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CASE REPORT

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A rare presentation of *Legionella pneumophila* and Mycobacterium intracellulare co-infection masquerading as metastatic lung cancer in a patient with positive anti-interferon gamma antibody

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Abstract

Adult-onset immunodeficiency (AOID) syndrome due to the presence of anti-interferon gamma antibody (AIGA) is characterized by multiple opportunistic infections. We report a case of a 65-year old healthy woman who suffered from *Legionella pneumophila* and Mycobacterium intracellulare co-infection with clinical presentation mimicking metastatic lung cancer. She presented with chronic cough and weight loss. Her positron emission tomography scan showed a right upper lobe mass, mediastinal lymphadenopathy and multiple bone lesions. Acid fast bacilli culture of the lung mass and mediastinal lymph node revealed Mycobacterium intracellulare and she improved with prolonged antibiotic. Relapse of disseminated Mycobacterium intracellulare infection occurred 15 months post-treatment and AIGA was positive with functional neutralizing activity on downstream immune pathway. AOID syndrome secondary to AIGA was diagnosed. This case illustrated the importance of high index of suspicion of AOID syndrome and the difficulty of early diagnosis. Further studies on its predictive factors and AIGA-targeted treatment modalities are urgently needed.

KEYWORDS
adult-onset immunodeficiency syndrome, anti-interferon gamma antibody, *Legionella pneumophila*, mycobacterium Intracellulare, pneumonia

INTRODUCTION

Adult-onset immunodeficiency (AOID) syndrome due to the presence of anti-interferon gamma antibody (AIGA) is increasingly recognized and is predominantly found in Southeast Asia.[1,2] The neutralizing effect of AIGA on interferon gamma (IFNγ) leads to reduced anti-microbial activity of the T-Helper 1 (TH1) immune pathway,[3] resulting in increased susceptibility to intracellular organism infection including non-tuberculous mycobacterium (NTM).[1,4] Pulmonary involvement is common but the clinical presentation may be misleading, and therefore diagnosis of AOID syndrome could be delayed. Herein, we report a rare case of a patient with positive AIGA who presented with *Legionella pneumophila* and Mycobacterium Intracellulare co-infection mimicking metastatic lung cancer, highlighting the difficulty and importance of early diagnosis of AOID syndrome.

CASE REPORT

A 65 year-old non-smoking Chinese woman, with unremarkable past health, presented to our hospital with dry cough and weight loss for 2 months. Physical examination showed low grade fever, enlarged supraclavicular fossa (SCF) lymph node (LN) and reduced breath sound over the left lower chest. Blood test revealed leukocytosis (29×10^9 cells/L), hyponatremia (130 mmol/L) and elevated bilirubin (27 μmol/L). Chest x-ray (CXR) showed left lower lobe (LLL) consolidation and an irregular mass in right upper

lobe (RUL). In view of absence of purulent sputum despite significant consolidation, hyponatremia and deranged liver function, atypical pneumonia workup was performed. Sputum for acid fast bacilli (AFB) culture was also saved considering her prolonged duration of symptoms and weight loss. Urine Legionella antigen test and sputum for *L. pneumophila* polymerase chain reaction (PCR) were positive. She had no relevant risk factors associated with Legionella pneumonia. A 10-day course of azithromycin was given. Her white cell counts, sodium and bilirubin level had normalized. Interval CXRs showed resolution of the LLL consolidation (Figure 1) but persistence of the RUL mass, raising the suspicion of lung cancer.

Positron emission tomography (PET) scan revealed an irregular hypermetabolic mass (6.5 × 5.6 cm) in the posterior segment of RUL (Figure 2A), multiple mediastinal and supraclavicular lymphadenopathy, together with numerous mixed lytic and sclerotic bony lesions (involving whole spine, rib cage, pelvis, bilateral humeri and femur). Fine needle aspiration of right SCF LN was unrevealing. Repeated transbronchial biopsy of the lung mass showed lymphoplasmacytic infiltrates with no evidence of malignancy. Two sputum AFB culture tests performed during her index hospitalization later revealed Mycobacterium Intracellulare. Therefore, AFB culture was performed on her mediastinal LN obtained by endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA) and on the lung mass by transbronchial biopsy. The same NTM was identified in both cultures (Table 1). There was no granulomatous inflammation or visible acid fast bacilli in the tissue samples.

The diagnosis of disseminated Mycobacterium intracellulare infection was made. She had no known respiratory or immunocompromised disease. Human immunodeficiency virus (HIV) test was negative. She had completed 18-month treatment course including rifampicin, ethambutol and clarithromycin. Interval scans showed resolution of the aforementioned hypermetabolic lesions (Figure 2B) and sputum conversion was achieved 1 month after treatment commenced.

The disseminated Mycobacterium intracellulare infection relapsed 15 months after treatment. PET scan showed new bilateral hypermetabolic lung nodules, mediastinal lymphadenopathy and multiple bony lesions (Involving thoracolumbar spine, left humerus, pelvis and left femur) (Figure 2C). Erythrocyte sedimentation rate (ESR) was elevated (>100 mm/h). Repeated sputum AFB culture grew Mycobacterium Intracellulare. Treatment (rifampicin, ethambutol, azithromycin and amikacin) was started with clinical response.

In view of the history of repeated intracellular micro-organism infection (*L. pneumophila* and Mycobacterium Intracellulare), further workup on underlying immunodeficiency was performed. Her lymphocyte subset profile, including CD4 and CD8 counts, were essentially normal. Immunoglobulin G (IgG: 42.9 g/L; IgG4: 4.5 g/L) and globulin level (72 g/L) were elevated. Interferon Gamma Release Assay (IGRA) (QuantiFERON-TB Gold In-tube) result was indeterminate and revealed low IFNγ level in the mitogen control test (Positive control) (Table 2). AIGA was detected using Enzyme-linked immunosorbent assay (ELISA). It demonstrated positive functional neutralizing activity on Signal Transducer and Activator of Transcription 1 (STAT1) phosphorylation using flow cytometry test (Table 2). Therefore, she was diagnosed with AOID syndrome secondary to presence of AIGA.

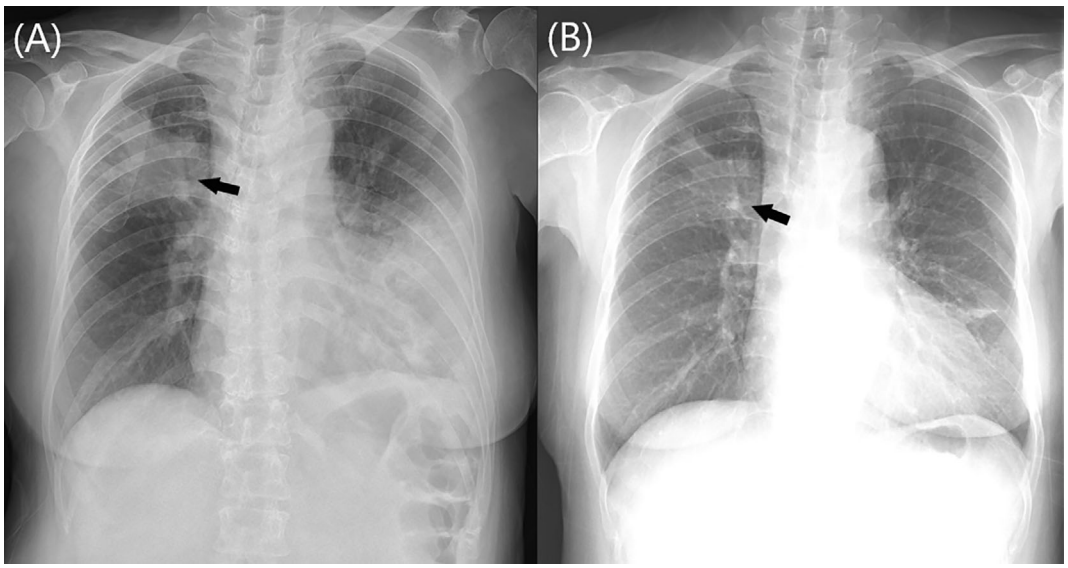

FIGURE 1 (A) (left) showed the CXR that revealed a RUL mass (4 × 5 cm) (black arrow) and left lower lobe (LLL) consolidation when our patient was first admitted for pneumonia. (B) (right) showed the resolution of the LLL consolidation 2 weeks after a 10-day course of azithromycin and the persistence of RUL mass (black arrow).

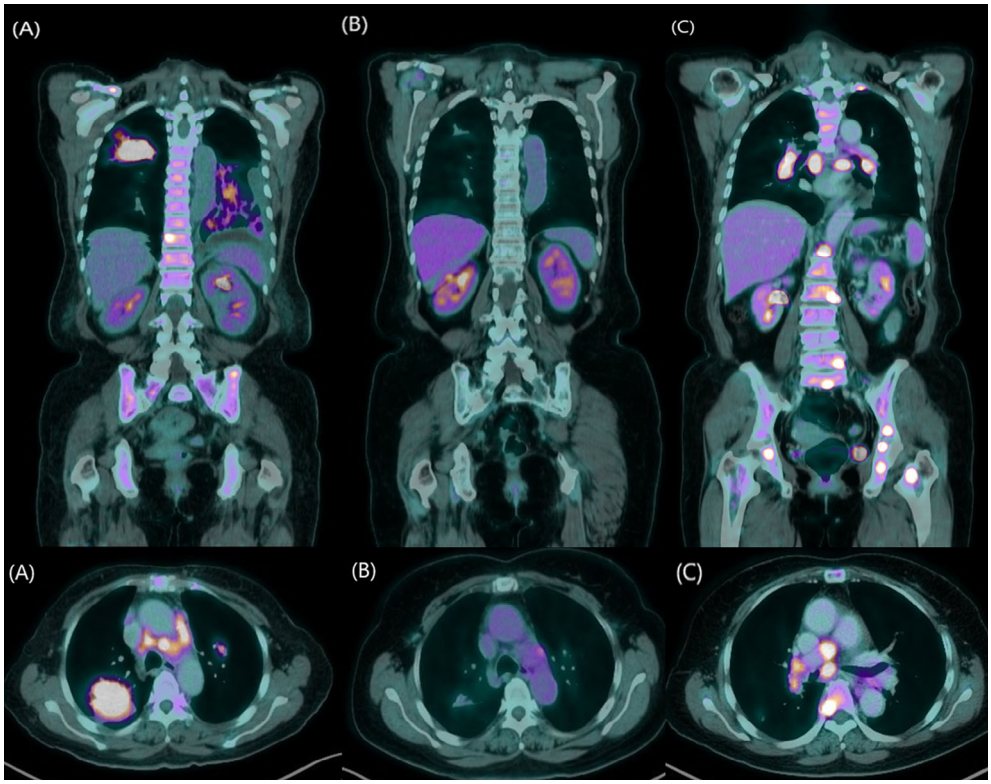

FIGURE 2 (A) (coronal view) showed the PET scan that revealed a hypermetabolic RUL mass and multiple bony lesions in thoracolumbar spine and pelvis. (A) (Axial view) Revealed the same RUL mass with multiple hypermetabolic mediastinal lymphadenopathy. (B) (Both coronal and axial view) demonstrated resolution of the hypermetabolic lesions in PET scan. (C) (Both coronal and axial view) showed the PET scan when the patient suffered from relapse of NTM infection. There were recurrence of hypermetabolic mediastinal lymphadenopathy and multiple bony lesions in thoracolumbar spine, left femur and pelvis.

TABLE 1 Mycobacterium Intracellulare was identified in different respiratory samples. Drug susceptibility test revealed that the mycobacterium was sensitive to amikacin and clarithromycin.

Sample of acid fast bacilli culture	**Species of Mycobacterium**	
Sputum	Mycobacterium intracellulare	
Right upper lobe lung mass (transbronchial biopsy)	Mycobacterium intracellulare	
Mediastinal lymph node (transbronchial needle aspiration)	Mycobacterium intracellulare	
Bronchoalveolar lavage	Mycobacterium intracellulare	
Minimum inhibitory concentration (MIC)	**(μg/mL)**	**Resistance threshold**
Amikacin	4	≤16 (Susceptible)
		32 (Intermediate)
		≥64 (Resistant)
Clarithromycin	1	≤8 (Susceptible)
		16 (Intermediate)
		≥32 (Resistant)
Linezolid	16	≤8 (Susceptible)
		16 (Intermediate)
		≥32 (Resistant)
Moxifloxacin	2	≤1 (Susceptible)
		2 (Intermediate)
		≥4 (Resistant)

TABLE 2 Suppression of interferon gamma (IFNγ) level was demonstrated in interferon gamma release assay (IGRA) positive control test (mitogen control) (A) and functional neutralizing activity of anti-interferon gamma antibody (AIGA) on signal transducer and activator of transcription 1 (STAT1) phosphorylation was demonstrated by Flow Cytometry (B). STAT1 responsive cells remained at 10.8% only despite 1:100 plasma dilution compared with more than 80% in normal control.

A. IGRA – QuantiFERON TB Gold In-tube	
Negative control (Nil control)	0.02 IU/mL
Positive control (Mitogen control)	0.02 IU/mL
TB1 (TB antigen)	<0.01 IU/mL
TB2 (TB antigen)	<0.01 IU/mL
Final result	Indeterminate
B. Neutralizing activity of AIGA Control	**STAT1 responsive cells (%)**
Normal control	87.7
Neutralizing antibody positive control	1.6
Patient serum dilution	**STAT1 responsive cells (%)**
Neat	17.3
1:10	10.9
1:100	10.8
1:10,000	77.3
1:10,000	87.9

DISCUSSION

AOID syndrome is strongly associated with opportunistic infection in middle-aged HIV-negative patients.[2] Upon AIGA binding of IFNγ, the downstream pathway including STAT1 phosphorylation and IL-12 production will be hampered. This in turn inhibits macrophage activation and its phagocytosis ability[3] against pathogens, of which most are intracellular micro-organisms. While NTMs are commonly detected in these patients, *L. pneumophila* was seldom reported. A recent multicentre retrospective study in China showed that NTM was the most common pathogens (83.5%) and there were only two Legionella cases.[1] To our knowledge, this is the first reported case of *L. pneumophila* and Mycobacterium Intracellulare co-infection masquerading as metastatic lung cancer in a patient with AOID syndrome.

Our patient was first suspected to have lung cancer because NTM infection is uncommon in HIV-negative patients without chronic respiratory or immune-compromised diseases. This unfortunately led to delayed diagnosis of AOID syndrome. Therefore, factors that predict this syndrome should be identified early. One retrospective study, which was conducted in Guangxi, suggested AIGA screening should be considered if there is the presence of the following: double/multiple opportunistic disseminated infections; negative HIV test; low CD4 count; elevated IgG, globulin and ESR.[5] Previous analysis showed that AIGA belongs to IgG subtypes (IgG1 or IgG4).[3] Our patient suffered from double infections of which one was disseminated and had markedly elevated IgG, IgG4, globulin and ESR. These markers may give hints of early AIGA screening.

AOID syndrome is diagnosed when there is positive AIGA together with significant neutralizing activity on STAT1 phosphorylation.[3,5] Enzyme-linked immunosorbent assay (ELISA) test for AIGA detection is commonly used.[3] Other methods have also been applied to detect AIGA, including immunoblot test, particle based assay and even IFNγ release assay (e.g., QuantiFERON-TB Gold In-tube).[3] Our patient's IGRA test showed low level of IFNγ despite strong stimulation by mitogens in positive control test. It revealed inability of lymphocytes to produce IFNγ. IGRA is easily available and further tests for AIGA may be warranted if a healthy patient with disseminated NTM infection has indeterminate QuantiFERON result.[6] Evaluation of STAT1 phosphorylation, commonly assessed by flow cytometry, is another crucial step to demonstrate the inhibitory function of AIGA. There were reports of normal individuals with positive AIGA but limited neutralizing activity on STAT1 phosphorylation and AIGA titre does not correlate with the prognosis of infection.[3] It brings the message that checking AIGA alone is not adequate for making the diagnosis.

The management approach of AOID syndrome is divided into two parts: anti-microbial treatment and reduction of AIGA level. Although this is an increasingly recognized disease, there are so far no standard treatments with strong scientific evidence. One proposed treatment was Rituximab, an anti-CD20 monoclonal antibody, which works by depleting B-cells that produce AIGA. Other immunotherapies including glucocorticoid, cyclophosphamide, daratumumab or even plasmapheresis have also been used in the past.[1] Clinical trials are urgently needed in this area.

In conclusion, our case highlights the difficulty of AOID syndrome diagnosis due to its obscurity in clinical presentation. A high index of suspicion is crucial for early detection. Further large-scale studies are required to identify its predictive factors and to evaluate the efficacies of different treatment modalities.

AUTHOR CONTRIBUTIONS

Hei-Shun Cheng, Pui-Hing Chiu and Charles Wong contributed to the concept, clinical data collection and drafting of the manuscript. Chun-Wai Tong and Pui-Ling Flora Miu contributed to the final review of the manuscript and the editing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

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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