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CASE REPORT

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Mixed *Mycobacterium kansasii* and *Mycobacterium smegmatis* infection in an adult-onset immunodeficiency patient with anti-interferon-γ autoantibodies

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Abstract

Anti-interferon-gamma autoantibody (AIGA) is a rare adult-onset immunodeficiency disease that increases the risk of occult infection. Nontuberculous mycobacteria (NTM) infections represent a diverse group of species and subspecies, and mixed infections with two or more NTM species have been reported. However, there is no consensus on the optimal antibiotics or immune modulator treatments for mixed NTM infections in AIGA patients. Here, we present the case of a 40-year-old female who initially presented with suspected lung cancer with obstructive pneumonitis. Tissue samples obtained through bronchoscopy, endoscopy, and bone marrow biopsy revealed disseminated mycobacterium infection. PCR-based testing confirmed a mixed pulmonary infection with *Mycobacterium kansasii* and *Mycobacterium smegmatis*, as well as *M. kansasii* bacteremia. The patient received 12 months of anti-NTM medications for *M. kansasii*, and the symptoms improved. Additionally, the images showed resolution after 6 months, even without the need for immune modulator treatment.

KEYWORDS
adult-onset immunodeficiency, anti-interferon-γ autoantibodies, interferon-γ deficiency, mycobacteria infection

INTRODUCTION

Anti-interferon-gamma autoantibody (AIGA) is a rare adult-onset immunodeficiency disease that produces neutralizing autoantibodies against interferon-gamma, leading to immune compromise and an increased risk of occult infections, such as disseminated mycobacterial infections.[1] Nontuberculous mycobacteria (NTM) comprise a diverse group of species and subspecies, and the emergence of new PCR-based diagnostic tools has led to a growing number of reports on mixed infections with two or more NTM species.[2] However, due to the limited availability of antibiotics that are effective against multiple NTM species, patients with mixed NTM infections have a high rate of disease recurrence,[3] and optimal antibiotic treatment for mixed NTM infections in AIGA patients remains unclear.

In this case report, we present a newly diagnosed AIGA patient who initially presented with disseminated mycobacterial infection. PCR-based testing revealed a mixed pulmonary infection with *Mycobacterium kansasii* and *Mycobacterium smegmatis*, as well as disseminated *M. kansasii* infection. After completing 12 months of antibiotics treatment, the infection resolved, and there was no evidence of reactivation, even in the absence of AIGA-specific treatment.

CASE REPORT

This is a case report of a 40-year-old female with a history of uterine myoma and myomectomy who presented with intermittent fever, productive cough of yellowish sputum, and significant weight loss over 3 months. The patient also

developed jaundice and tea-coloured urine in the past month. She was brought to the emergency department due to severe dyspnea, and on examination, exhibited low-grade fever, desaturation, and bilateral crackles in breath sounds. Laboratory tests revealed leukocytosis with bandemia (white blood cell count of 30,500/μL, with 18.0% bands and 77.0% segments), microcytic anaemia (haemoglobin level of 7.1 g/dL), hyponatremia (129 mmol/L), and cholestatic pattern of liver injury (alkaline phosphatase level of 1020 U/L, total bilirubin level of 5.4 mg/dL, and direct bilirubin level of 5.3 mg/dL). The patient's condition deteriorated, and she was intubated and supported with mechanical ventilation due to profound hypoxemia. The chest computerized tomography (CT) scan demonstrated extensive consolidations and lymphatic interstitial thickening in bilateral lungs with bilateral pleural effusion (Figure 1). There were also lymphadenopathies in the bilateral supraclavicular regions and mediastinum. Dilatations of the common bile duct and bilateral intrahepatic ducts were also observed. The tentative diagnosis for this patient was lung cancer with mediastinal lymphadenopathies with obstructive pneumonia. Therefore, we administered empirical antibiotics of piperacillin/tazobactam. However, despite receiving empirical antibiotics, the patient continued to experience episodes of fever and chest films showed persistent consolidations without improvement. For the above reasons and the tissue-proved diagnosis, bronchoscopic intervention was performed. The bronchoscopy revealed the presence of polypoid masses on the tracheal wall, particularly in the left main bronchus, causing almost complete obstruction along with inflamed mucosa. Gastroduodenoscopy and cholangiography showed a middle to distal common bile duct stricture. Pathologic results from bronchoscopy and gastroduodenoscopy-guided biopsies indicated suppurative granulomatous inflammation composed of mixed epithelioid histiocytes and acute inflammatory cells with acid-fast positive bacilli (Figure 2). Due to suspicion of disseminated mycobacterial infection, a bone marrow biopsy was performed, and the results also suggested mycobacterial infection (Figure 2). Additionally, the sputum, blood, BAL fluid, and bronchial biopsied tissue samples showed growth of non-tuberculosis mycobacteria (NTM) confirmed by PCR (Table 1). The growth was observed in liquid culture.

To confirm the species of mycobacterium from the patient's blood, bronchus tissue biopsy, and bronchoalveolar lavage, we used the Applied Biosystems™ 2720 Thermal

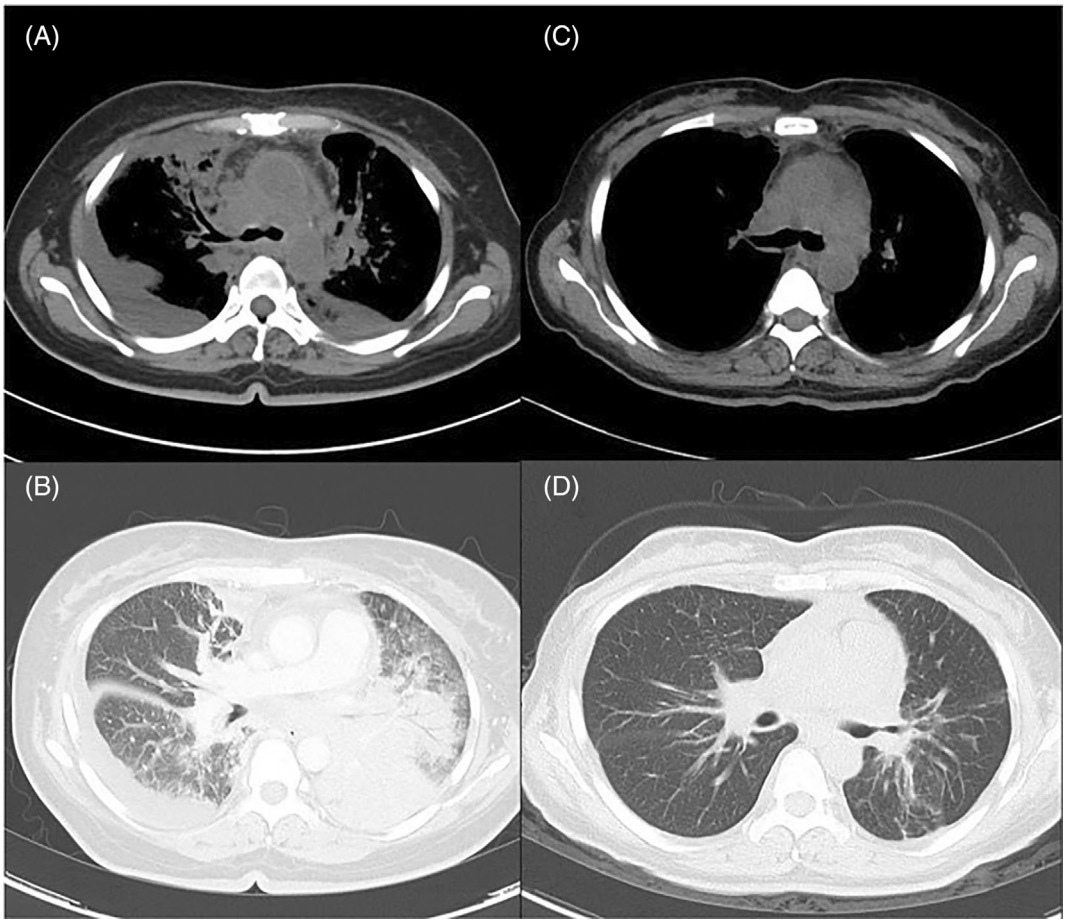

FIGURE 1 Chest CT scan images of the patient. (A and B) Pre-treatment CT scan showing extensive consolidations and lymphatic interstitial thickening in bilateral lungs with bilateral pleural effusion. (C and D) Post-treatment CT scan taken after 9 months of medications, demonstrating near complete resolution of the previously observed abnormalities.

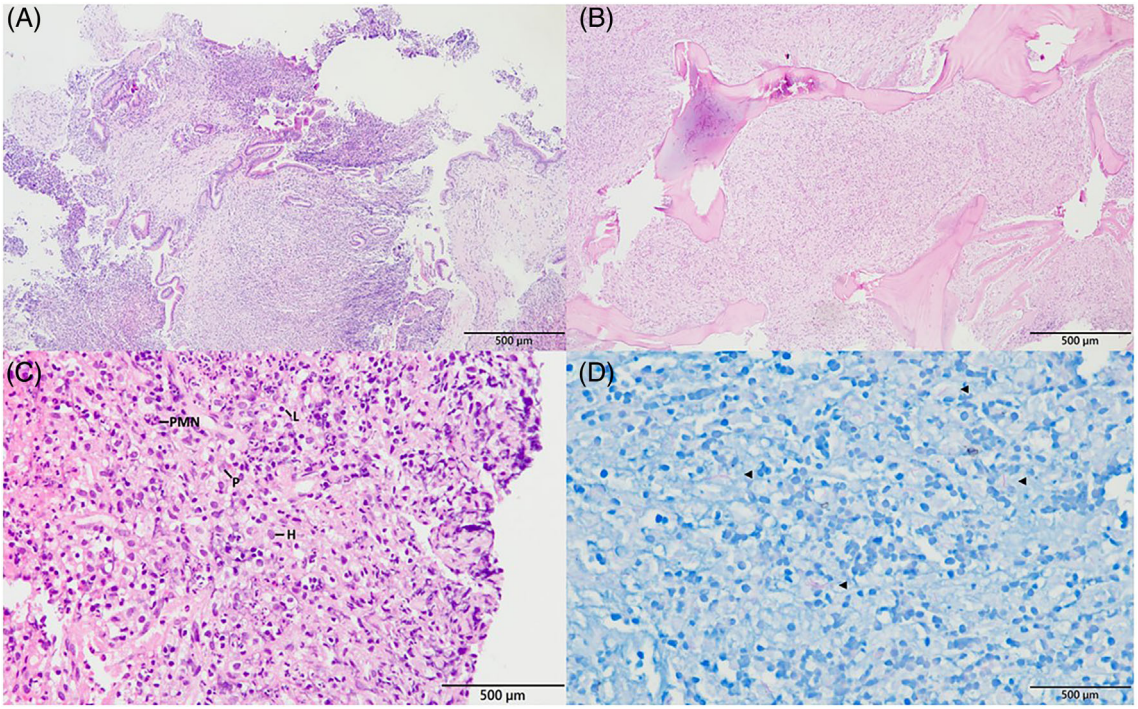

FIGURE 2 Microscopic findings of biopsied tissues from the patient. (A) Suppurative granulomatous inflammation with mixed epithelioid histiocytes and acute inflammatory cells infiltration is observed in the bile duct lamina propria. (B) Granulomatous inflammation and foamy histiocytes aggregation are present in the bone marrow space. (C and D) Histopathologic findings of biopsied bronchial tissue. (C) H-E staining showed ill-defined granulomatous inflammation composed of mixed epithelioid histiocytes and acute inflammatory cells. Histiocytes (H) are aggregated with clear to foamy cytoplasm, accompanied by some small lymphocytes (L), plasma cells (P), and polymorphonuclear leukocytes (PMN). (D) Acid-fast stain reveals several acid-fast bacilli (arrow).

TABLE 1 The test results of the mycobacterium in different specimens.

Date	Specimen	Method	Culture[a]	DNA hybridization
2021/10/25	Sputum	ETA	NTM	Not perform
2021/10/26	Sputum	ETA	NTM	Not perform
2021/10/26	Blood	Peripheral blood drawing	NTM	*M. kansasii*
2021/10/29	BAL fluid	BAL	NTM	Not perform
2021/10/29	Bronchial tissue	Bronchoscopy biopsy	NTM	*M. kansasii*
2021/11/09	Bile duct	EGD biopsy	Not perform	Not perform
2021/11/10	Bronchial tissue	Bronchoscopy biopsy	NTM	*M. smegmentis*
2021/11/10	BAL Fluid	BAL	NTM	*M. kansasii*
				M. smegmentis
2021/11/10	BM	Core biopsy	No growth	Not perform

Abbreviations: BAL, bronchoalveolar lavage; BM, bone marrow; EGD, esophagogastroduodenoscopy; ETA, endotracheal aspirate; NTM, non-tuberculosis mycobacterium.
[a]NTM was confirmed by microscopic examination and negative TB-PCR result.

Cycler (Thermo Fisher Scientific, USA) to perform PCR and identify the strain of mycobacterium by DNA hybridization with BluePoint MycoID® (Bio Concept Corporation, Taiwan).[4] The results of PCR-based speciation are listed in Table 1. *M. kansasii* was detected in the blood, bronchial tissue, and bronchoalveolar lavage fluid. The patient underwent repeated bronchoscopy due to new progression of consolidations in a different bronchus, which revealed the presence of acid-fast positive bacilli in the bronchial tissue. Tissue culture and PCR-based speciation of this sample also identified *M. smegmatis*. Therefore, we considered *M. smegmatis* as an infectious pathogen, rather than mere colonization. Mixed Pulmonary *M. smegmatis* and *M. kansasii* infection, and *M. kansasii* bacteremia were noted. For the bacteremia, we planned to treat *M. kansasii* prior to *M. smegmatis*. The results of drug susceptibility tests for *M. kansasii* by using Sensititre™ Myco SLOMYCOI AST plate (Thermo Fisher Scientific, Waltham, MA, USA)

TABLE 2 The results of drug susceptibility testing of *M. kansasii*.

Antimicrobial agent	MIC break point (μg)		
	No resistance	Resistance	MIC
Clarithromycin	≤16	≥32	1
Rifabutin	≤2	≥4	<0.25
Ethambutol	≤4	≥8	>16
Isoniazid	–	–	2
Moxifloxacin	≤2	≥4	<0.12
Rifampicin	≤1	≥2	0.5
Trimethoprim/sulfamethoxazole	≤2/38	≥4/76	>8/152
Amikacin	≤32	≥64	4
Linezolid	≤16	≥32	4
Ciprofloxacin	≤2	≥4	4
Streptomycin	–	–	16
Doxycycline	–	–	8
Ethionamide	–	–	<0.3

Abbreviation: MIC, minimal inhibitory concentration.

were listed in Table 2. Therefore, we administered azithromycin, moxifloxacin, and rifampin. Immunodeficiency was suspected due to the disseminated mycobacterial infection, but the human immunodeficiency virus testing and immunoglobulin levels were unremarkable. The screen for anti-interferon-gamma autoantibodies was positive, leading to a diagnosis of adult-onset immunodeficiency. After initiating anti-NTM medication, the patient's clinical condition gradually improved, allowing for successful weaning from mechanical ventilation and discharge from the hospital. Culture conversion for sputum, bronchoalveolar lavage fluid, and blood was noted after about 1 month of initiating the regimen. The bile duct and bronchial biopsies, which were performed separately after 4 and 9 months of treatment initiation, respectively, did not reveal any signs of mycobacterial infection. Chest CT scan exhibited significant resolution of pulmonary consolidation and mediastinal lymphadenopathy (Figure 1). The initial diagnosis of AOID revealed a titre of 12.7 Units for AIGA. After a duration of 20 weeks, the subsequent titre showed a slight increase to 17.5 Units. We did not administer rituximab or cyclosporin since the mycobacterium infection was well controlled, and no newly discovered occult infection was identified. The patient did not exhibit any further infectious signs in the outpatient department. Therefore, we opted for active surveillance by performing chest imaging and laboratory tests, without treating the underlying immunodeficiency state after completing 12 months of anti-NTM medications. There was no sign of recurrent NTM infection after ceasing the anti-NTM medication 6 months later. However, she still required scheduled revision of endoscopic retrograde biliary drainage and she still has persistent wheezing breath sounds caused by post-inflammation stricture of the left main bronchus.

DISCUSSION

Adult-onset immunodeficiency is primarily characterized by the presence of anti-interferon-γ autoantibodies, leading to susceptibility to disseminated opportunistic infections by affecting the interleukin-12/interferon-γ axis.[1] When determining appropriate screening times for patients at risk of developing AOID, several factors should be considered, such as presenting with disseminated opportunistic infections without any known primary or secondary immunodeficiencies and onset in adulthood. Among adult-onset immunodeficiency patients with disseminating opportunistic infections, NTM infection accounts for approximately 85% of cases, with about 17.6% of patients being infected with more than one species of NTM. Patients have different species of mycobacterial infections depending on their geographical location. For instance, Hong et al. demonstrated that *Mycobacterium abscessus* was the most common nontuberculous mycobacterium in Thailand, whereas *Mycobacterium avium* complex was the most common in the United States.[5] Chen et al. reported that *M. abscessus* is the most commonly isolated NTM in a medical center in Southern Taiwan.[6] Mixed infections of *M. kansasii* and *M. smegmatis* are rarely reported. *M. smegmatis* is an uncommon pathogen among rapidly growing mycobacteria, typically infecting skin or soft tissue following traumatic injury or cardiac surgery in immunocompetent people. 2007 IDSA guideline suggested treating *M. smegmatis* with doxycycline and trimethoprim–sulfamethoxazole and use parenteral amikacin or imipenem for severe infections.[7] There are no treatment guidelines available for mixed NTM infections in immunodeficient patients at present. In the case of our patient, we treated *M. kansasii* prior to *M. smegmatis* due to the involvement of multiple organ systems, including positive blood cultures.

There is currently no definitive treatment for anti-interferon-γ autoantibodies. Generally, the autoantibody levels decrease over time, and there are no differences in the initial autoantibody levels or trends of level decrease between genders or age groups.[5] Immunosuppressants such as cyclophosphamide and rituximab have been used clinically to reduce the production of autoantibodies.[5] A small-scale prospective trial showed similar duration of clinical remission and adverse events between patients treated with cyclophosphamide and rituximab.[8] However, the efficacy of immunosuppressants for this disease, the best candidate for immunosuppressants, and the choice between rituximab and cyclophosphamide are still unclear and require further investigation.

In conclusion, this case report presents a rare and intriguing case of disseminated *M. kansasii* and pulmonary *M. smegmatis* infections in an adult with anti-interferon-gamma autoantibodies. This report highlights the clinical challenges and management strategies for this unique patient population. Further research is necessary to optimize the treatment and long-term outcomes.

AUTHOR CONTRIBUTIONS

Yun-Tse Chou and Chin-Wei Kuo conducted literature searches and wrote the manuscript. Wei-An Liao provided the pathological report and suggestions. All authors contributed to and have approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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