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Case Report

Disseminated *Mycobacterium genavense* infection mimicking TAFRO syndrome

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ABSTRACT

TAFRO syndrome is a rare variant of idiopathic multicentric Castleman's disease, for which disseminated non-tuberculous mycobacteria (NTM) infection must be excluded. However, due to the slow and fastidious growth of the organisms, identification of the pathogen is often challenging. We herein describe a case of disseminated *Mycobacterium genavence* infection, in which manifestations of the patient were confusingly similar to those of TAFRO syndrome. A 69-year-old Japanese man presented with prolonged fever accompanying pain in his back and ribs on the right side. Systemic investigations revealed thrombocytopenia, marked elevation of alkaline phosphatase, anasarca (pleural effusion and ascites), megakaryocytosis in the bone marrow, and hepatomegaly. Magnetic resonance imaging (MRI) showed diffuse, T1-and T2-low-intensity spotted lesions on his vertebral bodies, but biopsy showed inconclusive results. The patient met the diagnostic criteria of TAFRO syndrome and was started on prednisolone, which improved his general condition shortly thereafter. Blood culture after 42 days of incubation revealed the presence of *Mycobacterium*; however, we considered it a contamination at that time because no organisms grew on conventional agars, and the patient was discharged. Ten weeks after the isolation of *Mycobacterium*, he developed persistent fever and was readmitted. This time, vertebral bone mallow biopsy demonstrated a large amount of mycobacterium, which was later successfully identified as *M. genavense* by sequencing analysis. Under a final diagnosis of disseminated *M. genavense* infection, we treated the patient with clarithromycin, rifampicin, and ethambutol. This case highlighted that disseminated NTM infection may follow a similar clinical course as that of TAFRO syndrome.

1. Introduction

Mycobacterium genavense is one of the non-tuberculous mycobacteria (NTM) classified as an Runyon III slow-growing organism. Since its first isolation from a patient with human immunodeficiency virus (HIV) in 1992 [1], the organism has been reported to cause disseminated infections in severely immunocompromised patients [2,3]. Identification of the fastidious bacterium is generally challenging because it does not grow on solid media commonly used in mycobacterium culture. Recent advances in diagnostic techniques, however, have uncovered that *M. genavense* can cause infection in various organs including the lungs [4], spleen [5], and intracranial regions [6] and may cause aneurysms [7].

TAFRO syndrome is an emerging variant of idiopathic multicentric Castleman disease characterized by thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), megakaryocytosis, and organomegaly (O) [8,9]. Patients with TAFRO syndrome often follow fatal courses, and the case fatality rate of the disease has been reported as approximately 15% within 2 years [10]. In the diagnostic criteria of TAFRO syndrome, various infectious diseases including NTM-associated infections are listed as exclusion criteria [11]. However, thus far, there are no clinical cases that report disseminated NTM-associated infection was indistinguishable from TAFRO syndrome. Herein, we report a challenging case of

Abbreviations: NTM, non-tuberculous mycobacteria; TAFRO, thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly.

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disseminated *M. genavense* infection that showed a similar clinical course as that of TAFRO syndrome.

2. Case report

A 69-year-old Japanese man was admitted to our hospital due to persistent fever for more than a month. His medical history included Sjogren's syndrome and mandibular osteomyelitis. His vital signs on admission were as follows: body temperature, 37.8 °C; blood pressure, 109/70 mmHg; pulse rate, 80 beats/minute; and oxygen saturation, 98% (room air). On physical examination, there was tenderness in the back and ribs on the right side. Otherwise, rest of the examination did not reveal any abnormalities. No lymphadenopathy was seen. Blood tests showed elevations in white blood cell count [normal range] (29,750/μL [3300–8600]), C-reactive protein (20.31 mg/dL [<0.14]), alkaline phosphatase (ALP, 1457 U/L [106–322]), and soluble interleukin-2 receptor, (14,280 U/mL [122–496]). The serum level of lactate dehydrogenase, immunoglobulins (IgG, IgA, and IgM), complements, and lymphocyte counts and fractions were all within the normal range. The patient tested negative for T-SPOT and HIV (Table 1). Non-contrast-enhanced magnetic resonance imaging (MRI) examination showed diffuse, T1-and T2-low-intensity lesions on the vertebral bodies (Fig. 1A). Needle biopsy of the vertebral body was performed under a suspected diagnosis of malignant lymphoma or mycobacterium infection, which revealed an increase in megakaryocytes but not any malignant findings. We could not find any evidence of mycobacterial infection, as acid-fast staining and mycobacterial culture of biopsy material resulted in negative.

Respiratory discomfort developed on day 9 after admission. Platelet counts were significantly reduced to 30,000/μL [158,000–348,000] on day 11. Computed tomography scan showed hepatomegaly, pleural effusion, and ascites retention in the bladder-rectal fossa, with no lymphadenopathy (Fig. 2). Considering persistent fever accompanying elevations in inflammatory markers, hepatomegaly, pleural effusion, ascites fluid, thrombocytopenia, accumulation of megakaryocytes in the bone marrow, the patient met 3 major and 2 minor items in the diagnostic criteria for TAFRO syndrome [8]. Additionally, the significant increase in ALP and the absence of immunoglobulin elevation were also suggestive of TAFRO syndrome, rather than other possible diseases [10]. Therefore, it appeared that other possible TAFRO-syndrome mimicking diseases like malignancies and infectious diseases have been ruled out. The patient's condition deteriorated rapidly, and we thus decided to initiate prednisolone (PSL) at a dose of 40 mg/day. Subsequently, his general condition improved and the levels of inflammatory markers normalized (Fig. 3). An additional liver biopsy was not performed because the clinical course after initiating systemic corticosteroid therapy was typically consistent with that of the TAFRO syndrome.

Six weeks after admission, we identified a positive reaction in mycobacterial blood culture (BACTEC Myco/F Lytic bottle, BACTEC™ FX blood culture system, Becton Dickinson, Sparks, MD, USA) that was obtained on admission day 3. Polymerase chain reaction (PCR) tests for both *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellular* complex were negative. The culture-positive blood medium was inoculated onto liquid media (Mycobacteria Growth Indicator Tube (MGIT), BACTEC MGIT 960 system), Ogawa's media, and blood agar plate, and incubated for up to 6 weeks, which also revealed no bacterial growth. Consequently, we could not correctly identify the bacterium at that time.

Due to successful PSL treatment, the patient was discharged on day 64. However, his condition gradually worsened, and hence, he was readmitted 7 weeks after discharge. Reexamination of the vertebral bodies revealed exacerbation of the diffuse, spotted lesions (Fig. 1B). We re-performed a bone marrow biopsy of the vertebral body, which revealed a large number of mycobacteria using Ziehl-Neelsen staining. With this finding, the patient was diagnosed with disseminated NTM infection, rather than with TAFRO syndrome.

To provide appropriate treatment, we performed an in-depth bacterial analysis. We re-inoculated the culture-positive blood media into the mycobacterial blood culture system and obtained positive results after 2 weeks of incubation. Subsequently, we performed a direct PCR sequence for 16s rRNA and *rpoB*. Primers for the targeted genes were as follows; 8UA (5′-AGA GTT TGA TCM TGG CTC AG-3′) and 1485B (5′-TAC GGT TAC CTT GTT ACG AC-3′) for 16S rRNA; and Forward (5′-CGA CCA CTT CGG CAA CCG-3′) and Reverse (5′-TCG ATC GGG CAC ATC CGG-3′) for *rpoB*. The sequence data were analyzed using BLAST sequence homology search programs, and eventually, the organisms were identified as *M. genavense*. The concordance rate in 16S ribosomal RNA was 99.6% (1,150bp/1,155bp) to reported strains of *M. genavense* (NR_029223 and X60070), and that in *rpoB* was 100% (310bp/310bp) to a reported strain of *M. genavense* (AB973497). The nucleotide data were deposited in the NCBI database with accession numbers of LC533965 (16S ribosomal RNA, partial sequence) and LC542631 (*rpoB*).

Under a final diagnosis of disseminated *M. genavense* infection, the patient was started on combination therapy with clarithromycin, rifampicin, and ethambutol. However, he developed lower-limb paralysis due to spinal cord injury secondary to a compression fracture of the thoracic vertebrae 8 days after starting treatment, although bisphosphonate, as prophylaxis for secondary osteoporosis, was started during the first hospitalization. Although his general condition was greatly improved, he eventually developed complete lower-limb paralysis due to the spinal cord injury.

Later, we performed QuantiFERON®-TB Gold to detect the presence of anti-interferon-γ (IFN-γ) autoantibodies as a possible underlying cause of the disseminated NTM infection. Consequently, we found that the positive control resulted in a negative result, suggesting that the patient could be in a state of cellular immunodeficiency due to *anti*–IFN–γ autoantibodies.

Table 1
Laboratory testing at the first admission.

WBC	29,750	/μL	TP	6.3	g/dL	BUN	13.5	mg/dL
Neutrophil	82	%	Alb	2.0	g/dL	Cr	0.87	mg/dL
Lymphocyte	10	%	T-Bil	0.38	mg/dL	CRP	20.31	mg/dL
Monocyte	5	%	AST	20	U/L	PCT	0.964	ng/mL
Eosinophil	2	%	ALT	17	U/L	IgG	1673	mg/dL
Basophil	0	%	ALP	1457	U/L	sIL-2R	14,280	U/mL
Hb	7.4	g/dL	LDH	172	U/L	IGRA	Negative	
PLT	31.2×10^4	/μL	γ-GTP	230	U/L	HIV	Negative	

WBC, White blood cell count: Hb, Hemoglobin; PLT, Platelet; TP, Total protein; Alb, Albumin; T-Bil, Total bilirubin; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ALP, Alkaline Phosphatase; LDH, Lactate Dehydrogenase; γ-GTP, Gamma-glutamyl transpeptidase; BUN, Blood urea nitrogen; Cr, Creatinine; CRP, C-reactive protein; PCT, Pro-calcitonin; sIL-2R, Soluble interleukin-2 receptor; IGRA, interferon-gamma releasing assay; HIV, human immunodeficiency virus.

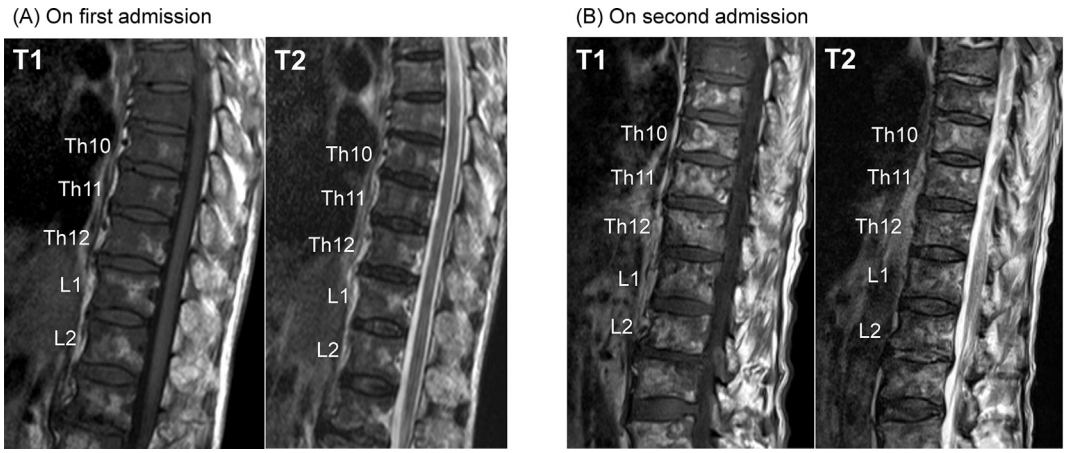

Fig. 1. Magnetic resonance imaging of the vertebrae. T1-and T2-low-intensity lesions were found at vertebral bodies on admission (A). The findings exacerbated, showing spotted appearance on second admission (B).

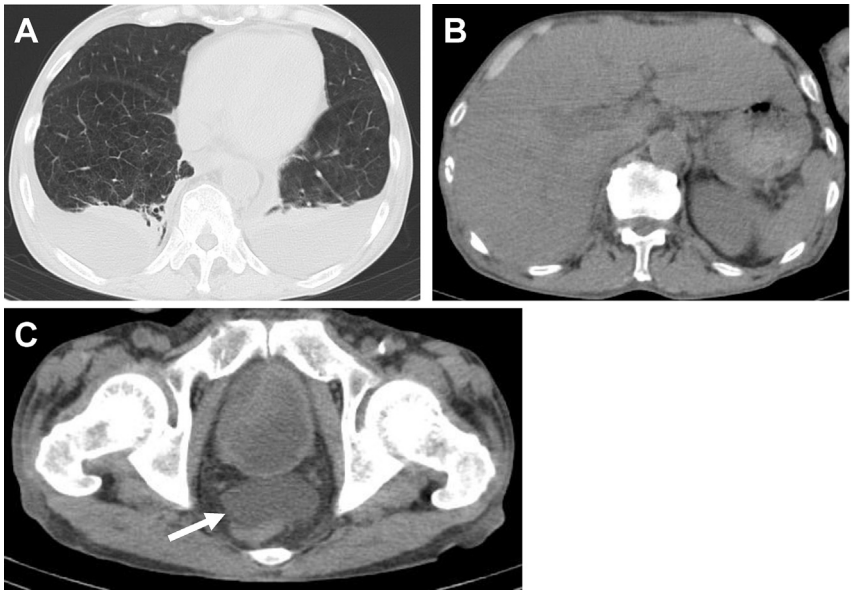

Fig. 2. Computed tomography findings. The image shows pleural effusion (A), hepatomegaly (B), and ascites (C, arrow).

3. Discussion

We described a case of disseminated *M. genavense* infection that was difficult to distinguish from TAFRO syndrome. Reasons for the difficulty in differentiation were (i) the similarity of the clinical course and test results with those of TAFRO syndrome, (ii) the difficulty in detecting *M. genavense* by routine culture procedures, and (iii) the failure to recognize a possible immunocompromising factor in our patient.

First, disseminated NTM infections potentially mimic TAFRO syndrome. Typical features of TAFRO syndrome are thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), megakaryocytosis, and organomegaly (O). In addition to these findings, a marked increase in serum ALP was observed in the present case, which is commonly seen in cases of TAFRO syndrome [11]. Diagnosis of TAFRO syndrome requires excluding other inflammatory diseases, including NTM infection, because their clinical characteristics resemble each other, while their treatment strategies contradict each other [11]. Despite the isolation of mycobacterium from blood culture, we could not diagnose this case at an appropriately early stage. Because of the positive response to the treatment with PSL, the difficulty in identifying NTM species, and the lack of immunodeficiency that could explain the development of NTM infection, we considered the blood-borne pathogen was contamination. However, patients with TAFRO syndrome are predisposed to be misdiagnosed with infectious diseases [9]. This case highlighted the importance of eliminating NTM infection, even when the clinical course of a patient is fully consistent with that of TAFRO syndrome.

Second, identification of *M. genavense* was laboriousness. Of various mycobacteria organisms, *M. genavense* is extremely difficult to identify, which requires Mycobactin J for growth and thus does not form colonies in routine solid agars. For positive identification, a direct sequencing technique using clinical samples has been applied in previous cases [12,13]. Hence, there may be more cases in which the organism remained unidentified and disseminated infections may have been overlooked.

Third, disseminated NTM infections usually occur in patients with underlying immunodeficiencies, especially those causing a cellular immune deficiency. Case series literature reported that *M. genavense* accounted for 12.8% of disseminated NTM infections in patients with HIV [2]. A review of *M. genavense* infection

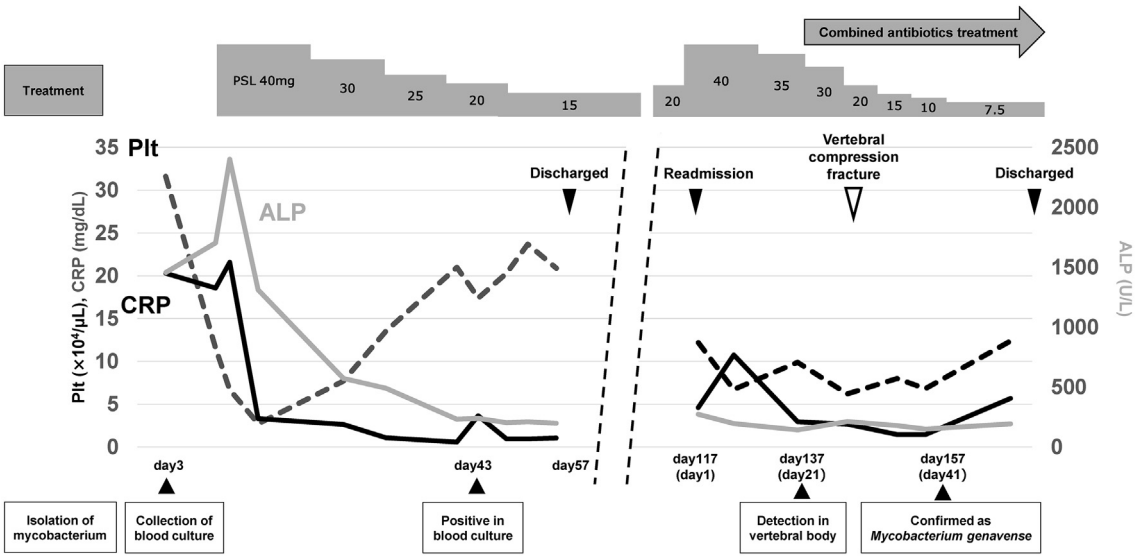

Fig. 3. Clinical course of the case. ALP, alkaline phosphatase; CRP, C-reactive protein; Plt, platelet count; PSL, prednisolone.

summarized the clinical characteristics of 44 non-HIV cases, describing that the following background diseases were reported: transplantation (40%), sarcoidosis (14%), and hematopoietic stem cell transplantation (7%) [3]. In the present case, no underlying immunodeficient condition was observed. Notably, we later found that a positive control of QuantiFERON®-TB Gold resulted in a negative result. Severe malnutrition and lymphocytopenia could yield such a result; however, no such conditions were present at the time of examination. Administration of an immunosuppressive drug, PSL in this case, could also cause the negative result of the positive control of the IFN-γ release assay. However, the dose of PSL was relatively lower, at 10 mg per day, when we did the QuantiFERON®-TB Gold assay. Therefore, we suspected another possible underlying cause of immunodeficiency, such as the presence of *anti*–IFN–γ autoantibodies in this patient. [14,15].

Recently, the importance of *anti*–IFN–γ autoantibody has been addressed as a cause of the acquired immunodeficiency. A previous study concluded that the *anti*–IFN–γ autoantibody was detected in 81% of Asian patients with disseminated NTM infection [16]. Another study also suggested the relation between *anti*–IFN–γ autoantibodies and the occurrence of NTM infections [17]. In fact, a case of disseminated *M. genavence* infection in a patient with *anti*–IFN–γ autoantibody has been reported [18]. Although we did not directly measure the serum *anti*–IFN–γ autoantibody, we speculate that acquired immunodeficiency due to *anti*–IFN–γ autoantibody could have triggered the onset of disseminated *M. genavence* infection in our patient.

In summary, we have described a patient suffering from disseminated *M. genavence* infection who manifested clinical symptoms and findings highly suggestive of TAFRO syndrome. Due to the difficulty in identifying the fastidious organism, initiation of appropriate antimicrobial treatment was delayed. Disseminated NTM infection should be suspected in patients with vertebral lesions, even in cases where the mycobacteria could not be detected from the initial tissue biopsy material.

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K. Oka, M. Yamane, Y. Yokota, M. Yasuda, K. Hasegawa, H. Hagiya, and F. Otsuka managed the patient. T. Fujimori and K. iio were responsible for the bacterial analysis. H. Hagiya was responsible for the description of the case and discussion. All authors contributed to the writing of the final manuscript.

Declaration of Competing Interest

None.

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