

| Hematology                  | Biochemistry                      |
|-----------------------------|-----------------------------------|
| WBC                  10,700/µL | AST                                  |
| Neutrophils       86.6%   | ALT                                  |
| Lymphocytes       9.1%     | LDH                                  |
| RBC                 336 × 10^6/µL | BUN                                  |
| Hemoglobin        9.3 g/dL | Creatinine                         |
| Hematocrit        29.2%    | Na                                   |
| Platelet          29.8 × 10^9/µL | K                                    |
| IgG                1,810 mg/dL | Cl                                   |
| IgA                419 mg/dL  | Total Protein                       |
| IgM                65 mg/dL   | Albumin                             |
| Complement 3      95.8 mg/dL | CRP                                  |
| Complement 4      32.9 mg/dL | ESR                                 |
| RPR               (−)       | MAC-Ab                               |
| TPHA               (−)       | CD4                                  |
| HBs-Ag            (−)       | CD8                                  |
| HCV-Ab            (−)       | Actual CD4 count                    |
| HIV-Ab            (−)       | 440/µL                              |
| Beta-D-glucan     (−)       |                                     |
| CMV-IgG (EIA)      (+)      |                                     |
| CMV-IgM (EIA)      (−)      |                                     |
| CMV-antigenemia   (−)       |                                     |
| RPR               (−)       | MAC-ab                               |
| TPHA               (−)       | 0.87 U/mL                            |
| HBs-Ag            (−)       |                                     |
| HCV-Ab            (−)       |                                     |
| HIV-Ab            (−)       |                                     |
| CD4               25%        |                                     |
| CD8               46%        |                                     |

WBC: white blood cells, RBC: red blood cells, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Na: sodium, K: potassium, Cl: chloride, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, RPR: rapid plasma reagin. TPHA: Treponema pallidum hemagglutination test, HBs-Ag: hepatitis B surface antigen, HCV-Ab: hepatitis C antibody, HIV-Ab: human immunodeficiency virus antibody, CD: cluster of differentiation, CMV: cytomegalovirus, EIA: enzyme immunoassay, MAC-ab: Mycobacterium avium complex antibody.

Figure 2. A chest computed tomography scan and bronchoscopic findings. a: Atelectasis of the right lower lobe. b: A tumor-like legion occluded the right lower bronchus.
Discussion

Disseminated MAC infections are generally encountered as opportunistic infections in patients with AIDS and a CD4-positive lymphocyte count of ≤50 cells/μL. Relationships between disseminated MAC infections in non-immunocompromised patients with positive serum IFN-γ autoantibodies have been reported in recent years (1-3). Browne et al. reported that 81% of patients with disseminated NTM infections without HIV infection are seropositive for IFN-γ autoantibodies (3). Patients with congenital Mendelian susceptibility to mycobacterial disease (MSMD) have been reported to have recurrent NTM infections without other immune suppression from their childhood due to insufficient immune responses involving the IFN-γ/interleukin (IL)-12 pathways (16-19). These patients are also susceptible to infections with Salmonella species and vaccine-associated Bacille Calmette-Guerin infec-

Figure 3. Pathological findings. a: Ziehl-Neelsen staining of the tumor-like legion that occluded the right lower bronchus (400×). The black arrowhead shows numerous acid-fast bacilli. b: Ziehl-Neelsen staining of the anterior chest nodule (400×). Numerous acid-fast bacilli were also detected (black arrowhead). c: Immunostaining of the anterior chest nodule (400×). The nodule was infiltrated by CD68-positive macrophages (black arrowhead).

Figure 4. Change in Mycobacterium avium-infected lesions before and after the patient underwent anti-mycobacterial chemotherapies. The right facial purulent lesions before treatment (a: black arrowhead) were improved after 4 months of undergoing the chemotherapies (b: white arrowhead). Swelling in the retrobulbar part of both optic nerves (c: inside of the black rectangles) disappeared after 2 months of undergoing the chemotherapies (d: inside of the white rectangles).
appropriate anti-mycobacterial treatment (3). In our case, autoantibodies remain actively infected with NTM despite which was confirmed by a PCR assay. However, in his sputum, 4 months of undergoing anti-mycobacterial chemotherapies, disappeared in his eye and right facial discharge after avium infection.

The patient’s medical history did not indicate any other opportunistic infections from his childhood; therefore, his anti-IFN-γ autoantibodies appeared to have been acquired before the infection. Browne et al. reported that many patients with anti-IFN-γ autoantibodies remain actively infected with NTM despite appropriate anti-mycobacterial treatment (3). In our case, M. avium disappeared in his eye and right facial discharge after 4 months of undergoing anti-mycobacterial chemotherapies, which was confirmed by a PCR assay. However, in his sputum, deoxynucleotides of M. avium were still detected by PCR, although his sputum smears were negative after 5 months of undergoing chemotherapy. The optimal duration of anti-mycobacterial chemotherapy for disseminated NTM infections has not yet been established. The American Thoracic Society guidelines state that chemotherapy drugs should be administered for non-disseminated pulmonary M. avium for 2 years (24), whereas Japan’s Committee on Management of Non-Tuberculous Acid-Fast Bacterial Infection, Japanese Society of Tuberculosis and Infection, and Tuberculosis Section of Japanese Society of Respiratory Diseases state that the prolonged administration of anti-mycobacterial agents for >2 years may lead to a better prognosis (25).

In our case, the patient had ophthalmic involvement of disseminated M. avium infection. Several reports have described ophthalmic NTM infections in patients with advanced AIDS (26-28). Bhikoo et al. reported a 48-year-old woman with disseminated NTM infection and AIDS who developed bilateral granulomatous panuvitis and multifocal choroiditis due to MAC (26). Zamir et al. reported a 41-year-old patient with AIDS and choroiditis, which was confirmed by a PCR analysis of a vitreous specimen (27). Cohen and Saragas reported a 27-year-old man with advanced AIDS who developed endophthalmitis due to MAC (28). Other than HIV patients, few reports have described ophthalmic NTM infections. Most cases with keratitis or scleritis caused by NTM were induced by trauma, contamination with foreign bodies, or postoperative complications (29). One report described a 56-year-old man with disseminated M. intracellulare in a patient with a positive serum autoantibody to IFN-γ (13). He developed bilateral panuvitis and finally lost his vision. Another report described a 12-year-old girl who had MSMD with a primary IL-12 receptor defect, and she simultaneously developed an ophthalmic infection and a disseminated M. avium infection (30).

There are several limitations associated with this report. Regarding the results of T-SPOT.TB performed before treatment, the positive control panel detected 21 spots in response to PHA stimulation. Six months after the initiation of anti-mycobacterial chemotherapy, the positive control panel detected 29 spots. Although both numbers of spots passed the assay limit for a positive control (above 20 spots), they were considerably low. Therefore, the patient’s poor nutritional condition and the severe M. avium infection may have affected the production of IFN-γ by lymphocytes. Additionally, we did not exclude the possibility of different types of immunosuppressive conditions, such as a decreased IL-12 production.

In conclusion, we herein reported a case of disseminated M. avium infection in a patient with a positive serum autoantibody to IFN-γ. The patient developed multiple lesions, including ophthalmic, thoracic, skin, and soft-tissue lesions. Although few reports are available regarding ophthalmic lesions induced by MAC in non-HIV patients, physicians must be aware of this rare complication that can be observed in cases of disseminated MAC infections.

Table 2. Case Reports of Disseminated Non-tuberculous Mycobacterial Infections in Patients with a Positive Serum Autoantibody to Interferon-γ in Japan.

| Reference no. | Age (years) | Sex | Mycobacterium | Co-infections | Underlying disease | Organ involvement | Treatment | Year reported | Outcome |
|---------------|-------------|-----|---------------|---------------|--------------------|------------------|-----------|--------------|---------|
| 4             | 54          | M   | MAC           | Streptococcus pneumonia | No                  | LN, lung, BM, pleura | CAM, EB, RFP, SM, ABPC/SBT, CLDM | 2007     | Improved    |
| 5             | 44          | F   | MAC           | No             | No                  | Bone, muscle      | CAM, EB, RFP, SM, MFX, IV, drainage | 2009     | Improved    |
| 6             | 66          | M   | M. avium      | No             | Hepatitis C        | LN, lung, bone, muscle, blood | CAM, EB, RFP, AMK, LVFX, MFX, surgery | 2013     | Improved    |
| 7             | 74          | M   | M. intracellulare | No            | No                  | Lung, BM          | CAM, EB, RFP, SM | 2013     | Improved    |
| 8             | 65          | M   | M. mantieli, M. gordonae | No            | No                  | LN, lung, bone, skin | CAM, EB, RFP | 2013     | Improved    |
| 9             | 65          | M   | M. avium      | No             | No                  | Lung, pleura, BM, liver | CAM, EB, RFP, KM | 2015     | Reinfection |
| Current study | 65          | M   | M. avium      | No             | No                  | LN, lung, skin, eye | CAM, EB, RFP | 2015     | Improved    |

M: male, F: female, MAC: Mycobacterium avium complex, LN: lymph node, BM: bone marrow, CAM: clarithromycin, EB: ethambutol, RFP: rifampicin, SM: streptomycin, KM: kanamycin, ABPC/SBT: ampicillin/sulbactam, CLDM: clindamycin, MFX: moxifloxacin, LVFX: levofloxacin

(20-22). It has been suggested that patients with serum IFN-γ autoantibodies have immunosuppressive conditions similar to patients with MSMD (23). Several reports have described disseminated NTM infections in Japanese non-HIV patients with IFN-γ autoantibodies (Table 2) (4-9). In 2007, Tanaka et al. first described a Japanese patient with disseminated MAC infection who had positive serum IFN-γ autoantibodies (4). As previously described, the sera of our patient had an elevated level of the anti-IFN-γ autoantibody. The patient’s medical history did not indicate any other opportunistic infections from his childhood; therefore, his anti-IFN-γ autoantibodies appeared to have been acquired before the infection.
The authors state that they have no Conflict of Interest (COI).

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