

[CASE REPORT]

Disseminated *Mycobacterium avium* Infection Complicated with Chylous Ascites in a Patient with Neutralizing Autoantibodies to Interferon- γ

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Abstract:

A 68-year-old man visited our hospital due to anorexia, weight loss and a fever. We diagnosed the patient with disseminated *Mycobacterium avium* complex (MAC) and confirmed the presence of interferon (IFN)- γ neutralizing autoantibodies (IFN- γ Ab). His lesions improved following antibiotic therapy, but chylous ascites (CA) developed seven months after treatment. CA was able to be controlled by subcutaneous octreotide and diet therapy. IFN- γ Ab is recognized as having a critical role in the pathogenesis of disseminated MAC disease, but its clinical features are not fully understood. CA may be a complication that develops during the treatment of disseminated MAC infection.

Key words: IFN- γ Ab, chylous ascites, disseminated nontuberculous mycobacteriosis

(Intern Med 59: 3195-3200, 2020)

(DOI: 10.2169/internalmedicine.3987-19)

Introduction

Disseminated nontuberculous mycobacteriosis (NTM) is a systemic disease that occurs in patients with underlying immunodeficiency (1). Although HIV is the most important background for disseminated NTM, interferon- γ (IFN- γ) has recently been recognized to play another critical role in antibacterial immunity against *Mycobacterium avium* infection (2-5). Indeed, reports of disseminated NTM disease with IFN- γ neutralizing autoantibodies (IFN- γ Ab) have increased (6-9). Most recently, the clinical features have been shown to differ between HIV-positive and IFN- γ Ab-positive disseminated NTM patients (10), but the clinical information is limited.

Chylous ascites (CA) is a possible complication in disseminated NTM (11) and is known to indicate a poor prognosis in HIV-positive disseminated NTM (12). However, CA has not been reported in patients with IFN- γ Ab-positive disseminated NTM.

We herein report the case of a 68-year-old man with disseminated *M. avium* infection and IFN- γ Ab that was further complicated by CA.

Case Report

A 68-year-old man who was an ex-smoker (30 pack-year history) and had no immunosuppressive history visited our hospital complaining of anorexia and 10-kg weight loss over 2 months.

His body temperature was 37.8°C, and oxygenation was within the normal range. Table 1 shows the results of a blood examination on admission. An increased white blood cell (WBC) count and C-reactive protein (CRP) level were seen. Soluble interleukin-2 receptor (sIL-2R) showed marked elevation. The QuantiFERON TB-3 G (QFT-3G) test result was indeterminate due to the negative result for the positive control. On chest X-ray, an infiltrative shadow was observed in left lower lung fields. Contrast-enhanced computed tomography (CT) showed a systemic lesion with an

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Received: October 2, 2019; Accepted: June 24, 2020; Advance Publication by J-STAGE: August 12, 2020

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Table 1. Laboratory Data on Admission.

Hematology		Biochemistry		Tumor markers	
WBC	21,720 / μ L	TP	7.2 g/dL	CEA	2.0 ng/mL
Neut	83 %	Alb	2.2 g/dL	CA19-9	8.5 U/mL
Lym	10 %	T-Bil	1.0 mg/dL	CYFRA	1.9 ng/mL
Mono	1 %	ALP	1,706 IU/L	SLX	28.2 U/mL
Eos	6 %	γ -GTP	320 IU/L	ProGRP	29 pg/mL
RBC	348 $\times 10^4/\mu$ L	AST	47 IU/L	NSE	7.9 ng/mL
Hb	8.1 g/dL	ALT	68 IU/L	sIL2-R	12,039 U/mL
Plt	15.8 $\times 10^4/\mu$ L	LDH	217 IU/L		
CD4/CD8		CK	7.0 IU/L	Infection	
CD4	39.8 %	BUN	11.8 mg/dL	HIV-Ab	negative
CD8	16.4 %	Cre	0.69 mg/dL	HTLV-1 Ab	negative
Serology		Na	136 mEq/L	MAC Ab*	>10.0 U/mL
CRP	17.8 mg/dL	K	4.9 mEq/L	QFT-3G	indeterminate
IgG	1,786 mg/dL	Cl	99 mEq/L	T-SPOT	negative
IgA	984 mg/dL	Ca	8.9 mg/dL		
IgM	143 mg/dL	Glu	105 mg/dL		

*anti-MAC GPL core IgA antibody. WBC: white blood cells, Neut: neutrophils, Lym: lymphocytes, Mono: monocyte, Eos: eosinophils, RBC: red blood cells, Hb: hemoglobin, Plt: platelet, CD4: cluster of differentiation 4, CD8: cluster of differentiation 8, CRP: C-reactive protein, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, Tp: total protein, Alb: albumin, T-Bil: total bilirubin, ALP: alkaline phosphatase, γ -GTP: γ -glutamyl transpeptidase, AST: aspartate amino transferase, ALT: alanine amino transferase, LDH: lactate dehydrogenase, CK: creatinine kinase, BUN: blood urine nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, Glu: glucose, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, CYFRA: cytokeratin-19, SLX: sialyl Lewis-x antigen, ProGRP: pro-gastrin releasing peptide, NSE: neuron-specific enolase, sIL2-R: soluble interleukin-2 receptor, HIV-Ab: human immunodeficiency virus antibody, HTLV-1 Ab: human t-cell leukemia virus type 1 antibody, MAC Ab: anti-mycobacterium avium complex glycopeptidolipid core IgA antibody, QFT: quantiferon

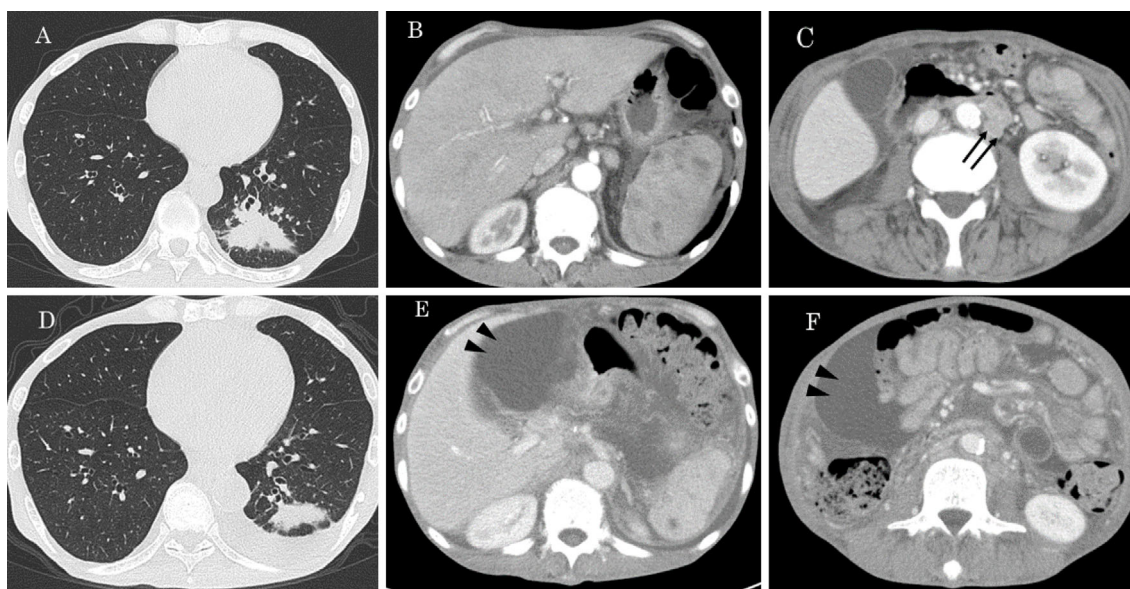


Figure 1. Chest and abdominal contrast-enhanced CT on admission (A-C) and 7 months after treatment (D-F). By treatment, lung lesions, spleen lesions and intra-abdominal lymphadenopathy (arrows) have been improved but ascites increased (arrow heads).

infiltrative shadow in the left lower lobe, osteolytic change in left 8th rib, hepatosplenomegaly, sporadic observation of a poor-contrast area in the spleen, enlargement of multiple intra-abdominal lymph nodes and ascites fluid (Fig. 1A-C). On 18 F fluorodeoxyglucose (FDG) positron-emission tomography (PET)/CT, the increased accumulation of FDG was

observed in the lesions detected by enhanced CT (Fig. 2).

Because severe bacterial infection was suspected, antibiotic treatment (meropenem: 1,500 mg/day) was initiated, but the inflammatory reaction and imaging findings did not im-

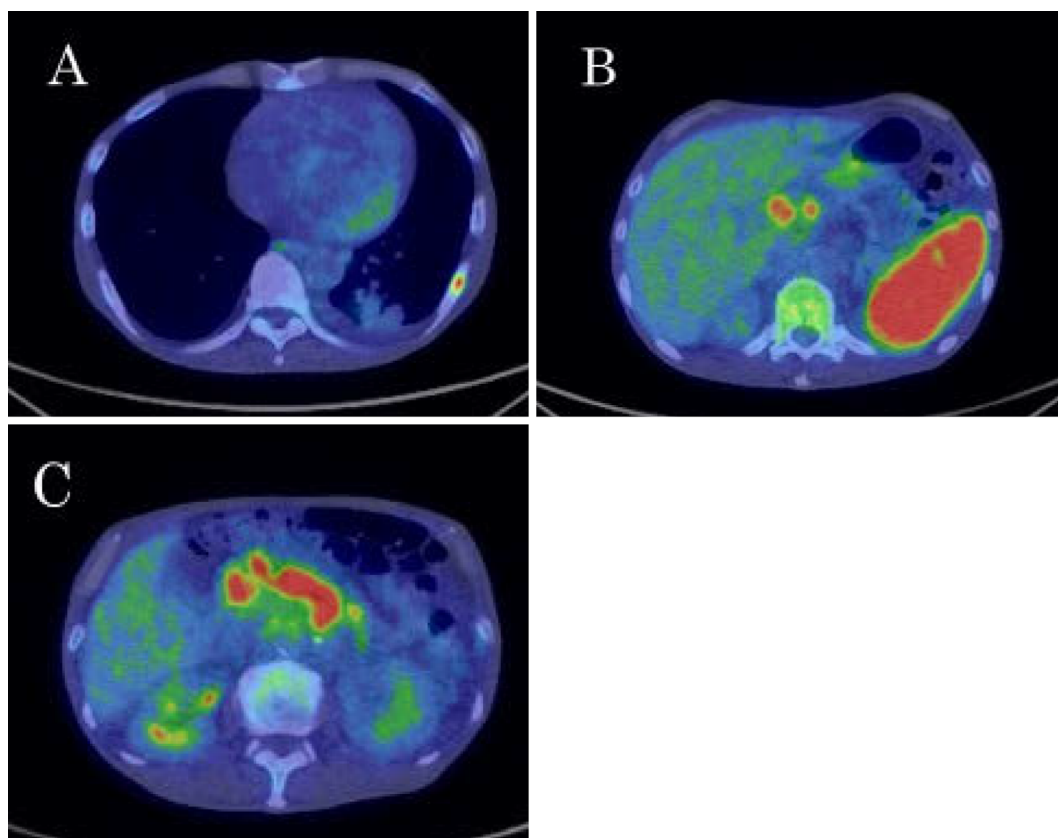


Figure 2. FDG PET/CT on admission. Increased FDG accumulations were observed in left 8th rib (A), spleen (B) and multiple intra-abdominal lymph nodes (B, C).

Table 2. Results of Serum IFN- γ Neutralizing Autoantibodies.

STAT1-PI	17.76 (control: 556.59)
IFN- γ antibodies	1,210.97 E.U. (control: 1.91 E.U.)

STAT1-PI: signal transducer and activator transcription 1 phosphorylation index, IFN- γ : interferon- γ

prove. Because of the negative IFN- γ release response to mitogen, we suspected disseminated NTM disease with IFN- γ Ab. For a definitive diagnosis, samples were harvested from lesions of the lung, bone marrow and abdominal lymph node. *M. avium* was detected from bronchial wash and abdominal lymph nodes collected by a CT-guided biopsy, and sporadic granulomas with multinucleated giant cells were found from a bone marrow clot. We therefore diagnosed the patient with disseminated *M. avium* infection. Furthermore, we assessed the serum IFN- γ Ab level because he had no immunosuppressive history, and the positive control of QFT-3G showed a negative result and confirmed the presence of IFN- γ Ab (Table 2).

For treatment of disseminated *M. avium* infection, we administered antibiotherapy comprising clarithromycin (600 mg/day), rifampicin (450 mg/day), ethambutol (750 mg/day) and streptomycin (660 mg/day; twice weekly for the first 3 months of treatment). Sitaflaxacin (100 mg/day) was added during the second month of treatment.

Five months after treatment initiation, his inflammatory



Figure 3. Milky white ascites was obtained from the aseptic fluid puncture fluid.

reaction had improved (WBC: 6,500/ μ L, CRP: 6.5 mg/dL), and sIL2-R had decreased to 2,492 U/mL. In addition, enhanced CT showed the resolution of most of the previously abnormal findings. For ascites, temporary drainage was performed several times. Consequently, one month after the start of treatment, abdominal fullness improved, and temporary drainage became unnecessary. However, seven months after treatment initiation, the patient complained of abdominal fullness again, and increased ascites was found without

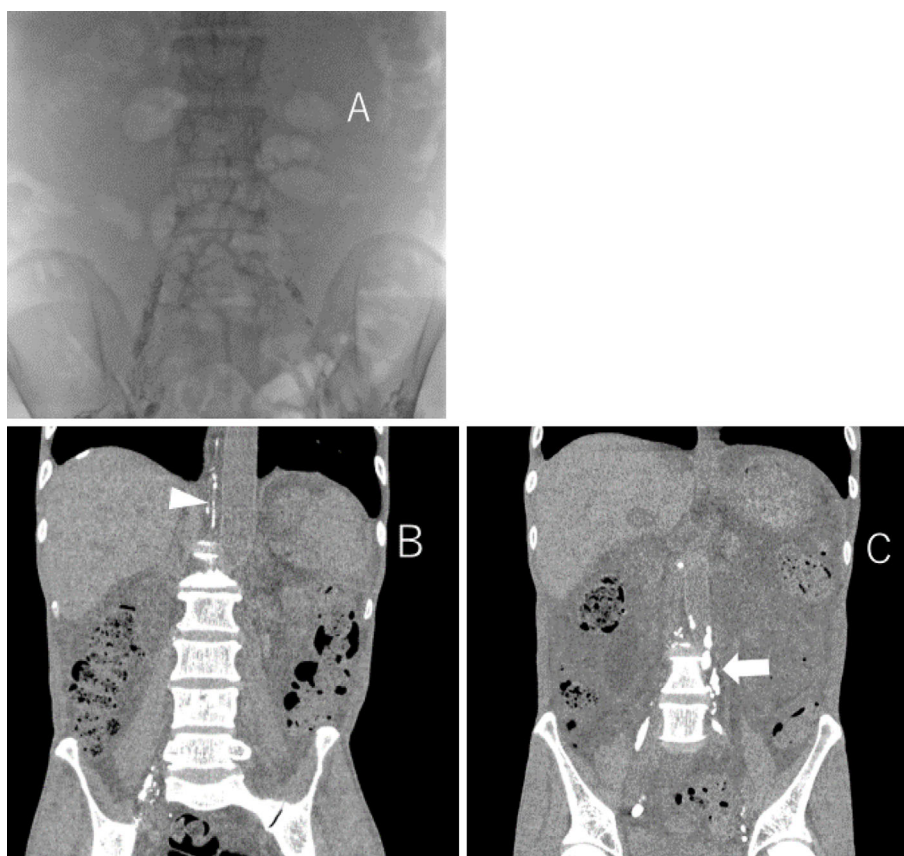


Figure 4. Lymphangiogram was performed from the left and right inguinal lymph nodes (A) and abdominal CT was taken the day after lymphangiography. Inflow to the thoracic duct can be confirmed by lymphangiography performed from the right inguinal lymph node (arrow head) (B) but, lymphangiography performed from the left inguinal lymph node showed that the lymph vessels were occluded at the level of the 4th lumbar spine (arrow) (C).

recurrence of the other lesions (Fig. 1D-F). In addition, the ascites color had changed from a clear-yellowish color to milky white (Fig. 3), and CA was diagnosed based on the markedly high triglyceride level of the ascites fluid.

The patient was subsequently hospitalized and started on a fat-restricted diet and subcutaneous octreotide (300 μ g/day). On day 5 of hospitalization, lymphangiogram was performed using iodized oil emulsion (Lipiodol[®], Guerbet Japan, Tokyo, Japan) from the left and right inguinal lymph nodes. Abdominal CT taken the next day showed normal lymph vessels on the right side but disrupted lymph vessels on the left side at the level of the 4th lumbar spine (Fig. 4). His abdominal fullness subsequently improved, and he was discharged on day 9 of hospitalization.

At nine months after his first visit, the patient exhibited no increase in ascites or deterioration of each lesion.

Discussion

We encountered a case of disseminated *M. avium* infection in a patient with IFN- γ Ab. Recently, it was reported that IFN- γ Ab was detected in 81% of Asian patients with disseminated NTM infection and normal CD4-positive cell counts (13). The evaluation of IFN- γ Ab has gained impor-

tance for the pathophysiological diagnosis of disseminated NTM in patients without obvious immunodeficiency (14).

The primary manifestations of disseminated NTM with IFN- γ Ab are nonspecific, and lesions are generally seen in multiple organs, such as the lungs, bones, lymph nodes and bone marrow (10). Furthermore, the diagnosis of disseminated NTM with IFN- γ Ab can be challenging for clinicians, as anamnestic immune deficiency usually has not been detected when clinicians encounter this disease. Indeed, the mean period from the disease onset to the diagnosis is four months (10). Therefore, disseminated NTM with IFN- γ Ab should be considered when systemic serious infections are suspected in individuals without anamnestic immune deficiency.

A high sIL-2R level is often seen at the diagnosis of disseminated *Mycobacterium avium* complex (MAC) disease (15), which may give attending physicians a false impression of malignant lymphoma (10). sIL-2R is released into the blood from T cells, B cells and monocytes (16-18). The measured values reflect T or B cell immune activation (19). In patients with pulmonary tuberculosis, sIL-2R levels increase as the lesion expands (20). In this case, the sIL-2R levels appeared to have increased due to the lesion spreading throughout the body. Accordingly, clinicians must

recognize disseminated NTM as a possible pathological condition in cases with elevated sIL-2R levels.

The present patient was complicated with CA during the treatment course for disseminated *M. avium* infection. CA is defined as the accumulation of triglyceride-rich fluid in the peritoneal cavity (21), and its clinical incidence is rare (22, 23). However, *Mycobacterium* infection is the third-most common etiology of atraumatic CA in adults after malignancy and liver cirrhosis (11). Koizumi et al. also reported a case of disseminated MAC with IFN- γ Ab complicated with CA (24). In their case, lymph node swelling and CA occurred during the discontinuation of antimicrobial therapy, and the patient died three months after the disease onset. In contrast, in the present case, CA occurred after lymph node swelling had improved by antibacterial therapy. Phillips et al. reported six HIV-infected patients who were complicated with CA related to intra-abdominal MAC immune reconstitution syndrome (25). MAC was cultured from ascites in only one of these six patients, and only that patient died. These results suggest that disseminated MAC infection control is important and may improve the survival in patients with CA.

Various mechanisms may be responsible for the production of CA in patients with mycobacterial infection, including the obstruction of the lymphatic system due to enlarged lymph nodes or lymph nodal fibrosis (26). In the present case, CA developed after the improvement of lymph node swelling. Therefore, we speculate that obstruction of the lymphatic system due to lymph nodal fibrosis occurred after inflammation, which subsequently led to CA.

Serum IFN- γ Ab concentration was quantified using an enzyme-linked immunosorbent assay, as reported previously (14). However, the measurement of serum the IFN- γ Ab concentration requires specialized equipment. In the present case, indeterminate QFT-3G results prompted us to suspect the presence of IFN- γ Ab in the patient's serum. Ishi et al. reported that the discrepancy between QFT-3G and T-SPOT-TB results indicates the presence of IFN- γ Ab (27). In the present case, the T-SPOT test result was negative because the patient had no history of tuberculosis, and the QFT-3G test result was indeterminate due to the presence of neutralizing antibodies. Even if IFN- γ Ab is present in the patient's serum, care must be taken in interpreting the results, as there is no marked difference between the T-SPOT and QFT-3G results in patients without tuberculosis infection, as seen in the present case.

In conclusion, we encountered a case of disseminated *M. avium* infection complicated with CA in a patient with IFN- γ Ab. When examining a patient who has multiple organ findings and elevated inflammation, it is necessary to consider the possibility of this disease. In addition, CA should be recognized as a possible complication of disseminated MAC induced by IFN- γ Ab.

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

Acknowledgement

The authors thank Dr. Kazutaka Yoshizawa for performing IFN- γ neutralizing autoantibody measurements.

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