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Case Report

Disseminated Nontuberculous Mycobacterial Infection in a Patient with Anti-IFN-γ Autoantibodies

Masakuni Tanimizu[a]*, Kenji Mizuno[b], and Masayuki Hashimoto[c]

Department of [a]Internal Medicine, of [b]Surgery, of [c]Radiology,
Tottori Municipal Hospital, Tottori 680-8501, Japan

We treated a 72-year-old Japanese female with sustained high fever and overall body exhaustion. An infectious liver cyst and right lung pneumonia were suspected causes. Hepatic cystectomy and various antibiotics did not resolve symptoms. Pneumonia exacerbation and ascitic fluid retention, left lumbar spinal osteomyelitis, and peri-gastric lymph node abscess penetrating the stomach were observed. Mycobacterium avium was identified in sputum, ascites, vertebral body abscess puncture specimen, and pus mucus secretion in the stomach. We diagnosed a disseminated nontuberculous mycobacterial infection. She seemed immunocompetent, without signs of AIDS or hematological malignancy. Serum anti-IFN-γ autoantibodies tested positive and were suspected to be involved in the illness onset.

Key words: disseminated nontuberculous mycobacterial infection, anti-IFN-γ autoantibodies

The main infection site of nontuberculous mycobacterial infection (NTM) is the lungs, and disseminated NTM infection is rare in general. A disseminated NTM infection is an opportunistic infection accompanied by congenital or acquired immunodeficiency disease such as AIDS, hematological malignancy, or immunosuppressive therapy [1-3]. The presence of serum anti-interferon-gamma (IFN-γ) autoantibodies was recently reported to be involved in the onset of disseminated NTM infection in immunocompetent patients in Asia [3]. Here we report a case of disseminated NTM infection in a patient with anti-IFN-γ autoantibodies.

Case Report

A 72-year-old Japanese female was admitted to our hospital due to sustained high fever and overall body exhaustion. An infectious liver cyst (S2 subarea) and right lung pneumonia were suspected causes. However, hepatic cystectomy and the administration of various antibiotics did not resolve the symptoms. On the contrary, the pneumonia worsened (Fig. 1A), and ascitic fluid retention (Fig. 1B) and left back pain appeared.

A blood biochemical analysis revealed anemia, neutrophil dominant leukocytosis, and a high C-reactive protein (CRP) value. Several bacterial blood and sputum culture tests were negative. Echocardiography did not show vegetations. Acid-fast bacteria were not indicated by sputum smear microscopic observation. Although an ascites puncture test showed an increase in lymphocyte-dominant cells, a bacterial culture examination and mycobacterium tuberculosis polymerase chain reaction (TB-PCR) analysis of ascites were negative. Increased levels of adenosine deaminase (ADA) in ascites were not observed (Table 1).

We were unable to determine the causes of these

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*Corresponding author. Phone: +81-857-37-1522; Fax: +81-857-37-1553
E-mail: masaniku18@hotmail.com (M. Tanimizu)

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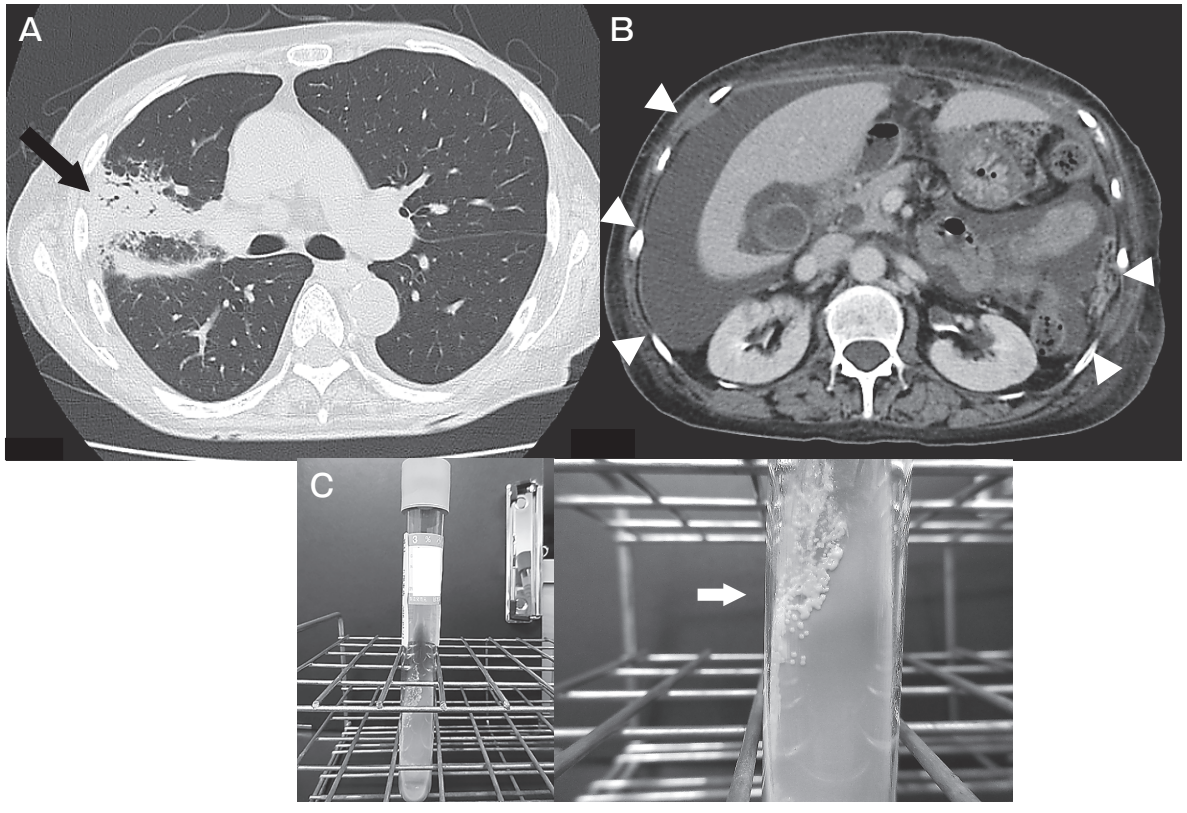

Fig. 1 A, Computed tomography of the chest showed an invasive shadow in the upper right lobe (➡); B, Computed tomography of the abdomen showed ascites after hepatic cyst surgery (▷); C, Cultured acid-fast bacteria at 2 weeks (⇨).

symptoms. One month after the patient's admission, a high titer of serum anti-mycobacterium avium complex (MAC) antibodies was indicated. Mycobacterium avium (M. avium) was identified by cultures of both ascites and sputum at 2 weeks post-cultivation (Fig. 1C). Subsequently, the patient's left lower back pain was diagnosed as purulent spondylitis with bone destruction of the fifth lumbar vertebra (Fig. 2A). M. avium was identified by smear microscopic observation and a MAC-PCR analysis of a specimen obtained by abscess puncture (Fig. 2B).

A computed tomography (CT) scan of the abdomen and esophagogastroduodenoscopy (EGD) indicated that a peri-gastric lymph node abscess had ruptured inside the gastric lumen (Fig. 3A, B). M. avium was also identified in the previous examination from the discharged pus (Fig. 3C). Although both blood and bone marrow culture of mycobacteria were negative, based on these results, disseminated NTM infection was finally diagnosed.

The patient did not have any inherited immune system disorders. Although the patient seemed to be immunocompetent, we considered the possibility of adult-onset immunodeficiency. Tests for viral infections that cause impaired immune function, such as human immune deficiency virus (HIV), human T-cell leukemia virus (HTLV-1) and Epstein Barr virus (EBV), were negative. No steroids or anticancer/anti-cytokine drugs were used. Diabetes and hematological malignancies were not indicated. According to the immunological examination, serum immunoglobulin was within normal levels, and no decrease in lymphocyte or actual CD4 count was observed. The result of a 3rd-generation IFN-γ release assay (IGRA) was indeterminate because the positive control was a very low titer at 0.05 IU/ml. Consequently, we suspected some immune disorders related to IFN-γ as the underlying cause.

A high titer of IFN-γ autoantibodies was detected in the patient's serum at 51,442 AU (IgG type using an in-house enzyme-linked immunosorbent assay). These were recognized as neutralizing antibodies based on our

Table 1 Laboratory data

Blood biochemical test	
WBC	17,800/μl
Ba	0.1%
Eo	3.6%
Nt	84.8%
Ly	7.8%
Mo	3.7%
Hb	9.1 g/dl
PLT	48.0×10^4/μl
AST	15 IU/L
ALT	11 IU/L
LDH	207 IU/L
ALP	486 IU/L
γ-GTP	155 IU/L
BUN	10.8 mg/dl
Cr	0.61 mg/dl
FPG	104 mg/dl
HbA1c (NGSP)	5.8%
CRP	16.4 mg/dl
ESR	111 mm/hour
Ascites	
Rivalta reaction	(+)
Cell count	2,099/m^3
(Nt. : Ly. ratio	3 : 7)
ADA	10.9 U/L
Bacterial culture	(−)
Acid-fast smear	(−)
TB-PCR	(−)
Cytology	(−)
Viral infection	
HCV-RNA	(−)
HBs-antigen	(−)
HIV	(−)
HTLV-1	(−)
IgG-VCA	×80
EBNA	×40
C7-HRP	(−)
β-D-glucan	< 5.0 pg/ml
IGRA	Undecidable
(®QuantiFERON TB-3G)	
Anti-MAC antibody	10.0 U/ml
Immunological test	
IgG	1,250 mg/dl
IgA	320 mg/dl
IgM	95 mg/dl
IgE	92.6 IU/ml
sFLC ratio	0.664
CD4	45.1%
CD8	22.5%
Actual CD4 count	478/μl
IFN-γ autoantibody	51,442 AU
HLA typing	
HLA-DRB1 allele	
allele 1	04 : 05
allele 2	08 : 03
HLA-DQB1 allele	
allele 1	04 : 01
allele 2	06 : 01

observation that the phosphorylation of signal transducer and activator of transcription 1 (STAT1), which is generated as intracellular signaling upon stimulation of a human peripheral blood lymphocytic cell line with IFN-γ, was suppressed by the patient's serum.

Multi-drug combination chemotherapy was initiated with rifabutin (RBT) 300 mg once daily orally, ethambutol hydrochloride (EB) 750 mg once daily orally, clarithromycin (CAM) 800 mg twice daily orally and streptomycin sulfate (SM) 0.5 g 3 times per week intramuscular injection. After the administration, gradual improvement in constitutional symptoms and left back pain, a decrease in ascites, and shrinkage of the shadow on the right lung were observed. As of this writing, recurrence was not reported and this multi-drug combination chemotherapy has been continued for 14 months with careful observation.

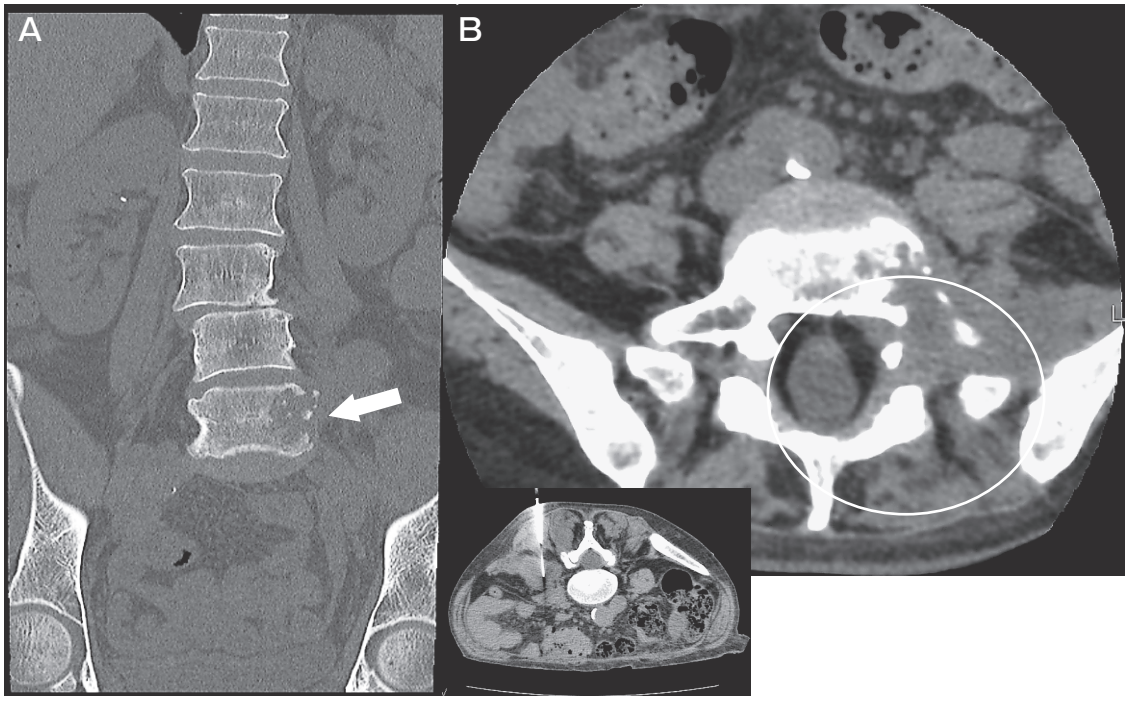

Fig. 2 A, X-ray of the spine showed bone destruction in the left fifth vertebral body (⇨); B, Computed tomography of the abdomen showed abscess in the left fifth vertebral body (○).

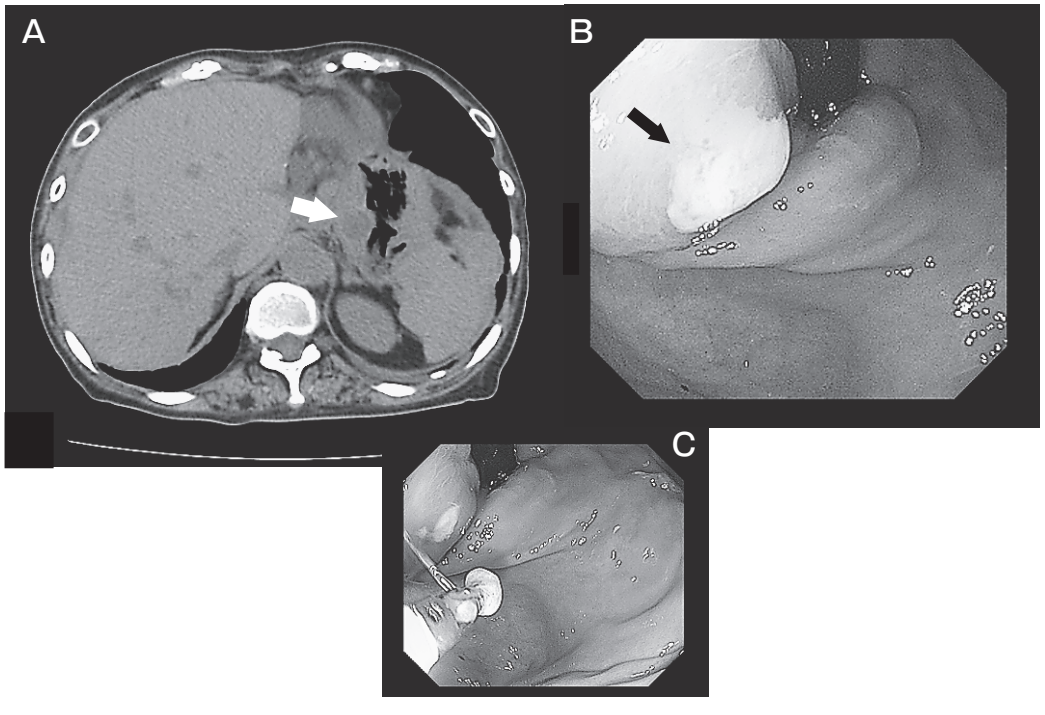

Fig. 3 A, Computed tomography of the abdomen showed peri-gastric lymphadenopathy with low CT value (⇨); B, Lymph node abscess ruptured inside the stomach (➡); C, Pus in the stomach collected using forceps.

Discussion

NTM is an environmental bacterium, and disseminated NTM infection is generally rare. Disseminated NTM infection often develops as an opportunistic infection due to AIDS, immunosuppressive therapy such as steroids, hematological malignancy or congenital immune disorder [1-3]. An increasing number of disseminated NTM infections have recently been reported in Asia, especially strains that produce neutralizing autoantibodies to IFN-γ [3]. Some similar cases have also been reported in Japan [4,5]. In our patient's case, adult-onset immunodeficiency was not indicated from her medical history and various immunological tests. Since the IGRA result was undecidable, we suspected some underlying disorders in the interleukin (IL)-12/IFN-γ pathway, which is an important defense mechanism against acid-fast bacterial infections [2,6]. A high titer of autoantibodies to IFN-γ was detected in our patient's blood, and was also shown have a neutralizing effect. As a result, this is considered to be involved in the onset of the patient's disseminated NTM infection.

Florent *et al.* summarized the characteristics of 64 patients with anti IFN-γ autoantibody-related NTM infection [7]. In their report, the median age was 48 years old, and Asian-born patients and female gender predominated. M. avium is the most common species that causes disseminated NTM infection, but other species of mycobacteria such as M. abscessus, a rapid-growing NTM, have been reported as causes of this condition. Also, according to the Florent *et al.* report, infectious sites of high frequency were lymph node and lung, bone and/or joint. Other opportunistic infections, especially reactivation of herpes and salmonella infections, have often been observed in disseminated NTM infections in patients with anti-IFN-γ autoantibodies [7,8].

Our patient was a Japanese woman, older than the median age in the Florent *et al.* report. The etiological agent was M. avium, one of the most frequent species of mycobacteria. In our patient's case, the disseminated NTM infection was diagnosed by isolating M. avium from sputum, ascites, an abscess in a lumbar vertebra and pus in the gastric lumen from a peri-gastric lymph node. The isolation of M. avium from the peritoneum is relatively rare. The reported opportunistic infections were not observed in our patient (Table 2).

Table 2 Summary of our case

SEX	Women
Age	72 years old
Infectious site	Sputum Ascites, Abscess in the lumbar vertebrae Peri-gastric lymph node
Etiological agents	Mycobacterium avium
Other opportunistic infections	
Herpesviridae reactivation	Not observed
Salmonella spp.	Not observed
Two HLA alleles that is presumed to be related to the onset	
HLA-DRB1*16 : 02	Not Detected
HLA-DQB1*05 : 02	Not Detected

The question of why many more cases of disseminated NTM with anti-IFN-γ autoantibodies are reported in Asians compared to Caucasians has not been answered. Chin *et al.* reported that HLA-DRB1* 16: 02 and HLA-DQB1* 05: 02 are associated with disseminated NTM infection with anti-IFN-γ autoantibodies expression in Asians [8]. According to their report, aspects of a patient's genetic background such as race may be a factor in the onset of illness.

In our patient, an HLA test was also performed with informed consent, but recognized types of HLA were not detected (Table 2). Treatment for disseminated NTM infection with anti-IFN-γ autoantibodies has not been standardized. Conventionally, prolonged multidrug regimens are implemented. Florent *et al.* reported that among patients with a long-term administration of a multi-drug regimen, approx. 37.5% of the cases resulted in recovery, 10.7% were fatal, and over 51.8% were resistant or recurrent [7]. Consequently, in addition to anti-infection treatment, other strategies including IFN-γ replacement therapy [9,10] and intravenous immunoglobulin (IVIG) [11], and the combined use of plasmapheresis and cyclophosphamide [12] have been implemented. However, the efficacy has been inconclusive.

In recent years, an improvement in refractory patients with high titers of anti-IFN-γ autoantibodies by rituximab administration has been reported; not only did clinical symptoms improve but the serum anti-IFN-γ autoantibodies titer also decreased along with its neutralizing activity [13]. This treatment is considered

to be effective, and further findings to support this are expected.

In our patient's case, a favorable clinical course could be obtained by anti-infection treatment. However, serum anti-IFN-γ autoantibodies titers have been reported to remain high for a long time even when infection control was obtained [13]. A careful follow-up of the transitional course is needed.

In conclusion, we treated a patient with disseminated NTM (M. avium) infection with anti-IFN-γ autoantibodies. When the presence of a disseminated NTM infection is detected in an immunocompetent patient, the presence of serum anti-IFN-γ autoantibodies should be considered.

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