Multiple intracellular pathogen infections with ocular immune damage associated with adult-onset immunodeficiency due to anti-interferon-γ autoantibodies: A case report

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Case Report

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Abstract

**Background:** Autoantibodies to interferon-γ (IFN-γ) can inhibit IFN-γ-dependent signal transducer and activator of transcription (STAT)1 phosphorylation thus predispose those patients with susceptibility to infections with normally considered low virulence pathogens, such as *Talaromyces marneffei* (TM), nontuberculous mycobacteria (NTM), and *Mycobacterium tuberculosis*. But they are not as commonly associated with TM and NTM co-infected with *Mycobacterium tuberculosis*.[1][2]

**Case presentation:** Herein, we report a case of a middle-aged woman with a history of recurrent rash, cough, and expectoration. She was successively diagnosed with NTM, TM, and *Mycobacterium tuberculosis* infection and allergic conjunctivitis without conventional immunosuppression-associated factors in the past. The most conspicuous characteristics were recurrent infection and immune compromise.

**Conclusions:** High-titer anti-IFN-γ autoantibodies (AIGAs) are strongly associated with severe and disseminated infections, such as NTM, TM, and *Mycobacterium tuberculosis*. It is characterized by persistently elevated levels of inflammation and immunoglobin.

**Background**

Adult-onset immunodeficiency syndrome (AOIDS) due to anti-interferon (IFN)-γ autoantibodies is a distinct and emerging clinical entity, usually found in Asia, Thailand, and Taiwan,[1][3] which was first described in 2012 by Browne et al.[1][7][8] Neutralizing anti-IFN-γ autoantibodies (nAIGAs) were detected in 88% of Asian adults with multiple opportunistic infections and were associated with an adult-onset immunodeficiency akin to that of advanced HIV infection.[1][3][5][6] AIGAs are considered to be a susceptibility factor for multiple intracellular pathogens infections, especially nontuberculous mycobacteria, *Talaromyces marneffei*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and so on. In patients with high-titer AIGAs, the clinical presentations may be variable from site of infection and related pathogens. Current studies showed that the common clinical features of infected patients were multiple lymph node enlargement, lung lesions, bone destruction, skin lesions, liver and spleen can also be involved. But ocular immune damage caused by AIGAs is rare reported previously. Here, we report a patient with high-titer serum AIGAs who suffered from multiple disseminated intracellular pathogens infections with ocular lesions and explore the mechanism.

**Case presentation**

A 61-year-old Chinese woman was admitted to the hospital on February 3, 2021 due to a 4-month history of cough and expectoration, accompanied by multiple red rashes, edema, and painful subcutaneous nodules in bilateral legs. She was nonresponsive to piperacillin-tazobactam and hormone therapy at another hospital. She had no previous history of medical illness or medication. Physical examination on admission revealed a body temperature of 36°C and a skin mass of 2 × 2 cm on the left leg. Blood test...
results indicated a severe infection with significantly elevated levels of white blood cells (WBCs) and C-reactive protein (CRP) as well as an increased erythrocyte sedimentation rate (ESR) and immunoglobulin E (IgE) levels. Notably, lymphocyte subset counts and percentages were normal. And human immunodeficiency virus (HIV) serology was negative. Chest computerized tomography (CT) revealed bilateral pulmonary consolidation with hilar and mediastinal lymphadenopathy (Fig. 1A). Mycobacterium tuberculosis (TB) was identified using metagenomic next-generation sequencing (mNGS) technology from the skin biopsy of the left leg, but the alveolar lavage fluid was negative. Despite the lack of evidence of NTM infection, empirical anti-NTM therapy was also initiated, as the patient presented with both skin and lung lesions and rapid disease progression, making NTM co-infection highly suspected.

After 2 weeks, the patient was hospitalized twice for recurrent cough and expectoration, and began with fever. Chest CT displayed the progressed consolidation in the bilateral lungs (Fig. 1A). We sent bronchoalveolar lavage fluid (BALF) for mNGS again, and Mycobacterium intracellular was detected. According to definitive pathogen evidence, the patient continued antibacterial therapy (comprising Rifampicin, Ethambutol, Moxifloxacin, Azithromycin). However, the patient was hospitalized third for multiple skin lesions subsequently increased (including submental and right submandibular skin, hands and back) during 2 months of follow-up (Fig. 1C). Ultrasound showed bilateral cervical lymphadenopathy. Re-examination of chest CT indicated that the lung lesions were slightly absorbed (Fig. 1A). The emission CT showed a significantly increased uptake in multiple bones, including skull, sternum, multiple ribs, left iliac bone, right forearm and femur, bilateral ankle joints (Fig. 1B). To gain definitive pathogen evidence, mycobacterium gene test and pathogen cultures were performed from the right cervical lymph node. TM was cultured and Mycobacterium tuberculosis was detected the latter was resistant to Amikacin, Kanamycin and Capreomycin. Subsequently, amphotericin B was added as antifungal therapy. And the antibacterial regimen was simultaneously adjusted to rifampicin, ethambutol, isoniazid, and levofloxacin due to the adverse reaction of azithromycin in the gastrointestinal tract. The patient was anti-IFN-γ autoantibody positive with a titer of 1:2500, as determined by enzyme-linked immunosorbent assay (ELISA). After nearly 6 months of anti-infective treatment, the patient's clinical condition remained stable with skin symptoms improvement and lung lesions absorption.

However, the patient complained of amaurosis, redness, photophobia and tearing of right eye with obvious fatigue (Fig. 1D). The patient's white blood cell count was normal, but immunological and inflammatory testing revealed elevated CRP (47.64 mg/L), ESR (123mm/h), and IgE (269.8 g/L) concentrations. The ophthalmic clinic examination revealed conjunctivitis, hyperemia, and edema of right eye and the corneal fluorescein staining showed pseudodendritic lesions. We suspected that the root cause may be the immune-mediated allergic conjunctivitis by anti-IFN-γ autoantibodies, following the pattern of a type I and type IV hypersensitivity mechanism. Corticosteroid treatment (methylprednisolone 16mg/d) was initiated according to these symptoms. After 2 weeks, the ocular symptoms improved dramatically with reduction of the inflammation (CRP, ESR), immunoglobulin level, and the titer of anti-IFN-γ antibody (Fig. 1D). Thereafter, the patient's clinical condition remained stable, without relapse.
Table 1
Inflammation and immunoglobin and pathogens during previous hospitalizations

<table>
<thead>
<tr>
<th>Time</th>
<th>WBC ($\times 10^9$/L)</th>
<th>CRP (g/L)</th>
<th>ESR (mm/1h)</th>
<th>IgE (IU/ml)</th>
<th>Pathogen</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021.2.3-2021.2.9</td>
<td>13.44</td>
<td>136.9</td>
<td>82</td>
<td>185.4</td>
<td>Mtb</td>
<td>Skin biopsy of the left leg</td>
</tr>
<tr>
<td>2021.2.25-2021.3.12</td>
<td>12.44</td>
<td>159.65</td>
<td>126</td>
<td>202.5</td>
<td>M. intracellulare</td>
<td>The alveolar lavage fluid</td>
</tr>
<tr>
<td>2021.4.23-2021.5.21</td>
<td>9.12</td>
<td>47.67</td>
<td>108</td>
<td>213.1</td>
<td>TM; Mtb</td>
<td>Right cervical lymph node</td>
</tr>
</tbody>
</table>

TM = Talaromyces marneffei, Mtb = Mycobacterium tuberculosis, M. intracellulare = Mycobacterium intracellulare

**Discussion and conclusions**

AOIDS usually presents as chronic, recurrent, hard-to-control infections, or unusual serious infections that can be effectively treated with aggressive antibiotic therapy. Skin manifestation is a frequent feature of the syndrome including infections of the skin itself and reactive conditions, such as Sweet syndrome, pustular eruption, and panniculitis. Multiple organ involvement was another feature of AOIDS. The lungs were affected most frequently, followed by the lymph nodes, skin, bones/joints, liver, and spleen. The patient started with lung and skin involvement, and gradually developed lymph nodes and bones. In the previous studies, AOIDS due to high-titer of AIGA was the most common underlying immunodeficiency in patients who are HIV-negative. This patient had no previous medical illness, and was infected with Mycobacterium tuberculosis, NTM, and TM as a result of positive AIGAs. It is extremely rare for a patient to be co-infected with these three rare opportunistic pathogens. We highlight that when HIV-negative hosts, especially those infected by TM with or without other opportunistic infections, develop intracellular opportunistic infections, clinicians should be vigilant for the immunodeficiency due to AIGAs. IFN-γ plays a key role in activating phagocytes to clear engulfed pathogens in humans. Browne et al. showed that neutralizing anti-IFN-γ autoantibody was detectable in 88% of adults with multiple opportunistic infections in Asia. AIGAs with high titers in serum interrupt the activation of the downstream responsive pathway by blocking the combination between IFNs and their receptor and the consequence is increased infection risks. At present, accumulated reports and studies strongly suggested that the AOIDS is highly associated with two specific HLA class II alleles: HLA-DRB1*16:02/DQB1*05:02 and HLA-DRB1*15:02/DQB1*05:01. Nevertheless, the detailed mechanism by which IFN-γ contributes to the control of *T. marneffei* and NTM in vivo remains to be determined.

In addition, autoimmunity caused by the AIGAs plays an important role as well. The ocular symptoms were also associated with intracellular opportunistic infections. However, after nearly 6 months of active...
anti-infection, therapeutic response supports the patient's clinical condition remained stable. But ocular symptoms appeared with increased immunoglobulin (IgE and IgG) level and anti-IFN-γ titers. We guess our case to allergic conjunctivitis mediated by AIGAs, given the absence of evidence of infection. Persistent elevated inflammation and immunoglobulin are the most conspicuous characteristics. Corticosteroid therapeutic response also support our suspect. But reports in humans of how the AIGAs cause systemic autoimmunity are rare.

Therapies for AOIDS due to AIGA are directed against either infectious complications or the autoantibodies themselves. But treatment guidelines and expert consensus are lacking, corticosteroid was used in some cases to improve systemic symptoms. Rituximab, exogenous IFN-γ, plasmapheresis, and cyclophosphamide have been used to treat refractory infections. However, more attention should be paid to balancing of the benefits of corticosteroid treatment and infection risk. The timing and dose of corticosteroid need further attention.

In summary, we reported a case of an HIV-negative woman with AIGA who developed multiple disseminated intracellular organism infection and allergic conjunctivitis. Her ocular symptoms maybe relate to elevated immunoglobulin (IgE and IgG) and anti-IFN-γ titers. Long-term anti-infective and corticosteroid treatment improved clinical manifestations.

**Abbreviations**

**IFN-γ**  
Interferon-gamma

**NTM**  
Non-tuberculous mycobacteria

**TM**  
Talaromyces marneffei

**Mtb**  
Mycobacterium tuberculosis

**M. intracellulare**  
Mycobacterium intracellulare

**WBC**  
White blood cell

**ESR**  
Erythrocyte sedimentation rate

**CRP**  
C-reactive protein

**CT**  
Computerized tomography

**BALF**  
Bronchoalveolar lavage fluid
ELISA
Enzyme-linked immunosorbent assay

Declarations

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Contributions

Yan Ning and Qingliang Yu wrote the main manuscript text. Xiaona Liang and Hanlin Liang prepared figure 1 and table 1. Hanlin Liang completed the experiment. Siyao Wu and Zhiyi He was responsible for case diagnosis and treatment. All authors reviewed the manuscript. All authors read and approve the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

Informed consent was obtained from the patient to publish this case report in an online open-access publication.

Patient had provided written consent to publish this case. Documentation available upon request. All identifying information has been removed from this manuscript and figures. Informed consent was
obtained from the patient to publish this case report in an online open-access publication.

**Consent for publication**

Informed consent was obtained from the patient to publish this case report in an online open-access publication.

**Competing interests**

The authors declare no competing interests.

**References**


Figures
**Figure 1**

See image above for figure legend.

**Fig.1** A Computed tomography dynamic monitoring series: pulmonary lesions (the middle lobe of the right lung and the upper lobe of the left lung) and lymphadenopathy (hilus and mediastinum), worsening of lung lesions before antifungal therapy, and obvious absorption with regular antifungal and antibacterial regimen use. B Emission computed tomography: significantly increased uptake in multiple bones including skull, sternum, multiple ribs, left iliac bone, right forearm and femur, bilateral ankle joints. C Multiple skin lesions (submental and right submandibular skin, hands and back) D Ocular lesions, hyperemia and edema of right eye and the corneal fluorescein staining showed pseudodendritic lesions before and after glucocorticoid use, showing dramatic improvement.