

[ CASE REPORT ]

## Anti-interferon- $\gamma$ Antibody-seropositive Disseminated Nontuberculous Mycobacterial Infection Mimicking POEMS and TAFRO Syndromes

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### Abstract:

Disseminated nontuberculous mycobacterial infection (DNTM) is typically observed in immunocompromised hosts. Recently, it has been reported that healthy individuals with serum neutralizing autoantibodies for interferon (IFN)- $\gamma$  can also develop DNTM. We herein report a case of anti-IFN- $\gamma$  antibody-seropositive DNTM caused by *Mycobacterium kansasii* with symptoms mimicking TAFRO or POEMS syndrome, including anasarca, organomegaly, skin pigmentation, polyneuropathy, osteosclerotic change, thrombocytopenia, serum M protein, high C-reactive protein level, and reticulin fibrosis. The combination of antimicrobial chemotherapy with glucocorticoid and intravenous immunoglobulin improved his symptoms. Glucocorticoids may be an effective method of suppressing the production of anti-IFN- $\gamma$  antibodies in DNTM.

**Key words:** disseminated nontuberculous mycobacterial infection, anti-interferon- $\gamma$  antibody, *Mycobacterium kansasii*, TAFRO syndrome, POEMS syndrome

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### Introduction

Disseminated nontuberculous mycobacterial infection (DNTM) is observed in immunocompromised hosts, including patients with acquired immunodeficiency syndrome (AIDS), malignancies, diabetes mellitus, and congenital immunodeficiency diseases and those receiving immunosuppressive therapy. Because it is very rare for a healthy person to develop DNTM, this condition is not often considered as a differential diagnosis in patients without underlying diseases. Recently, however, it was reported that neutralizing autoantibodies for interferon (IFN)- $\gamma$  are commonly detected in the sera of DNTM patients who are otherwise healthy (1).

TAFRO syndrome and POEMS syndrome are rare sys-

temic diseases of unknown cause with elevated serum levels of vascular endothelial growth factor (VEGF) and interleukin (IL)-6 (2, 3). These two syndromes are often difficult to distinguish because they are accompanied by similar symptoms, including systemic edema, pleural effusion, ascites, renal damage, and lymphadenopathy with Castleman's disease-like histopathological findings (4). These symptoms can occur in a variety of diseases, including malignant tumors, collagen diseases, and infectious diseases. Immunosuppressive therapy, including glucocorticoids, is administered for these syndromes, and it is important to rule out the possibility of infectious diseases.

We herein report a case of a previously healthy patient with anti-IFN- $\gamma$  autoantibody-seropositive DNTM caused by *Mycobacterium kansasii* who presented with clinical features

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that mimicked TAFRO syndrome and POEMS syndrome and were improved by the combination of antimicrobial chemotherapy with glucocorticoids and intravenous immunoglobulin.

## Case Report

A 64-year-old Japanese man was transferred to our hospital because of polyarthralgia and multiple cellulitis. Six months before hospitalization, he had visited a neighborhood hospital because of elevated hepatobiliary enzyme levels. Although he did not have any abdominal symptoms at that time, the serum levels of  $\gamma$ -GTP and alkaline phosphatase (ALP) were high (217 U/L and 1,052 U/L, respectively). The serum C-reactive protein (CRP) level was also elevated to 12.32 mg/dL. Computed tomography (CT) revealed consolidation in the inferior lobe of the left lung, hepatosplenomegaly, and multiple lymphadenopathies. Biopsies were performed in the cervical lymph nodes, liver, and lungs, but only nonspecific infiltration of inflammatory cells was observed. He was treated with 20 mg prednisolone (PSL) for suspected systemic autoimmune disease. Four months later, he noticed swelling on the dorsal skin of the left hand and was treated with antibiotics for the diagnosis of cellulitis at another hospital. He was also suspected of having hepatobiliary disease because of the elevated hepatobiliary enzyme level, leukocytosis [white blood cell (WBC) count 24,000/ $\mu$ L], and high serum CRP level (16.55 mg/dL), but there were no findings suggesting infection or tumor in his gallbladder. Although high serum levels of soluble IL-2 receptor (13,400 U/mL) and multiple lymphadenopathies were observed, there were no findings of malignancy in the cervical lymph node biopsy.

On admission to our department, physical examination revealed significant tabescence, skin pigmentation, and edema of the lower extremities. He also had swelling of the axillary lymph nodes and knee joint pain. He had no abdominal symptoms or numbness. His blood pressure was 112/66 mmHg, pulse was 98/min, temperature was 36.4°C, and O<sub>2</sub> saturation was 96% on ambient air.

Laboratory data revealed increased levels of serum CRP, erythrocyte sedimentation rate, WBCs (especially neutrophils), and elevated ALP and soluble IL-2 receptor levels (Table 1). He had anemia, but his mean corpuscular volume and haptoglobin levels were within the respective normal ranges. Total protein and albumin levels were low, his renal function was normal, and the brain natriuretic peptide level was slightly increased. Serum M protein (IgG- $\lambda$  type Bence Jones protein) was also detected. We also examined the possibility of infectious diseases, including hepatitis B, hepatitis C, Epstein-Barr virus, HIV, human T-cell leukemia virus type 1, and tuberculosis, but all were negative.

Chest radiography showed a reticular shadow on both lower lungs and the right costophrenic angle was slightly dull. Electrocardiography findings were normal. Chest and abdominal CT revealed pleural effusion and ascites; hepa-

tosplenomegaly; paraaortic and pelvic lymphadenopathy; and osteosclerotic and osteolytic changes in the spine, ribs, and pelvis (Fig. 1a, b, c). A bone marrow biopsy showed an increase in reticulum fibers, appearance of collagen fibers, myeloid-rich hypercellular marrow with a variety of cells, and no monoclonal proliferation of plasma cells. The number and size of the bone marrow megakaryocytes did not increase remarkably. The bone marrow biopsy did not reveal any acid-fast bacilli and did not show any granulomatous formations. Because he also had hypesthesia in his lower extremities, we performed a nerve conduction velocity study, which revealed polyneuropathy.

Based on these findings, we suspected TAFRO syndrome due to anasarca (pleural effusion, ascites, and edema), thrombocytopenia, high CRP levels, reticulin fibrosis in the bone marrow, and organomegaly (hepatosplenomegaly and lymphadenopathy). However, findings of M protein, skin and bone lesions, and polyneuropathy are not consistent with TAFRO syndrome. A lymph node biopsy from the cervical region indicated lymphocyte infiltration and fibrosis in the lymph nodes, but there were no Castleman disease-like findings. Another differential diagnosis was POEMS syndrome due to his polyneuropathy, serum M protein (IgG- $\lambda$  type), osteosclerotic changes, organomegaly, fluid retention, and skin pigmentation. However, the serum VEGF levels were not markedly elevated (823 pg/mL), and there were no endocrine abnormalities. The osteolytic changes were also not consistent with POEMS syndrome. Given that the use of glucocorticoids might modify the condition, we tapered the PSL dose (Fig. 2).

On day 36, subcutaneous masses appeared on his left hand and thigh, and ulcers appeared on the left elbow, right finger, and middle toe. Skin biopsies revealed that the masses were due to subcutaneous abscess formation. Ziehl-Neelsen staining of the abscess revealed acid-fast bacilli. We also performed Ziehl-Neelsen staining of sputum and bile smears, and both samples were positive. Polymerase chain reaction of the sputum was negative for *Mycobacterium tuberculosis*, *M. avium*, and *M. intracellulare*. Due to suspected nontuberculous mycobacterial infection, we further tapered the PSL dose to 5 mg/day. Since the identification of the bacterial species was necessary for the selection of the treatment regimen, he was temporarily transferred to the previous hospital for rehabilitation on day 53 until the bacterial species were identified by the various cultures submitted.

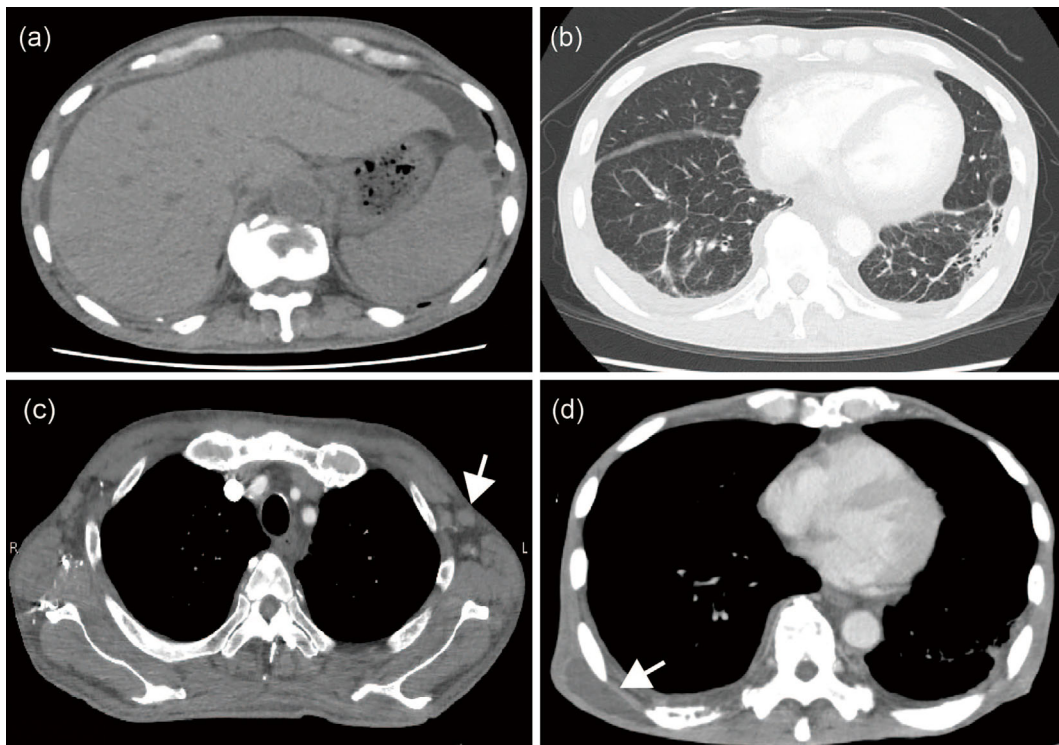
Ultimately, *M. kansasii* was identified from cultures of both gastric juice and subcutaneous abscesses using the DNA-DNA hybridization method. Susceptibility testing using the broth microdilution method (BrothMIC NTM; Kyokuto, Tokyo, Japan) revealed that the minimum inhibitory concentrations for the drugs were as follows: rifampicin, 0.125  $\mu$ g/mL; levofloxacin, 0.25  $\mu$ g/mL; clarithromycin, 0.125  $\mu$ g/mL; and ethambutol, 1  $\mu$ g/mL.

We diagnosed the patient with DNTM caused by *M. kansasii*. On day 140, the patient was transferred to our hospital

**Table 1. Laboratory Data on Admission.**

Variable	Reference range	On admission
Erythrocyte count ( $\times 10^4/\text{mm}^3$ )	414-534	307
Hemoglobin (g/dL)	13.8-17.2	9.2
Mean corpuscular volume (fL)	83-100	92.4
White blood cell count (/mm <sup>3</sup> )	3,300-9,400	20,800
White blood cell differential count (%)		
Neutrophils	37.5-66.0	88.5
Lymphocytes	19.5-47.0	4.5
Monocytes	2.2-10.4	6.0
Eosinophils	0-6.0	0.0
Basophils	0-1.8	0.0
Platelet count ( $\times 10^4/\text{mm}^3$ )	18.0-39.0	15.8
Erythrocyte sedimentation rate (mm/h)	2-10	74
PT (INR)	0.87-1.15	1.21
Activated partial thromboplastin time (s)	25.0-35.0	27
Fibrinogen (mg/dL)	186-385	444
FDP D-dimer ( $\mu\text{g/mL}$ )	0.0-0.7	5.27
Creatinine (mg/dL)	0.68-1.04	0.56
Urea nitrogen (mg/dL)	8-20	14
Creatine kinase (U/L)	64-255	6
Aspartate aminotransferase (U/L)	14-32	10
Alanine aminotransferase (U/L)	11-45	8
$\gamma$ -glutamyl transpeptidase (U/L)	10-58	129
Alkaline phosphatase (U/L)	112-334	875
Lactate dehydrogenase (IU/L)	125-225	101
Total bilirubin (mg/dL)	0.4-1.5	1.5
Sodium (mEq/L)	138-144	140
Potassium (mEq/L)	3.7-5.0	3.3
Chloride (mEq/L)	100-108	101
C-reactive protein (mg/dL)	0.0-0.20	8.77
Total protein (g/dL)	6.1	6.9-8.3
Albumin (g/dL)	4.1-5.1	2.3
HbA1c (%)	4.6-6.2	4.6
Serum ferritin (ng/mL)	25-280	302
Procalcitonin (ng/mL)	0.0-0.05	0.57
Soluble interleukin-2 receptor (U/mL)	145-519	5,369
ACE (U/L)	7.0-25	7.7
BNP (pg/mL)	0.0-18.4	110.8
Haptoglobin (mg/dL)	19-170	174
IgG (mg/dL)	870-1,700	1,666
IgA (mg/dL)	110-410	319
IgM (mg/dL)	33-190	113
IgG4 (mg/dL)	4.5-117	<2.0
C3 (mg/dL)	70-129	153
C4 (mg/dL)	12-36	25
Antinuclear antibody (n times)	0-40	<40
Rheumatoid factor (IU/mL)	0.0-15	329.8
MPO-ANCA (U/mL)	0-3.5	<1.0
PR3-ANCA (U/mL)	0-3.5	<1.0
ASO (IU/mL)	0.0-239	57
HTLV-I/II antibody	Negative	Negative
$\beta$ -D-glucan (pg/mL)	0.0-11	<6.0
T-SPOT	Negative	Negative
Nil (negative control)	$\leq 10$	0
ESAT-6	$\leq 5$	0
CFP10	$\leq 5$	0
Mitogen (positive control)	$\geq 20$	588
HIV antigen antibody testing	Negative	Negative
Urinalysis		
Uric protein	(-)	(1+)
Uric blood	(-)	( $\pm$ )
Urinary sediment		
Red cells (/HPF)	0-4	1-4
White cells (/HPF)	0-4	$\geq 50$
Albumin creatinine ratio (g/gCr)		0.20
Non-acid-fast bacteria culture		
Blood	Negative	Negative
Urine	Negative	Negative
Sputum	Negative	Negative
Subcutaneous abscess	Negative	Negative
Acid-fast bacteria culture		
Blood	Negative	Negative
Gastric juice	Negative	<i>Mycobacterium kansasii</i>
Subcutaneous abscess	Negative	<i>Mycobacterium kansasii</i>

PT: prothrombin time, INR: international normalized ratio, FDP: fibrin degradation products, HbA1c: hemoglobin A1c, ACE: angiotensin-converting enzyme, BNP: brain natriuretic peptide, Ig: immunoglobulin, MPO: myeloperoxidase, ANCA: antineutrophil cytoplasmic antibodies, ASO: antistreptolysin O, HTLV: human T-cell leukemia-lymphoma virus, HPF: high-power field



**Figure 1.** Axial contrast-enhanced computed tomography images. Hepatosplenomegaly and ascites (a) were observed on computed tomography (CT) three days before transfer to our hospital. Contrast-enhanced CT revealed consolidation in the lower lobe of the left lung (b) and multiple lymphadenopathies (c; arrow) at day 7 in our hospital. Many subcutaneous abscesses were observed in the CT images at approximately day 140 (d; arrow).

and treated with rifampicin [450 mg/day orally (p.o.)], clarithromycin (800 mg/day p.o.), and ethambutol (750 mg/day p.o.) (Fig. 2). He had scattered subcutaneous masses and osteolytic changes (Fig. 3, 4). Since his general condition temporarily worsened afterwards, we changed the treatment regimen to rifampicin combined with isoniazid (300 mg/day p.o.) and ethambutol.

In parallel, we investigated whether or not the patient had an immunodeficiency source that would cause DNTM. The serum IFN- $\gamma$  concentration was measured by an enzyme immunoassay and found to be below the detection limit ( $\leq 0.1$  IU/mL). Because the positive control antigen generated many IFN- $\gamma$ -producing T cells, we suspected the existence of a neutralizing antibody for IFN- $\gamma$  in his sera. An enzyme-linked immunosorbent assay revealed elevated anti-IFN- $\gamma$  antibody serum levels (308.7 E.U.; 5-50 for healthy control), and the phosphorylation index of signal transducer and activator of transcription 1 (STAT1), an IFN- $\gamma$  signaling downstream transcription factor, was suppressed (44.77;  $>200$  for healthy controls). These results suggest that the presence of serum anti-IFN- $\gamma$  neutralizing antibodies can exacerbate DNTM.

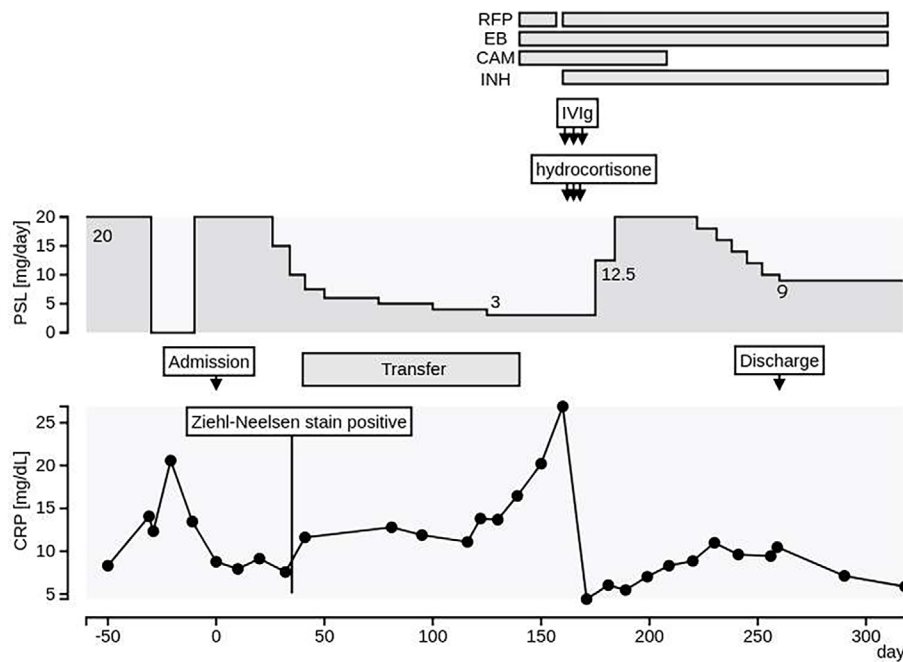
On day 163, he showed impaired consciousness and hypoglycemia, and adrenal insufficiency was suspected. After we administered 200 mg/day of intravenous hydrocortisone for 3 days, his condition improved. Following this, we increased the oral PSL dose to 20 mg/day in addition to ad-

ministering antibacterial chemotherapy to suppress anti-IFN- $\gamma$  autoantibody production (Fig. 2). We also added intravenous immunoglobulin (5 g/day) for the treatment of DNTM on days 160-162. His disease condition, including arthralgia and subcutaneous abscess, gradually improved. Blood tests also revealed a gradual improvement in the serum levels of CRP and liver enzymes. The serum IFN- $\gamma$  level became detectable (0.2 IU/mL) on day 210, and the anti-IFN- $\gamma$  antibody level showed a decreasing trend (190.53 E.U.). On day 260, the patient was discharged with a successfully tapered PSL dose (9 mg/day). Antibiotic therapy, including isoniazid, rifampicin, and ethambutol, was continued for 2 years, and the PSL dose was further tapered to 5 mg/day. There was no apparent sign of infection resurgence after two years of antibiotic therapy.

## Discussion

Nontuberculous mycobacteria are widely present in the environment, such as in the soil and water. Aerosols from the environment cause transrespiratory tract infections as immunity weakens. Nontuberculous mycobacteria typically produce local lesions mainly in the bronchi and lungs. In rare cases, nontuberculous mycobacteria can be hematogenously disseminated and form lesions in multiple organs, such as DNTM.

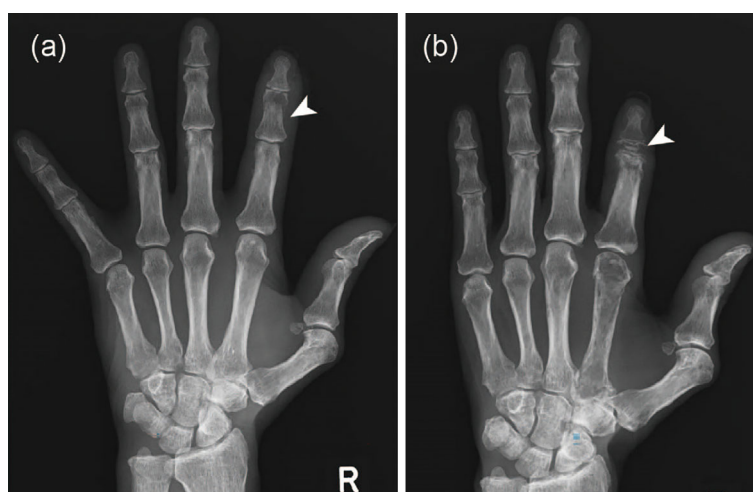
DNTM is typically observed in patients with immunodeficiency.



**Figure 2.** The patient's clinical course. After he was transferred to our hospital, the prednisolone (PSL) dose was gradually tapered. He was temporarily transferred to the previous hospital until the NTM species were identified (days 53-139). With the identification of *M. kansasii*, we re-transferred him to our hospital and started treatment with rifampicin (RFP), clarithromycin (CAM), and ethambutol (EB) on day 140. Since his general condition temporarily worsened, we added isoniazid (INH) to the treatment regimen. From day 163, we administered 200 mg/day of intravenous hydrocortisone for 3 days because of suspected adrenal insufficiency, followed by an increase in the oral PSL dose to 20 mg/day to suppress anti-interferon (IFN)- $\gamma$  autoantibody production. We also added intravenous immunoglobulin for the treatment of disseminated nontuberculous mycobacterial infection (DNTM) on days 160-162. On day 260, the patient was discharged with a successfully tapered PSL dose.



**Figure 3.** Multiple subcutaneous abscesses. Many subcutaneous masses were observed on the right anterior chest (a), right back (b), and right neck (c) at approximately day 140. Puncture of the subcutaneous mass on the right back revealed the presence of purulent fluid (d).



**Figure 4.** Osteolytic changes in the second middle phalanx of the right hand. On comparing hand X-ray images obtained on days 26 (a) and 182 (b), a diffuse reduction in bone density was noted. Osteolytic changes were observed in the second middle phalanx of the right hand, and the second finger was shortened (arrow).

ciency, such as AIDS, hematological malignancies, and congenital immunodeficiency diseases, and those using immunosuppressants (5). In this case, the patient had no underlying disease and no history of immunosuppressive drug use. It has been reported that anti-IFN- $\gamma$  neutralizing autoantibodies are often found in DNTM without underlying diseases (6). In recent years, an increasing number of case reports regarding anti-IFN- $\gamma$  antibody-positive DNTM have been published. Table 2 shows cases of anti-IFN- $\gamma$  antibody-positive DNTM reported from Japan. As in the present case, most of them have clinical characteristics of disseminated lesions, mainly in the bone and soft tissues.

IFN- $\gamma$  is an important cytokine in the host defense system against mycobacteria, and IFN- $\gamma$  deficiency increases the risk of mycobacteriosis. Regarding laboratory tests suggesting the presence of anti-IFN- $\gamma$  antibody, a discrepancy has been reported between the results of T SPOT-TB (T-SPOT) and QuantiFERON TB-3 G (QFT-3 G), both of which are IFN- $\gamma$  release assays (IGRA) (7). Since whole blood is used in QFT-3 G, the positive control becomes less sensitive in the presence of neutralizing antibodies; in addition, there is a discrepancy with regard to the results of T-SPOT using purified lymphocytes. It is possible that there was a discrepancy between the results of QFT-3 G and T-SPOT in this case as well, but we did not measure QFT-3 G because this evaluation is not performed daily at our hospital. As serum anti-IFN- $\gamma$  neutralizing antibodies were detected in this case, we concluded that deficiency in IFN- $\gamma$ -dependent cell-mediated immunity was the main cause of DNTM. Attenuation of the action of IFN- $\gamma$  by the anti-IFN- $\gamma$  antibodies also reduces the production of IL-12, which further reduces the production of IFN- $\gamma$ . Therefore, it is quite possible that the serum IL-12 levels were low in this case. In fact, severe NTM cases with mutations in genes involved in the IL-12/IFN- $\gamma$  pathway, such as *IL-12B*, *IL-12RB1*, *IFNGR1*, *STAT1*, and *IRF8*, have been reported (8). In this case, we did not

search for abnormalities in these genes, as anti-IFN- $\gamma$  antibodies were detected and there was no notable history of infectious diseases until later in life.

No consensus concerning the optimal treatment strategy for DNTM with anti-IFN- $\gamma$  antibodies has yet been reached. While some patients respond to conventional multidrug antibacterial chemotherapy, others are resistant. Treatment strategies that suppress autoantibody production have been attempted in intractable cases. There are some reports that immunoglobulin therapy, plasma exchange with cyclophosphamide, and rituximab, which target the reduction of antibody production by B cell suppression, were effective (9-11). In this case, PSL was started because the previous clinician suspected systemic autoimmune disease. In the process, IFN- $\gamma$  was measured multiple times, and positive conversion of IFN- $\gamma$  was observed after the oral PSL dose was increased to 20 mg/day, remaining positive even after glucocorticoid reduction. Whether or not this was related to disease activity is unclear, but the titer of anti-IFN- $\gamma$  neutralizing antibody decreased after increasing the glucocorticoid dose. We tapered glucocorticoids due to the risks of complications, including other opportunistic infections and osteoporosis progression, although we considered that it might suppress the production of anti-IFN- $\gamma$  neutralizing antibodies. Thus far, there have been no reports concerning the efficacy of glucocorticoids for anti-IFN- $\gamma$  neutralizing antibody-positive DNTM, and the further accumulation and analyses of such cases are expected in future studies.

In this case, *M. kansasii* was detected in the gastric juice and subcutaneous tissue. *M. kansasii* accounts for approximately 4% of nontuberculous mycobacterial disease cases in Japan (12). Many of the patients affected by *M. kansasii* are middle-aged, and some background diseases, such as chronic obstructive lung disease and malignancy, are reported as risk factors (13). Aoki et al. reported that there were many cases of seropositivity for anti-IFN- $\gamma$  neutralizing

**Table 2. Case Reports of DNTM Seropositive for Anti-IFN- $\gamma$  Antibodies from Japan.**

Case	Age (years)/ Sex	Underlying condition	Strain	Symptom/Findings	Treatment	Outcome	Reference
1	53/M	Unknown	<i>M. kansasii</i>	Dyspnea, anemia, mediastinal lymphadenopathy	RFP/EB/INH	Died	(22)
2	66/M	Hepatitis C	<i>M. avium</i> complex	Fever, back pain, joint pain, myalgia, lung lesion, mediastinal lymphadenopathy	RFP/EB/CAM/LVFX+drainage	Improved	(23)
3	74/W	None	<i>M. fortuitum</i>	Fever, cough, lung lesion, cervical lymphadenopathy	IPM/CS+AMK $\rightarrow$ LVFX/CAM	Improved	(24)
4	65/M	Unknown	<i>M. gordonae</i> / <i>M. manteni</i>	Fever, weight loss, cervical lymphadenopathy, lung lesion, bone lesion	RFP/EB/CAM	Improved	(25)
5	67/W	Diabetes mellitus	<i>M. avium</i> complex	Fever, weight loss, lumbago, hepatosplenomegaly, edema, osteolytic lesion	RFP/EB/CAM/STFX+RTX	Improved	(26)
6	79/W	None	<i>M. phlei</i>	Chest pain, erythema, multiple lymphadenopathy, osteolytic lesion, hepatosplenomegaly	RFP/EB/CAM/LVFX	Improved	(27)
7	74/W	Unknown	<i>M. avium</i>	Lymphadenopathy, abscess	RFP/EB/CAM	Improved	(28)
8	33/M	None	<i>M. kansasii</i>	Fever, cough, multiple lymphadenopathy, pericardial effusion, pleural effusion	RFP/EB/INH/PZA	Improved	(29)
9	68/M	None	<i>M. avium</i>	Fever, weight loss, lung lesion, osteolytic lesion, hepatosplenomegaly, ascites, intraperitoneal lymphadenopathy	RFP/EB/CAM/SM $\rightarrow$ add STFX	Improved	(30)
10	65/M	None	<i>M. avium</i>	Erythema, weight loss, numbness, multiple lymphadenopathy, osteolytic lesion, abscess	RFP/EB/CAM $\rightarrow$ CAM/RBT/EB/SM +IFN- $\gamma$ s.c.	Improved	(31)
11	78/M	Cervical spondylosis, hypertension	<i>M. abium</i>	Fever, weight loss, multiple lymphadenopathy, lung lesion, osteolytic lesion, pleural effusion	RFP/EB/CAM/SM	Improved	(32)
12	49/W	None	<i>M. abscessus</i>	Fever, multiple lymphadenopathy, bone lesion	MEPM/AMK/CAM	Improved	(33)
13	72/M	Hypertension hyperuricemia, ossification of cervical posterior longitudinal ligament	<i>M. abium</i>	Fever, abdominal pain, renal swelling, osteolytic lesion, lung lesion	RFP/CAM+ Glucocorticoid	Died	(34)
14	64/M	None	<i>M. kansasii</i>	Fever, polyarthralgia, multiple cellulitis, pleural effusion, ascites, hepatosplenomegaly, multiple lymphadenopathy, osteolytic lesion	RFP/EB/CAM $\rightarrow$ RFP/EB/CAM/INH +Glucocorticoid/IVIg	Improved	-

Case 14 is our case.

RFP: rifampicin, EB: ethambutol, INH: isoniazid, CAM: clarithromycin, LVFX: levofloxacin, IPM/CS: imipenem/cilastatin, AMK: amikacin, STFX: sitafloxacin, RTX: rituximab, PZA: pyrazinamide, SM: streptomycin, RBT: rifabutin, IFN- $\gamma$  s.c.: interferon-gamma subcutaneous injection, MEPM: meropenem, M: man, W: woman

antibodies in DNTM in Japan, the majority of which were caused by *M. avium* complex (70.3%), and only 1 of 31 cases was caused by *M. kansasii* (2.7%) (14). While skin lesions caused by *M. kansasii* are prone to manifest as raised lesions and ulcers in immune-responsive patients, there are reports of diffuse cellulitis and seroma in immunocompromised patients (15, 16). In the current case, the skin lesions showed cellulitis and abscesses with a highly viscous milky white fluid, similar to those of immunocompromised

patients with DNTM. The standard treatment regimen for *M. kansasii* DNTM is the same as that for *M. kansasii* pulmonary infection, which includes isoniazid (300 mg/day), rifampicin (600 mg/day), and ethambutol (15 mg/kg/day), according to the official statement of the American Thoracic Society and Infectious Diseases Society of America (13). However, several reports have shown the effectiveness of treatment with rifampicin, ethambutol, and clarithromycin for *M. kansasii* infection (17, 18). Although we started treat-

ment with these three drugs, we changed the regimen to rifampicin, ethambutol, and isoniazid as recommended by the American Thoracic Society and Infectious Diseases Society of America as the patient's general condition worsened. It is recommended that the duration of treatment of DNTM with *M. kansasii* be the same as that of DNTM with *M. avium* complex and that lifelong treatment be considered in DNTM with *M. avium* complex unless immune recovery is achieved. Even in the current case, in which the symptoms and laboratory findings improved considerably during hospitalization, treatment for DNTM will be continued for an extended period in the outpatient clinic.

This case initially showed liver damage and an increased inflammatory response and subsequently developed systemic symptoms including pulmonary lesions, lymphadenopathy, skin lesions, hepatosplenomegaly, and joint pain. Based on these findings, we suspected POEMS syndrome or TAFRO syndrome. The symptoms, such as fever, thrombocytopenia, pleural and ascitic fluid retention, and reticulin fibrosis of the bone marrow, met the Ministry of Health, Labor and Welfare, Japan diagnostic criteria for TAFRO syndrome (19). In general, however, hepatosplenomegaly and lymphadenopathy are often mild, and M protein is not observed in TAFRO syndrome. Progressive renal dysfunction, which is described as a minor criterion, was not observed in this case. Furthermore, we noted no pathological lymph node findings suggestive of TAFRO syndrome similar to the mixed type (mixture of vitreous vascular type and plasma cell type) of multicentric Castleman's disease in this case (3, 19, 20). One case report has described a DNTM case in which manifestations confusingly met the diagnostic criteria of TAFRO syndrome (21). In that case, the causative organism was *M. genavence*. The manifestations were similar to those in our case, including multiple lymphadenopathies, thrombocytopenia, hepatosplenomegaly, fluid retention, and fibrosis of the bone marrow. Although the authors did not measure the serum anti-IFN- $\gamma$  antibodies, they suspected the presence of anti-IFN- $\gamma$  antibodies because the positive control of QuantiFERON TB was negative. In common with our case, a high serum level of ALP, which is one of the important findings of DNTM (13), was also observed. In our case, the serum ALP level showed a persistently high level from the patient's first visit to the previous hospital. It is highly possible that DNTM was the main cause of the elevation of the ALP level. Because elevated serum ALP levels are seen in TAFRO syndrome, DNTM is important as a differential diagnosis when TAFRO syndrome is suspected. Indeed, the Ministry of Health, Labor and Welfare diagnostic criteria for TAFRO syndrome include mycobacteriosis as a differential diagnosis (19). POEMS syndrome was also suspected based on the M protein and multiple neuropathies in this case. Castleman's disease-like findings were observed on a lymph node biopsy, similar to TAFRO syndrome. Furthermore, the results of the bone marrow biopsy showed no neoplastic growth of plasma cells, and the serum VEGF levels increased only mildly and did not meet the diagnostic

criteria for POEMS syndrome.

In conclusion, we encountered a case of DNTM positive for anti-IFN- $\gamma$  neutralizing antibodies mimicking TAFRO and POEMS syndromes. Since patients with DNTM have various systemic symptoms, it is important to distinguish this condition from systemic autoimmune diseases by a detailed examination. As the combination of antimicrobial chemotherapy with glucocorticoid and intravenous immunoglobulin improved the symptoms in this case, glucocorticoids may be an effective method of suppressing the production of anti-IFN- $\gamma$  antibodies in DNTM. Since the treatment strategy for anti-IFN- $\gamma$  neutralizing antibody-positive DNTM has not yet been clearly defined, the further accumulation of such cases and the establishment of an optimal treatment strategy will be important in future studies.

Written informed consent for publication was obtained from the patient.

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

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