INTERNAL MEDICINE

□ CASE REPORT □

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

Hiroshi Ikeda[1], Kiwamu Nakamura[2,3], Mei Ikenori[1], Takahiro Saito[1], Keisuke Nagamine[1], Minoru Inoue[1], Takuro Sakagami[4], Hiroko Suzuki[5], Mariko Usui[2], Keiji Kanemitsu[3], Akinori Matsumoto[2,6] and Takuro Shinbo[1]

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 mycobacteria infection, 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

[1]Department of Internal Medicine, Ohta-Nishinouchi Hospital, Japan, [2]Infection Control Unit, Ohta-Nishinouchi Hospital, Japan, [3]Department of Infection Control, Fukushima Medical University, Japan, [4]Department of Respiratory Medicine and Infectious Disease, Niigata University Graduate School of Medical and Dental Sciences, Japan, [5]Microbiological Laboratory Unit, Ohta-Nishinouchi Hospital, Japan and [6]Department of Emergency Medicine, Ohta-Nishinouchi Hospital, Japan
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Correspondence to Dr. Hiroshi Ikeda, hiroshi.ikeda1214@gmail.com

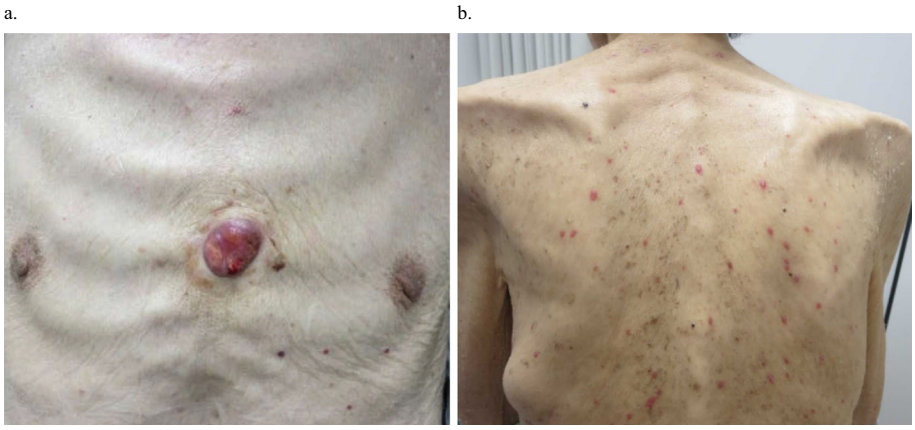

Figure 1. The patient's dermal manifestations. a: The anterior chest nodule (5 cm in diameter). A soft, painless lesion was attached to the patient's sternum. b: Small, red papules with clear margins were present on the patient's back.

publication of this case study.

Case Report

A 68-year-old man was admitted to our hospital for the following symptoms: a non-productive cough, malaise, gait difficulty, visual impairment, multiple skin rashes, and a nodule on his middle anterior chest. Until then, he had not visited any medical facilities for many years due to his economic status. According to the patient's recollection, the papules and nodule appeared 3 years previously. His visual impairment started 1 year previously and gradually worsened. His cough started 3 months before this admission, and it was initially wet and then became non-productive. In addition, he experienced general malaise, and he had difficulty walking since 10 days before the hospital visit.

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℃. 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 rash. A solitary red nodule (5 cm in diameter) was present on his anterior chest (Fig. 1a). Multiple small, red papules (maximum size: 2 mm) were present on his trunk (Fig. 1b). His extremities were edematous, and an erosive rash was present on his legs. Several lymph nodes (maximum size: 15 mm) were palpated around his superficial lateral cervical area. Aside from these lymph nodes, a thumb-sized, painless, soft subcutaneous mass was present on his right lateral neck. On chest auscultation, the breath sounds were weak in his right lower lung.

Laboratory results on admission are shown in Table 1. An increased white blood cell count, C-reactive protein level, and erythrocyte-sedimentation ratio were detected. Normocytic anemia and decreased total protein and albumin levels were noted. *M. avium* complex (MAC) antibody was slightly increased. Other than MAC antibody, antibodies for hepatitis B and C viruses, human immunodeficiency virus (HIV), and human T cell leukemia virus type 1 were negative. The number of CD4-positive T lymphocytes was 440 cells/μL. Results of an enzyme-linked immunospot assay for IFN-γ response to *Mycobacterium tuberculosis* antigens (T-SPOT®. TB, Oxford Diagnostic Laboratory, Marlborough, USA) on admission showed zero spots for ESAT-6 and CFP-10 antigens (the positive control panel detected 21 spots). When determining the IFN-γ response to *M. tuberculosis* antigens by an enzyme-linked immunosorbent assay (QuantiFERON® TB-3G, Cellestis, Chadstone, Australia), the test results were considered to be invalid because the IFN-γ response to phytohemagglutinin (PHA) was not detected in the positive control tube (0.00 IU/mL).

On chest computed tomography, the right inferior lobar bronchus was completely occluded by a tumor-like lesion (1 cm×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			
WBC	10,700/μL	IgG	1,810 mg/dL
Neutrophils	86.6%	IgA	419 mg/dL
Lymphocytes	9.1%	IgM	65 mg/dL
RBC	336 × 10^4/μL	Complement 3	95.8 mg/dL
Hemoglobin	9.3 g/dL	Complement 4	32.9 mg/dL
Hematocrit	29.2%	RPR	(−)
Platelet	29.8 × 10^4/μL	TPHA	(−)
		HBs-Ag	(−)
Biochemistry		HCV-Ab	(−)
AST	30 IU/L	HIV-Ab	(−)
ALT	30 IU/L	Beta-D-glucan	(−)
LDH	156 U/L	CMV-IgG (EIA)	(+)
BUN	12.4 mg/dL	CMV-IgM (EIA)	(−)
Creatinine	0.43 mg/dL	CMV-antigenemia	(−)
Na	139 mEq/L	MAC-ab	0.87 U/mL
K	2.9 mEq/L	CD4	25%
Cl	102 mEq/L	CD8	46%
Total Protein	5.9 mg/dL	Actual CD4 count	440/μL
Albumin	1.6 mg/dL		
CRP	6.08 mg/dL		
ESR	100 mm/h		

WBC: white blood cells, RBC: red blood cells, AST: aspartate amino transferase, ALT: alanine amino transferase, LDH: lactate dehydrogenase, BUN: blood urine 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

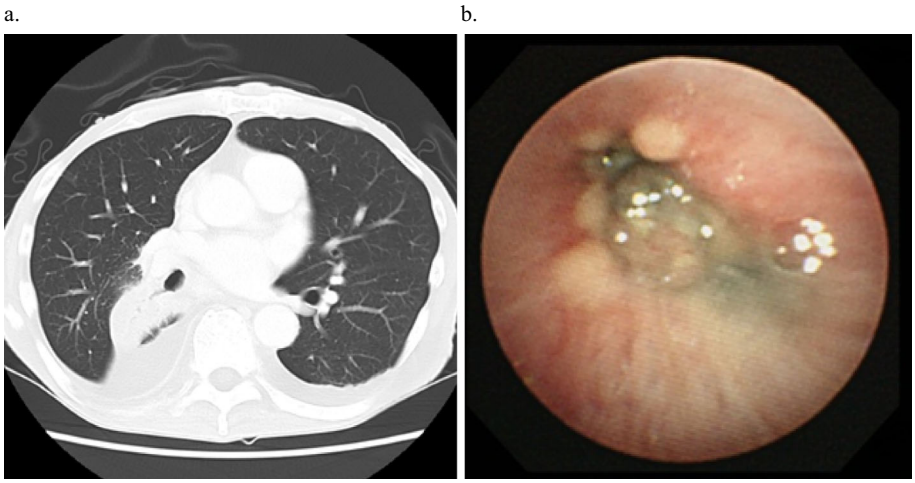

Figure 2. A chest computed tomography scan and bronchoscopic findings. a: Atelectasis of the right lower lobe. b: A tumor-like legion occluded the right lower bronchus.

chus indicated the formation of a histiocytic granuloma with numerous AFB (Fig. 3a). Additionally, numerous AFB (Fig. 3b) and a xanthogranuloma with histiocytic infiltration positively stained with CD68 (Fig. 3c) were detected in the chest nodule.

According to these results, the patient was finally diagnosed with disseminated *M. avium* infection. According to previous reports (1-9) on the relationship between serum autoantibodies to IFN-γ and disseminated NTM diseases, we performed an enzyme-linked immunosorbent assay (ELISA) for the autoantibody to IFN-γ (human interferon-γ antibody ELISA kit, Cusabio, Wuhan, China) using the patient's serum specimen. The optical density (450 nm) value of the patient's serum was 0.409, with 0.037 in a negative control well. In this assay system, a value 2.1-fold higher than the negative control well (i.e., 0.077 in this case) is considered to be positive for the presence of an autoantibody to IFN-γ. Subsequently, we tested the concentrations of anti-IFN-γ autoantibodies and the neutralizing capacity to recombinant human IFN-γ in the patient's serum using methods previ-

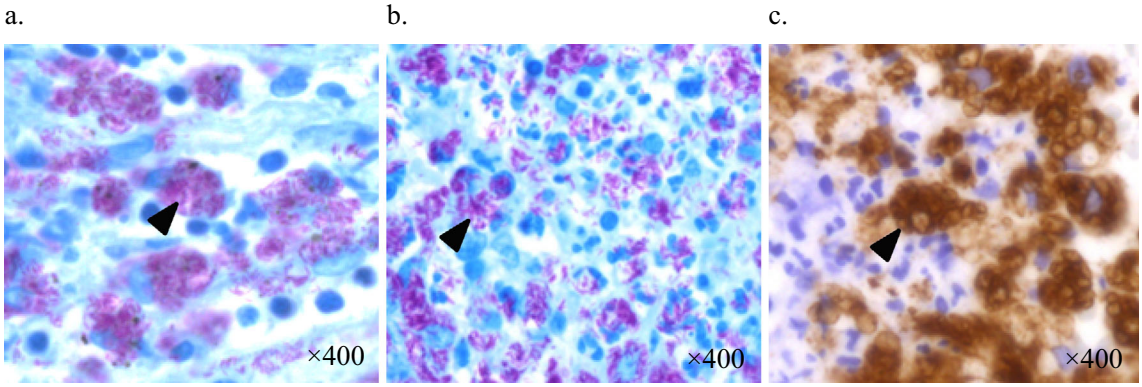

Figure 3. **Pathological findings. a: Ziehl-Neelsen staining of the tumor-like legion that occluded the right lower bronchus (400×). The black arrowhead shows numerous acid-fast bacilli. b: Ziehl-Neelsen staining of the anterior chest nodule (400×). Numerous acid-fast bacilli were also detected (black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

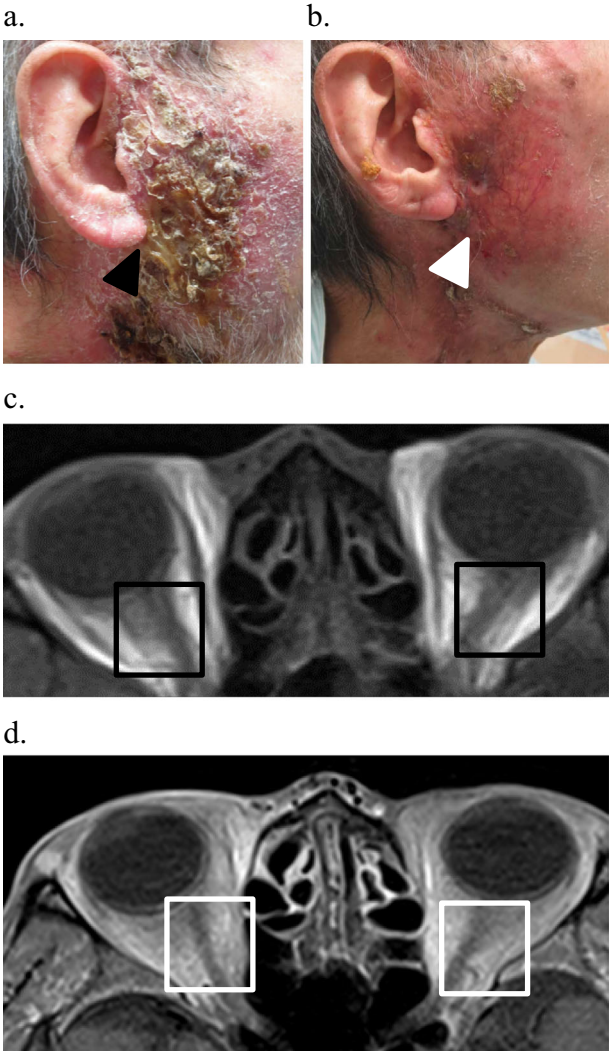

Figure 4. **Change in *Mycobacterium avium*-infected lesions before and after the patient underwent anti-mycobacterial chemotherapies. The right facial purulent lesions before treatment (a: black arrowhead) were improved after 4 months of undergoing the chemotherapies (b: white arrowhead). Swelling in 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).**

ously reported (15). The serum concentrations of the autoantibody to IFN-γ were 728.13 ELISA Units (EU) 1 month after treatment, 2015 (1 month after treatment) and 109.29 EU 6 months after treatment 28, 2015 (6 months after treatment). These titers were significantly higher than the normal range (5-50 EU). The signal transducer and activator of transcription-1 in immortalized human T cells was not phosphorylated after stimulation with IFN-γ by the presence of the patient's serum. According to these results, we determined that the patient's serum had retained neutralizing anti IFN-γ autoantibodies.

Anti-mycobacterial chemotherapy was started 30 days after admission. A combination of 800 mg of CAM daily, 600 mg of RFP daily, and 750 mg of EB daily was initiated. The rash on the right cheek temporarily worsened around 10 weeks after chemotherapy. After 4 months of chemotherapy, the patient's general condition and the appearance of his skin lesions markedly improved (Fig. 4a and b). Follow-up orbital MRI showed obvious improvement in swelling of both optic nerves (Fig. 4c and d).

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-

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 pyogenes*	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, MFLX, IVIG, drainage	2009	Improved
6	66	M	*M. avium*	No	Hepatitis C	LN, lung, bone, muscle, blood	CAM, EB, RFP, AMK, LVFX, MFLX, surgery	2013	Improved
7	74	M	*M. intracellulare*	No	No	Lung, BM	CAM, EB, RFP, SM	2013	Improved
8	65	M	*M. mantenii, 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, MFLX: moxifloxacin, LVFX: levofloxacin

tion (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.

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 panuveitis 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 panuveitis 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). To the best of our knowledge, this is the first report to describe a disseminated NTM infection involving multiple ophthalmic lesions occurring in a Japanese patient with an autoantibody to IFN-γ.

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.

The authors state that they have no Conflict of Interest (COI).

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