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ORIGINAL INVESTIGATION

Chylous ascites, anti-interferon-gamma autoantibody, and angioimmunoblastic T-cell lymphoma: a rare but intriguing connection over *Mycobacterium avium*

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Abstract
We report a case of non-AIDS (acquired immunodeficiency syndrome), non-CAPD (Continuous Ambulatory Peritoneal Dialysis), non-cirrhotic, *Mycobacterium avium* peritonitis, which is a rare form of mycobacterial infection. A 66-year-old Japanese man who had been treated previously for angioimmunoblastic T-cell lymphoma (AITL), had developed disseminated *M. avium* infection. Antimycobacterial regimen improved his symptoms; however, following an interruption in treatment, he developed chylous ascites. The patient died of uncontrolled peritonitis despite intensive treatment. Anti-interferon-γ autoantibody was positive, and AITL was presumed to be involved in autoantibody production. A rare coexistence of chylous ascites, autoantibody, and AITL taught us an intriguing lesson on the pathogenesis of *M. avium* infection. Particularly, we conclude that treatment strategies for *M. avium* infection should aim to restore immunity.

Keywords Disseminated *Mycobacterium avium* complex infection · Angioimmunoblastic T-cell lymphoma · Rituximab · Anti-interferon-γ autoantibody · Signal transducer and activator of transcription (STAT)1

Introduction

Chylous ascites is an uncommon disease, with a reported incidence of one in 20,000–187,000 admissions at large tertiary referral hospitals [1, 2]. In a systematic review, malignancies (25%) or liver cirrhosis (16%) were reported as the leading etiologies of chylous ascites [2]. Mycobacterial infection is the third cause of chylous ascites, constituting 15% of cases, and most of these cases are *Mycobacterium avium* peritonitis in acquired immunodeficiency syndrome (AIDS). There are only few cases of non-AIDS *M. avium* peritonitis, in which the underlying diseases are reported to be renal failure under continuous ambulatory peritoneal dialysis (CAPD), [3] or liver cirrhosis (LC) [4].

We encountered a rare case of non-AIDS, non-CAPD, non-LC, *M. avium* peritonitis with anti-interferon (IFN)-γ autoantibody. Of note, the autoantibody was supposed to be a product of an abnormal B-cell population stimulated by angioimmunoblastic T-cell lymphoma (AITL), a unique subtype of malignant lymphoma. Here we report an intriguing combination of these rare diseases.

Case report

A 66-year-old Japanese man with fever and multiple lymphadenopathy was admitted to our hospital. An intra-abdominal lymph node biopsy led to the diagnosis of AITL. After eight courses of the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen, complete remission was achieved, and the patient was followed up further. Three months later, he returned with high fever that persisted for 10 days. Hypoxia (SpO_2 88% under 5 L oxygen) and hepatosplenomegaly were the physical abnormalities at admission. Laboratory data (Table 1) showed marked

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Table 1 Laboratory findings at diagnosis of dMAC infection

WBC	25,600	/μL	TP	5.4	g/dL	Fe	56	mg/dL
Seg	85.5	%	ALB	1.7	g/dL	UIBC	97	mg/dL
Band	0.5	%	AST	15	U/L	Ferritin	968	ng/mL
Eosin	3	%	ALT	14	U/L	IgG	2457	mg/dL
Lymph	7	%	LDH	270	U/L	IgM	128	mg/dL
Mono	3.5	%	ALP	1781	U/L	IgA	545	mg/dL
Aty-lym	0.5	%	g-GTP	179	U/L	CRP	14.3	mg/dL
			CHE	77	U/L	sIL-2R	14,400	U/mL
RBC	3.09×10^6	/μL	T-BIL	1.2	mg/dL	Procalcitonin	1.48	ng/mL
Hb	8.4	g/dL	Ca	7.5	mg/dL			
Ht	26.1	%	Na	133	mEq/L	Quantiferon-gold®	Undeterminable	
MCV	81	fl	Cl	98	mEq/L	TB antigen	< 0.05	
PLT	228,000	/μL	K	4.8	mEq/L	**Mitogen**	**< 0.05**	
			UN	16.3	mg/dL	NIL	0.07	
			CRE	0.55	mg/dL			
			UA	4.8	mg/dL	β-D-glucan	< 5.0	pg/mL
			T-CHO	159	mg/dL	CMV antigenemia	(–)	
CD4 count	397	/μL	TG	163	mg/dL	HBs antigen	(–)	
CD8 count	384	/μL	AMY	21	U/L	HCV antibody	(–)	
			CPK	12	mg/dL	Cryptococcus-Ag	(–)	

Quantiferon Gold® was undeterminable because the reaction to mitogen was negative, suggesting the presence of anti-interferon-γ autoantibody

aGPL, anti-glycopeptidolipid; CMV, cytomegalovirus; RPR, rapid plasma reagin test; sIL-2R: soluble interleukin-2 receptor; TBGL Ab, tuberculous glycolipid antibody; UIBC, unsaturated iron-binding capacity

elevation of alkaline phosphatase (ALP), C-reactive protein (CRP), and immunoglobulin-G (IgG) levels. Anemia and leukocytosis were prominent, and the levels of soluble interleukin-2 receptor (sIL-2R) were markedly high. The clinical course for this case is shown in Fig. 1. Initially, a computed tomography (CT) scan revealed splenomegaly with a massive low-density area. Blood and sputum cultures detected *M. avium* after 7, and 14 days of incubation, respectively. There was only a slight depletion of CD4 and CD8 positive T lymphocytes (397 and 384/μL, respectively). To exclude cellular immunodeficiency, we screened for genetic abnormalities or mutations in the following nine genes: *IFNGR1* (encoding the ligand-binding chain of the IFN-γ receptor), *IFNGR2* (encoding the accessory chain of IFN-γR), *NEMO* (encoding NF-kappa-B essential modulator), *IL12B* (encoding the p40 subunit common to IL-12 and IL-23), *IL12RB1* (encoding the β1 chain common to the receptors for IL-12 and IL-23), *STAT1* (encoding signal transducer and activator of transcription 1), *CYBB* (encoding the major component of the phagocyte nicotinamide adenine dinucleotide phosphate oxidase complex), *IRF8* (encoding a transcription factor from the IRF family, that is inducible by IFN-γ), and *ISG15* (encoding an IFN-γ-inducing molecule that acts in synergy with IL-12). No mutations were identified in the above-mentioned genes. However, the anti-IFN-γ autoantibody assay [5] result was positive. STAT1 phosphorylation was inhibited by addition of patient's sera, suggesting that the autoantibody was compromising macrophage function. Under the diagnosis of disseminated *M. avium* complex infection (dMAC), 800 mg of clarithromycin (CAM), 600 mg (11 mg/kg) of rifampicin (RFP), and 900 mg (17 mg/kg) of ethambutol (EB) were administered daily according to the daily dosing listed in the ATS/IDSA statements [6]. The dose of clarithromycin was not increased above 800 mg because of gastrointestinal symptoms.

Three weeks later, the patient's chills and fever subsided, and he was discharged at day 50 (of antimycobacterial regimen). At day 90, the patient's lung lesion had disappeared. The regimen was continued for 10 months, until the adverse effect appeared. At day 333, the patient discontinued antimycobacterial drugs because of liver dysfunction and peripheral neuropathy. Two months after interruption, he complained of fever, epigastralgia, and lymph node swelling. A CT scan revealed massive ascites, intestinal edema, and intra-abdominal lymphadenopathy. Ascites was chylous, with 4053 cells/μL of white blood cells (polynuclear cells dominant, and without atypia). The ascites cytology, T-cell receptor rearrangement analysis, and lymph node biopsy excluded the relapse of AITL. Instead, *M. avium* was detected in ascites culture.

Under the diagnosis of *M. avium* peritonitis, 800 mg of CAM, 300 mg of rifabutin (RBT), and 200 mg of

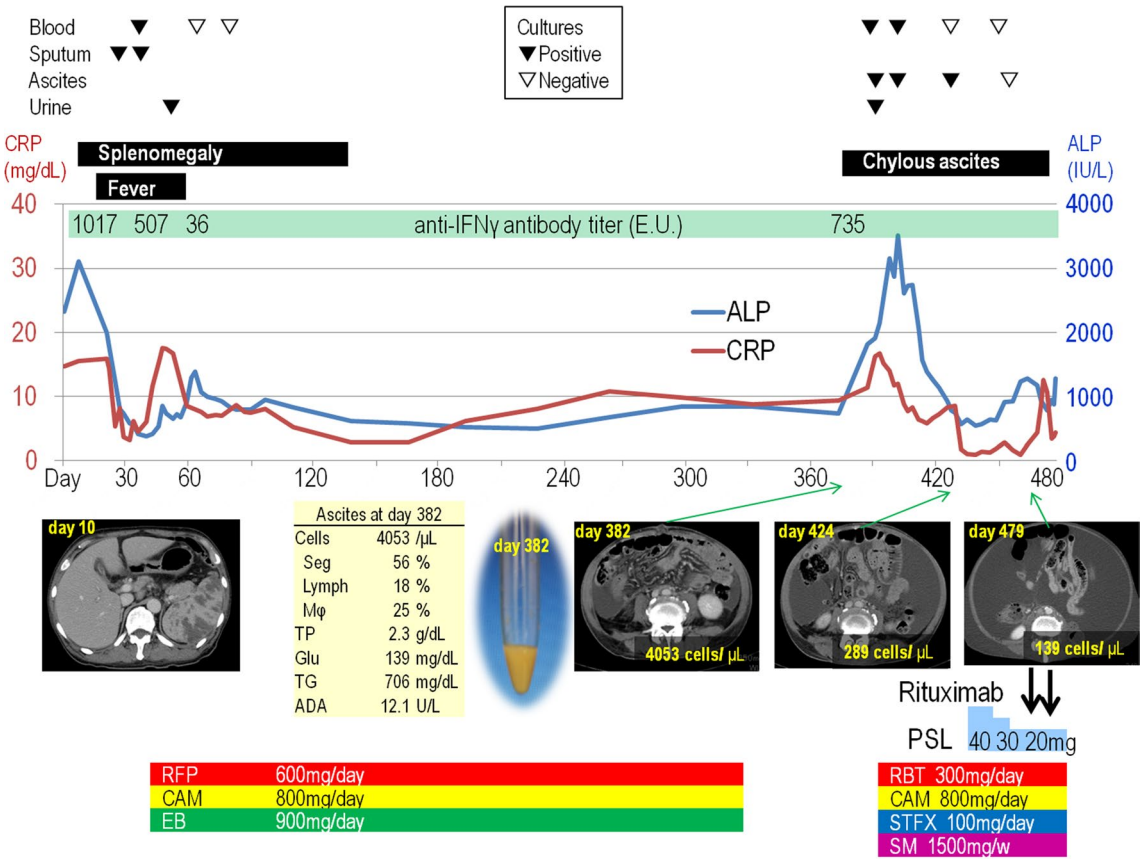

Fig. 1 Clinical course. The patient developed disseminated *Mycobacterium avium* infection (dMAC). Rifampicin (RFP), clarithromycin (CAM), and ethambutol (EB) therapy was administered. 3 weeks later, fever subsided, and the regimen was continued for 10 months until severe neurologic complications appeared. 2 months after treatment disruption, the patient complained of abdominal pain. In blood cultures, *M. avium* was detected again, and CT scan revealed ascites. Paracentesis was performed at day 382 (since the diagnosis of dMAC). The ascites was milky with triglyceride level of 706 mg/dL, containing 4053 cells/μL, with neutrophil predominance. The diagnosis of *M. avium* peritonitis was made, and CAM, rifabutin, sitafloxacin, and streptomycin were administered. Prednisolone and later rituximab were administered during the course, which transiently improved fever and wasting. Ascites culture yielded *M. avium* three times, and later turned to be negative at day 479. However, chylous ascites remained and the atrophy of intestine had become remarkable. The patient gradually became debilitated, and he finally died of renal failure. Note that anti-IFN-γ antibody titer correlated with the clinical course

sitafloxacin (STFX) were administered daily, while 750 mg of streptomycin (SM) was administered twice weekly. Subsequently, susceptibility test (BrothMIC NTM®; Kyokuto Pharmaceutical Industrial) results were reported: CAM 0.25 μ g/mL, RFP 0.125 μg/mL, RBT 0.06 μg/mL, EB > 128 μg/mL, SM 16 μg/mL, amikacin 16 μg/mL, and levofloxacin 2 μg/mL. Because the patient complained of severe abdominal pain after meals, total parenteral nutrition was commenced. Several weeks later, *M. avium* was not detected in the ascites culture, but chylous ascites remained. Prednisolone was administered to inhibit the anti-IFN-γ autoantibody, ease pain, and control wasting. The symptoms were relieved for weeks, but tapering was not possible. The patient complained cramping abdominal pain since then, and the intestines showed atrophy within a few weeks (Fig. 1). Rituximab was administered twice to decrease titers of the autoantibody, which did not improve the clinical course.

Gradually the patient became debilitated, and died of renal failure on day 96 of readmission.

Discussion

Nontuberculous mycobacteria (NTM) are environmental bacteria with low virulence. Although they are major opportunistic pathogens in compromised hosts, they rarely cause peritonitis. The few peritonitis cases reported so far occurred in the CAPD, AIDS, or LC populations [3, 4, 7]. The causative agents of CAPD-associated mycobacterial peritonitis are usually rapidly growing mycobacteria (RGM) such as *M. fortuitum* or *M. chelonae* [7]. *M. fortuitum* peritonitis

cases present with abdominal pain or fever, and paracentesis reveals neutrophil dominant pleocytosis [median 3637 (270–13,500) cells/μL] in the ascites. Because cultures require at least 4 days until detection, most of the RGM peritonitis cases are first regarded as refractory culture-negative CAPD peritonitis. Sometimes months pass before the correct diagnosis can be made. Nonetheless, the prognosis of CAPD peritonitis caused by *M. fortuitum* is relatively fair, which is also true of *M. chelonae*, the drug-resistant species [8].

MAC peritonitis shows different features. In the literature, the great majority of MAC peritonitis cases are AIDS patients with an extremely low CD4 positive T cell count [9, 10], with a rare exception [11]. Most of the patients complain abdominal pain, and show chylous ascites. Notably, the outcome is poor despite intensive treatment with three-to-five antimycobacterial agents. Shu et al. made comparisons between NTM (most of which are *M. avium*) and *M. tuberculosis* peritonitis cases [9]. They also found that NTM peritonitis cases showed poorer prognosis with 48% mortality within 6 months. Unlike tuberculosis, NTM peritonitis had been left untreated (80 vs. 35% in tuberculosis), and the lack of treatment was the independent poor prognostic factor (hazard ratio 5.83; 95% confidence interval 2.10–16.17). In many of the cases, diagnosis of NTM peritonitis was made after death [9]. Diagnosis of MAC peritonitis is even more difficult because it takes a longer time to grow MAC in cultures than RGM. Besides, a higher pathogenicity might explain the poorer prognosis of MAC peritonitis compared with that of other NTMs.

It is generally accepted that dMAC is a hallmark of AIDS, but recently non-AIDS dMAC has been focused on for its unique clinical features. Along with Mendelian susceptibility to mycobacterial diseases (MSMD) [12], anti-IFN-γ autoantibody has been increasingly reported, especially in Asian populations, to explain the pathogenesis of adult-onset dMAC [13, 14]. This anti-cytokine autoantibody has a neutralizing effect on IFN-γ and compromises the lysosomal function of macrophages, the main players in antimycobacterial defense [13, 14]. It is hypothesized that cross-reactivity to *Aspergillus* species is a cause of this autoantibody [15]. However, the etiology in many anti-IFN-γ antibody positive cases has been unexplained.

AITL is a distinct subtype of malignant lymphoma whose origin is a follicular helper T cell. The tumor cells excrete several chemokines or cytokines, and activated B cells, which in turn, cause various immunological abnormalities. For example, polyclonal hypergammaglobulinemia and autoantibodies such as antinuclear antibody, rheumatoid factor, or cold agglutinin are commonly detected in AITL cases [16]. Thus, it is tempting to hypothesize that anti-IFN-γ autoantibody was produced as a part of AITL-related immune dysregulation. We believe this is the first case of MAC peritonitis with anti-IFN-γ antibody positivity. In anti-IFN-γ antibody positive dMAC cases, lymph nodes, lung, bone, liver, spleen, skin, muscle, or central nervous system are commonly involved. However, our case was somewhat different from the typical cases. The severity of immunodeficiency might be one reason. Alternatively, it can be attributed to malignant lymphoma, which is another major cause of chylous ascites [2]. We speculate that AITL not only caused autoantibody production, but also the anatomical damage leading to chylous ascites.

Fortunately, we made a prompt diagnosis when we saw chylous ascites because the patient had already been suffering from dMAC for a year. We restarted antimycobacterial regimen before the culture result returned, and we tried to treat with several approaches, such as administration of (1) rifabutin, (2) aminoglycosides, (3) sitafloxacin, (4) steroid therapy, or (5) rituximab. However, we could not stop the disease progression and the patient died 3 months after the onset of peritonitis. At least, drug resistance of *M. avium* was unlikely to explain the refractory ascites. One of the important questions was how to inhibit the anti-IFN-γ autoantibody, to restore phagocyte function. We selected prednisolone first, because it is a mainstay of treatment in antibody-related autoimmune diseases such as systemic lupus erythematosus, autoimmune hemolytic anemia, or myasthenia gravis. In addition, we expected prednisolone to stop wasting and the inflammatory reaction, or to recover appetite. Later, we made another attempt with rituximab, the anti-CD20 monoclonal antibody. This was an attempt to reduce autoantibody titer as reported [17, 18], but none of the treatments succeeded. In retrospect, it seems that prednisolone therapy was not a reasonable strategy. Corticosteroid might decrease the titers of autoantibody, but at the same time, it would also inhibit cellular immunity, which is essential for defending against mycobacterium infection. Another problem was the anatomical irreversibleness of peritonitis. Even after the disappearance of mycobacterium in cultures, chylous ascites persisted. Because of poor general conditions, we had to give up further treatment, although the anti-IFN-γ autoantibody titer was decreased after rituximab administration. Probably the lymphatic system had been irreversibly destroyed already. In that sense, we should have administered rituximab earlier, or plasmapheresis might have been an option to decrease the autoantibody without immunosuppression.

In conclusion, we encountered a complex of rare diseases: AITL, anti-IFN-γ autoantibody positivity, and *M. avium* peritonitis. The pathogenesis could be explained by the intriguing connection among these immunological abnormalities. We reconfirmed that discontinuation of antimycobacterial therapy should be avoided in anti-IFN-γ autoantibody-positive dMAC cases. In addition, more importantly, treatment strategy should aim to restore, or at least, maintain immunity in the management of dMAC.

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Compliance with ethical standards

Conflict of interest None of the authors has financial relationships with any commercial entity with an interest in the subject of this manuscript.

Ethics approval All the procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient after verbal and written information provision.

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