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ORIGINAL RESEARCH

Clinical Characteristics Analysis of 30 Cases of Interferon-γ Autoantibody-Positive Patients with Concurrent Mycobacterial Infection: A 6-Year Retrospective Study

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Purpose: This study aimed to investigate and elucidate the clinical characteristics, immune status, infection types and patterns, treatment responses, and disease progression in patients with positive anti-interferon-gamma (IFN-γ) autoantibodies in combination with Mycobacterium infections.

Patients and Methods: We conducted a retrospective analysis of clinical data from patients with positive anti-IFN-γ autoantibodies and concurrent Mycobacterial infections, including Mycobacterial infections (MTB) and non-tuberculous mycobacteria (NTM). The study included cases treated at the Fourth People's Hospital of Nanning, Guangxi, from 2018 to 2023. Data collected comprised symptoms, clinical signs, laboratory test results, imaging findings, and other relevant clinical information. Patients were also followed up to evaluate treatment responses and long-term therapeutic outcomes.

Results: A total of 30 patients with MTB and NTM infections were analyzed. The majority presented with common symptoms, such as cough, sputum production, weight loss, extrapulmonary tuberculosis (TB), and a range of opportunistic infections. Laboratory and imaging studies revealed complex infection patterns and various pathological changes. Treatment primarily involved targeted anti-infective therapy combined with immunosupportive measures. However, frequent treatment relapses and side effects were observed, resulting in two deaths.

Conclusion: Immune deficiency associated with positive anti-IFN-γ autoantibodies resembles the immunosuppression seen in advanced stages of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rendering patients highly susceptible to opportunistic infections. These infections were predominantly caused by NTM, followed by MTB and *Talaromyces marneffei* (TM). This represents a novel immune deficiency syndrome that predisposes patients to a spectrum of opportunistic infections.

Keywords: anti-interferon-gamma autoantibodies, *Mycobacterium tuberculosis*, nontuberculous mycobacteria, clinical characteristics, treatment

Introduction

Mycobacterium tuberculosis (MTB) infection remains a major global public health concern. Although significant progress has been made in preventing and treating various infectious diseases, this issue is particularly severe in immunocompromised or immunodeficient individuals, where the incidence of MTB infection and its associated disease burden have significantly increased.[1] Disseminated infections primarily occur in individuals with profound

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immune deficiencies, such as patients with hairy cell leukemia, post-transplant recipients, patients with advanced human immunodeficiency virus (HIV) infection, individuals undergoing glucocorticoids or immunosuppressive therapy, and patients with Mendelian defects in the IL-12/IFN-γ axis.

Interferon gamma (IFN-γ) is an important cytokine that performs multiple key roles in the immune system. These roles include enhancing the phagocytic and cytotoxic activities of macrophages, upregulating major histocompatibility complex (MHC) molecule expression to enhance antigen presentation, inducing the expression of antiviral proteins to inhibit viral replication, inhibiting cell proliferation and promoting apoptosis, promoting the differentiation of Th1 cells, and facilitating the transport of white blood cells to infection sites.[2–4] Recent studies have identified a specific immune deficiency in individuals who produce autoantibodies against IFN-γ. These autoantibodies neutralize IFN-γ, rendering patients highly susceptible to severe infections caused by MTB.[5,6] IFN-γ, a crucial immune regulatory protein, is secreted by T cells, natural killer (NK) cells, and natural killer T (NKT) cells. Its production is regulated by immunocyte factors such as interleukin (IL)-12 and IL-18, which serve as essential links between infection events and the generation of IFN-γ during innate immune responses.[7] The cellular effects of IFN-γ include pathogen recognition, upregulation of antigen processing and presentation, induction of an antiviral state, inhibition of cell proliferation, and induction of apoptosis, activation of microbicidal effector functions, immune regulation, and leukocyte trafficking.[8] The most widely accepted mechanism involves IFN-γ binding to its receptor, and activating the downstream Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. This pathway consists of Janus-activated kinases (JAKs) and STAT proteins.[9] Autoantibodies against IFN-γ disrupt its binding to its receptor, leading to a reduction in the phosphorylation of STAT1. This disruption impairs IFN-γ-induced STAT1 phosphorylation, thereby affecting downstream signaling processes.[10] STAT1 is a key transcription factor in the JAK-STAT signaling pathway and is crucial for various immune responses. When the IFN-γ receptor is blocked, STAT1 cannot be effectively activated, resulting in the suppression of relevant gene expression. This, in turn, compromises antigen presentation, cytotoxic T-cell activity, and other immune responses. Consequently, the immune defense of the body is weakened, leaving individuals vulnerable to bacterial, viral, and other pathogens. Acquired idiopathic generalized anhidrosis (AIGA) was first identified in patients with severe mycobacterial infections and is considered an autoimmune phenotype of congenital errors in the IL-12/IFN-γ axis.[11] Browne et al defined this HIV-negative immunodeficiency syndrome "adult-onset immunodeficiency" (AOID).[5] Many opportunistic infections, including fungal infections, TB, NTB, viral infections, and severe disseminated infection states, are strongly associated with AOID.[12–17] The first case of an "acquired" IFN-γ-mediated immune defect caused by autoantibodies was described in 2004. According to previous reports, genetic factors (HLA-DRB1*16:02/DQB1*05:02 haplotype) are the main cause of AOID.[6,18,19] One patient with this condition developed disseminated MTB and NTM infections, which ultimately led to death despite chemotherapy.[20] A study conducted in China followed 13 patients with AOID over an extended period, analyzing their clinical manifestations, laboratory findings, infection sites, and pathogen types. Of these patients, 12 patients developed NTM infections, and 5 were infected by two or more types of NTM.[21]

Previous case reports and small case series have revealed that AIGA-positive patients are particularly susceptible to specific strains of mycobacteria and exhibit a clinical course distinct from traditional MTB or NTM infections.[22–24] This susceptibility may be linked to the interference of autoantibodies with systemic and local immune responses, especially their impact on the activation and function of macrophages. However, the underlying mechanisms remain poorly understood, and no standardized treatment protocol has yet been established for these patients. To address this gap, the present study analyzed the data from 30 AIGA-positive patients with concurrent MTB infection who were treated at a hospital in Guangxi, China, between 2018 and 2023. The study evaluated their clinical manifestations, laboratory findings, radiological features, and treatment responses. Additionally, this study aimed to clarify the core features of this unique and complex condition, with the ultimate goal of advancing personalized treatment approaches and potentially improving the long-term prognosis for affected patients.

Materials and Methods

Test Subjects

A retrospective analysis was conducted on the clinical data of 30 patients with positive anti-IFN-γ autoantibodies who were consecutively admitted to the Fourth People's Hospital of Nanning from June 2018 to December 2023 and had concurrent mycobacterial infections. This study was approved by the Ethics Committee of the Fourth People's Hospital of Nanning ([2023]24), and all participants provided signed an informed consent. The inclusion criteria are as follows: (1) Patients diagnosed with avoidant dementia; (2) Confirmed mycobacterial infection through microbiological detection methods. Specific detection methods included, positive mycobacterial culture from specimens such as sputum, tissue fluid, and blood, and identification of pathogenic mycobacteria through species identification, or detection of mycobacterial-specific gene sequences through nucleic acid testing techniques (eg, polymerase chain reaction(PCR)), combined with clinical symptoms, imaging findings, and other comprehensive assessments to confirm mycobacterial infection. The exclusion criteria are as follows: (1) Patients who declined to sign the informed consent form, or whose legal guardians did not agree to participate. (2) Patients with incomplete diagnostic data, making it impossible to confirm a clearly diagnosis of mycobacterial infection. (3) Patients with HIV patients. (4) Patients with severe systemic diseases, such as end-stage malignant tumors (with a short expected survival period, which could interfere the follow-up and r outcome assessment result judgment of the study). Severe cardiovascular diseases (eg, acute myocardial infarction in the acute phase, or severe decompensated heart failure, where the patient's physical condition may not permit study-related examinations or follow-up). Severe liver and kidney failure (which may affect drug metabolism and immune status, interfering with the analysis of study factors). (5) Patients who had used immunosuppressants within three months prior to study inclusion.

Diagnosis Criteria

For IFN-γ antibody testing, 2 mL of venous blood was collected from each subject using a dry tube and EDTA-K2 as an anticoagulant. All samples were stored at 4°C and processed within 12 hours. The serum from the dry tube was aliquoted into 1.5 mL EP tubes, while the EDTA blood tubes were centrifuged at 800 g for 5 minutes. The upper plasma was then aliquoted into 1.5 mL EP tubes and stored at −80°C for subsequent plasma IFN-γ autoantibody detection. Recombinant human IFN-γ was prepared into a 1000 pg/mL working solution using the sample diluent from the ELISA kit. Plasma samples were diluted 1:200 in the sample diluent for testing. Specifically, 2 μL of plasma was mixed with 98 μL of diluent, followed by further dilution by 6 μL of the initial dilution was mixed with 234 μL of diluent. An indirect enzyme-linked immunosorbent assay (ELISA) was used to detect plasma IFN-γ antibodies. A transparent flat-bottom 96-well plate was coated with 100 μL of recombinant human IFN-γ working solution (2 μg/mL) per well and incubated at 4°C for 24 hours. After incubation, the wells were washed three times with 300 μL of freshly prepared washing solution, soaking for 1 minute during the final wash. Next, 100 μL of blocking solution (PBS containing 5% human serum albumin) was added to each well and incubated at room temperature for 2 hours. The plate was washed four times with 300 μL washing solution, and the last two washes were soaked for 3 minutes each. Plasma samples were then diluted in three gradients (1:100, 1:500, 1:2500) with sample diluent, and 100 μL of each gradient was added to wells, followed by incubation at room temperature for 2 hours. After washing three more times, 100 μL of horseradish peroxidase-labeled IgG (diluted 1:5000) was added to each well and incubated at room temperature for 1 hour. The wells were washed a final time, and 100 μL of TMB substrate was added to each well. After incubating at 37°C in the dark for 15 minutes, 100 μL of TMB stop solution was added to each well. The absorbance (OD value) at 450 nm was measured within 5 minutes using a multifunctional microplate reader and recorded. Samples with an OD value ≥ 0.5 were considered positive for IFN-γ autoantibodies, while those with OD values < 0.5 were considered negative.

The diagnosis of MTB infection was based on clinical evaluation and the "WS 288–2017 Diagnostic Criteria for Pulmonary Tuberculosis (TB)" published by the Chinese Center for Disease Control and Prevention. Pulmonary TB was confirmed if one or more of the following criteria were met: (1) positive microbiological results, including positive acid-fast bacilli (AFB) smear results or culture of M. tuberculosis from a specimen; AFB positivity was determined based on the number of acid-fast bacilli observed under fluorescence staining, following specific field-of-view requirements and

quality control standards, with a negative result defined as 0 bacilli per 50 fields of view. Mycobacteria were inoculated onto modified Lowenstein-Jensen solid medium, observed on the 3rd and 7th days, and monitored weekly thereafter. A positive smear result was reported immediately, with results within 7 days indicating rapid-growing mycobacteria, while results beyond 7 days indicated slow-growing mycobacteria. Negative results were reported after 8 weeks. TB was also diagnosed based on lung tissue biopsy findings consistent with TB pathology or if lesions reduced or disappeared after three months of anti-TB treatment. (Cases not meeting these criteria were classified as non-TB. For NTM infection or lung disease, diagnostic criteria followed guidelines from the American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Disease Society of America,[25] and the "Diagnosis and Treatment Guidelines for NTM Disease" (2020 Edition) issued by the Chinese Medical Association.[26]

Data Collection

Patient information was retrospectively collected using the electronic medical record system. The data included: (1) basic personal information, such as age, gender, place of origin, and other demographic information, (2) clinical data, such as fever, cough, other clinical symptoms, history of chronic diseases, and relevant symptoms of MTB infection, (3) radiological features, such as lesion range, cavity condition, and (4) treatment plans and disease outcomes.

Statistical Processing

Data analysis was performed using SPSS 23.0 statistical software. Categorical data were presented as "number of cases" and "rate (%)". Continuous variables following a normal distribution were expressed as mean ± standard deviation ($x \pm s$). Comparisons of means across multiple groups were conducted using one-way analysis of variance (ANOVA). A P value of less than 0.05 was considered statistically significant, indicating the differences between groups were unlikely due to random variation.

Results

Epidemiological Data

This article describes 30 cases of patients with AOID, all originating from Guangxi. HIV tests were negative for all cases. Based on the final comprehensive diagnosis by clinical doctors and the identified mycobacterial species, the patients were divided into three groups: 13 cases in the NTM group, 10 cases in the MTB, and 7 cases in the group co-infected with both NTM and MTB.

Clinical Feature Data

Among the 30 patients, cough and sputum production were the most common symptoms. NTM infections were predominantly extrapulmonary and disseminated, often accompanied by opportunistic infections caused by Mycobacterium avium complex (MAC) and other complications. The average time from onset to diagnosis was 10.2 months.

Cough was observed in 21 patients (70.00%), sputum production in 20 patients (66.67%), and lymphadenopathy in 16 patients (53.33%), making these the most frequent symptoms, experienced by over half of the patients. In patients with NTM or MTB infections, cough and sputum production were nearly universal, occurring in all cases. Other symptoms, though less common, were also reported: fever (14 patients, 46.67%), weight loss (12 patients, 40.00%), fatigue (10 patients, 33.33%), chest pain and shortness of breath (each 6 patients, 20.00%), night sweats (4 patients, 13.33%), and hemoptysis (1 patient, 3.33%) (Table 1). These symptoms provide valuable diagnostic clues, aiding clinicians in understanding patients' conditions and formulating appropriate treatment plans.

Among the 30 patients, over half had systemic disseminated NTM infections, while nearly half experienced extrapulmonary NTM infections. This suggests that NTM infections are not confined to the lungs but can widely affect multiple organs and systems. Opportunistic infections caused by MAC were the most common, with the majority presenting as disseminated infections. Additionally, blood abnormalities were prevalent among these patients, with 25 cases exhibiting varying degrees of anemia, and 15 cases presenting with hypoalbuminemia. These findings reflect

Table 1 Comparison of Clinical Features Among Patients with NTM, MTB, and Mixed Infections

Clinical Features	Total (%)	NTM (%)	MTB (%)	NTM&MTB (%)
Ethnicity				
Han	16 (46.67%)	7 (53.85%)	6 (60.00%)	3 (42.86%)
Zhuang	14 (53.33%)	6 (46.15%)	4 (40.00%)	4 (57.14%)
Gender				
Male	15 (50.00%)	3 (23.08%)	8 (80.00%)	4 (57.14%)
Female	15 (50.00%)	10 (76.92%)	2 (20.00%)	3 (42.86%)
Place of residence				
Rural	23 (76.67%)	9 (69.23%)	10 (100.00%)	4 (57.14%)
Urban	7 (23.33%)	4 (30.77%)	0 (0.00%)	3 (42.86%)
Age				
30~39	5 (16.67%)	2 (15.38%)	1 (10.00%)	2 (28.57%)
40~49	10 (33.33%)	5 (38.46%)	4 (40.00%)	1 (14.29%)
50~59	8 (26.67%)	5 (38.46%)	2 (20.00%)	1 (14.29%)
60~69	5 (16.67%)	0 (0.00%)	3 (30.00%)	2 (28.57%)
70~79	2 (6.67%)	1 (7.69%)	0 (0.00%)	1 (14.29%)
Symptoms				
Cough	21 (70.00%)	7 (53.85%)	7 (70.00%)	7 (100.00%)
Sputum production	20 (66.67%)	7 (53.85%)	6 (60.00%)	7 (100.00%)
Fever	14 (46.67%)	6 (46.15%)	7 (70.00%)	1 (14.29%)
Hemoptysis or coughing up blood	1 (3.33%)	0 (0.00%)	1 (10.00%)	0 (0.00%)
Night sweats	4 (13.33%)	1 (7.69%)	3 (30.00%)	0 (0.00%)
Fatigue	10 (33.33%)	3 (23.08%)	4 (40.00%)	3 (42.86%)
Weight loss	12 (40.00%)	6 (46.15%)	2 (20.00%)	4 (57.14%)
Chest pain	6 (20.00%)	3 (23.08%)	1 (10.00%)	2 (28.57%)
Shortness of breath	6 (20.00%)	1 (7.69%)	4 (40.00%)	1 (14.29%)
Swollen lymph nodes	16 (53.33%)	6 (46.15%)	5 (50.00%)	5 (71.43%)

a decline in overall health and the extensive impact of the infections on the body. The time from symptom onset to diagnosis ranged from 0.5 to 24 months, with an average of 10.2 months. This prolonged diagnostic timeline highlights the complexity of NTM infections and the challenges associated with their diagnosis (Table 2).

Table 2 Infection Types and Site Distribution in Patients with NTM, MTB, and Mixed Infections

	Total	NTM	MTB	NTM&MTB
Mycobacterium avium complex (MAC) infection	13	2	7	4
Lymph nodes	5	1	3	1
Bone	3	1	2	0
Bronchi	2	0	0	2
Pericardium	1	0	0	1
Peritoneum	1	0	1	0
Disseminated (≥3 sites)	20	11	9	0
Other Infections				
Mycobacterium marinum infection	18	4	9	5
Pulmonary infection (other bacteria)	6	3	2	1
Pulmonary infection (other fungi)	4	1	2	1
Pulmonary infection (bacterial and fungal co-infection)	10	2	5	3

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Laboratory Examination

The test results in Table 3 and Table 4 show specific changes in immune cell counts among patients in the NTM and MTB groups, and a diversity in tuberculosis-related microbiological test results. These findings may reflect the complexity of the patients' infection status and immune responses. A detailed hematological analysis of the three patient groups included indicators, such as white blood cell count and the proportion of neutrophils. However, no statistically significant differences were observed between these groups ($P > 0.05$) (Table 3). It is important to note that the limited sample size may have introduced selection bias, potentially affecting the generalizability and reliability of the results. In terms of microbiological testing, we identified several key points. The detection rate of the IGRA/ QuantiFERON test was relatively low. However, other diagnostic methods, including AFB, mycobacterium solid culture, Xpert, and TB-DNA, provided important

Table 3 Comparison of Laboratory Indicators Among Patients with NTM, MTB, and Mixed Infections

Laboratory Indicators	Total	NTM	MTB	NTM&MTB	P value
CD3+T lymphocytes (cells/μL)	1134.57±653.11	1120.92±566.38	1098.6±750.1	1211.29±752.77	0.940
CD4+T lymphocytes (cells/μL)	593.33±344.5	576±311.15	556.4±332.53	678.29±450.32	0.764
CD8+T lymphocytes (cells/μL)	494.8±325.6	511.31±311.62	486±379.79	476.71±317.36	0.971
CD4+/CD8+	1.58±1.12	1.29±0.54	1.93±1.74	1.62±0.77	0.409
Eosinophils (10^9/L)	0.65±0.44	0.63±0.49	0.56±0.37	0.8±0.46	0.559
Neutrophils (10^9/L)	13.73±7.98	15.21±9.34	13.08±6.83	11.89±7.32	0.657
White blood cell count (10^9/L)	16.85±8.41	18.52±9.63	15.61±7.65	15.52±7.61	0.652
C-reactive protein (mg/L)	93.71±35.45	104.98±29.01	82.13±33.49	89.33±46.77	0.298

Table 4 Comparison of Detection Methods (Tuberculosis Antibody, AFB, Xpert, TB-DNA, mNGS, Mycobacterium Culture (Roche), and TB-Related Interferon-Gamma Release Assay) for Patients with NTM, MTB, and Mixed Infections

Detection Methods	Total	NTM	MTB	NTM&MTB
Tuberculosis Antibody	25	12	8	5
Negative	8	2	4	2
Weakly Positive	5	4	1	0
Positive	12	6	3	3
AFB	30	13	10	7
Negative	23	9	9	5
Positive	7	4	1	2
Xpert	21	7	8	6
Negative	17	7	6	4
Positive	4	0	2	2
TB-DNA	27	10	10	7
Negative	21	10	6	5
Positive	6	0	4	2
mNGS	13	5	5	3
Negative	4	0	4	0
Positive	9	5	1	3
Mycobacterium Culture (Roche)				
Negative	18	5	7	6
Positive	12	8	3	1
TB-Related Interferon-Gamma Release Assay				
Negative	12	2	5	5
Positive	2	1	1	0
Uncertain	14	9	4	1

information regarding TB infection, and contributed to a more comprehensive understanding of the infection status. Additionally, metagenomic next-generation sequencing (mNGS) results showed 9 positive cases and 4 negative cases (Table 4).

Imaging Studies

Imaging studies revealed varying degrees of pathological changes in each patient's lungs (Table 5). The most common findings included scattered punctate, patchy, and fibrous streak shadows (Figure 1A and B), reflecting the widespread impact of the infection on the lung tissue. In some cases, further inflammatory developments, such as consolidation and ground-glass changes were observed, potentially indicating early signs of fibrosis (Figure 1C and D). Pleural effusion and pleural thickening were also common, suggesting that the pleura has been affected by the infection. Additionally, an increase in the size and number of hilar and mediastinal lymph nodes was frequently observed. Notably, imaging examinations of nearly all patients revealed involvement of multiple lung lobes, underscoring the extensive and systemic nature of the infection.

Bronchoscopy, Pathological Examination Results

Bronchoscopy mainly revealed airway inflammation and tumor formation, while inflammation was more commonly observed in the biopsy of lesion tissues.Fourteen patients underwent bronchoscopy (Table 6), with results indicating airway inflammation in six cases, tumor formation in six cases, and two cases exhibiting other types of specific types of lesions (some patients exhibited multiple concurrent pathological changes) (Supplementary Figure 1).

Biopsies of lesion tissues were performed on 16 patients. Inflammation was observed in 12 cases, and mass growths, such as granulomas and tumors, were identified in 3 cases. One biopsy showed no abnormalities (Table 7). Specifically, a pleural tissue biopsy from one patient revealed atypical granuloma formation, polymorphic giant cells, and localized necrotic tissue (Supplementary Figure 2). These include tissue abnormalities not visible to the naked eye, such as ulcers and necrosis.

Table 5 Comparison of Imaging Features in Patients with NTM, MTB, and Mixed Infections: Lesion Distribution, Pulmonary Signs, Pleural Changes, and Extrapulmonary Manifestations

Image Features	Total	NTM	MTB	NTM&MTB
Lesion area				
Unilateral distribution	2	2	0	0
Bilateral distribution	28	11	10	7
Pulmonary signs				
Cavity	2	1	1	0
Calcification	4	0	3	1
Spots/plaque shadows	26	13	9	4
Fibrous streak shadows	24	13	9	2
Ground glass shadow	8	5	2	1
Miliary shadow	2	2	0	0
Exudation/consolidation	14	9	3	2
Bronchiectasis	3	2	1	0
Emphysema	4	2	1	1
Atelectasis	4	1	2	1
Pleural changes				
Pleural effusion	10	5	3	2
Thickening of the pleura	11	8	3	1
Extrapulmonary manifestations				
Pericardial effusion	6	2	2	2
Thickening of the pericardium	2	1	1	0
Bone destruction	9	4	4	1
Increased or enlarged mediastinal and hilar lymph nodes	19	6	8	5

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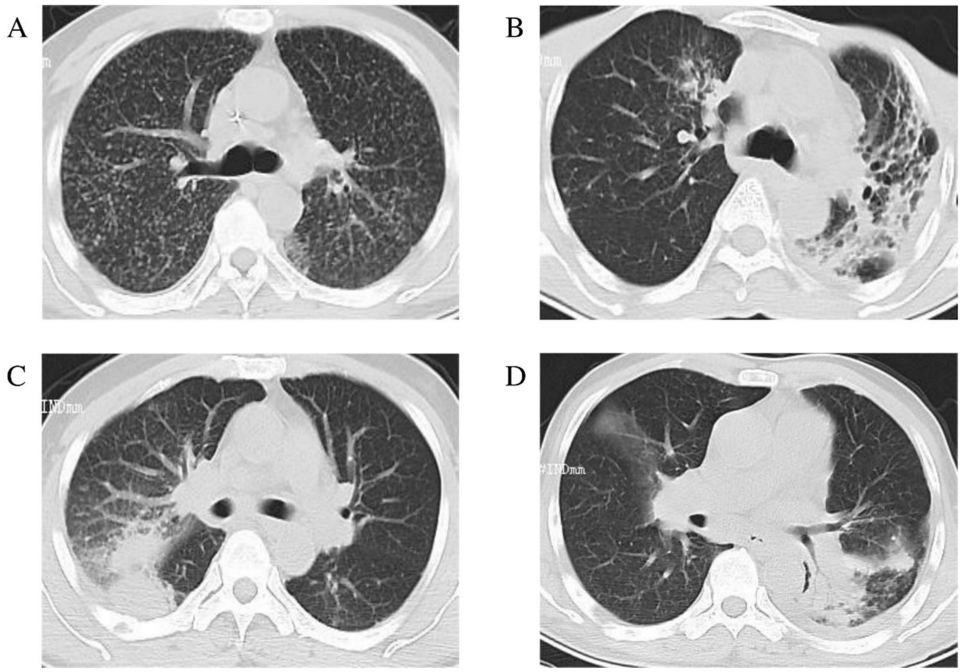

Figure 1 Imaging examinations. (**A**) Type II TB, with miliary nodules and scattered patches throughout both lungs. (**B**) Mycobacterium intracellulare, patchy shadows observed in each lobe of both lungs, multiple translucent areas in the lesion of the upper lobe of the left lung, indicating honeycomb changes. (**C**) TB, multiple patchy and nodular shadows observed in both lungs, consolidation shadow can be seen in the right upper lobe. (**D**) TB, combined with miliary TB, nodules, and patches were observed in both lungs, with partial consolidation in the lower lobe of the left lung.

NTM Classification and Prognosis

This study included detailed description of 20 NTM-positive patients (Supplementary Table 1). Two patients were diagnosed with NTM infections at other hospitals but lacked complete medical records, including specimen test results, and NTM subtype classification. Additionally, culture samples from three patients were confirmed as NTM, but specific species were not identified. One clinically diagnosed NTM patient did not undergo subtype typing.

Table 6 Comparison of Bronchoscopy Findings Among Patients with NTM, MTB, and Mixed Infections

Bronchoscopy	Total	NTM	MTB	NTM&MTB
Normal	2	1	1	0
Inflammation	6	2	2	2
Swelling	6	0	3	3
Other	2	0	1	1

Table 7 Comparison of Pathological Features in Patients with NTM, MTB, and Mixed Infections: Inflammation, Swelling, and Other Manifestations

Pathological Features	Total	NTM	MTB	NTM&MTB
Normal	1	0	1	0
Inflammation	12	4	4	4
Swelling	3	2	0	1
Other	0	0	0	0

Other: unidentifiable fragmentary necrosis, proliferation of unknown nature, etc.

Excluding patients with incomplete data, we found that most infections among NTM-positive cases were caused by MAC and Mycobacterium abscessus.

Treatment and Follow Up

Treatment measures included antimicrobial therapy and immunosupportive therapy. However, treatment discontinuation and loss to follow-up were common due to adverse drug reactions, high recurrence rates, and opportunistic infections. Specific treatment measures primarily cover the two aspects, such as immunoglobulin injection for immunosupportive therapy and antimicrobial therapy (including targeted treatment according to the type of pathogen, including anti-TB, anti-NTM, antifungal, and other anti-infective treatments).

Eight patients experienced adverse drug reactions, including fever, blurred vision, nausea, vomiting, allergic reactions, and renal dysfunction. Despite receiving treatment, many patients experienced recurrent infections and required repeated hospitalizations, primarily due to opportunistic infections. Two out of 30 patients died: one from respiratory failure, and the other after multiple hospitalizations (22 admissions, totaling 9 years) due to multiple organ failure related to opportunistic infections.

Unfortunately, most patients were unable to complete the full course of treatment, especially those requiring long-term treatment. Some abandoned treatment after experiencing temporary recovery, complicating follow-up efforts and preventing a thorough evaluation of treatment outcomes. As a result, the medical team struggled to track and assess long-term health statuses, leading to a high rate of loss to follow-up. The incomplete follow-up data further impacted the accuracy of assessing treatment efficacy and patient prognosis.

Discussion

IFN-γ is an important immunoregulator and anti-pathogenic factor produced by immune cells such as T cells and NK cells, which are crucial in enhancing the body's antibacterial defense, antigen processing capabilities, and inflammatory responses. IFN-γ regulates the differentiation of M1 macrophages, and processes related to growth control, cell apoptosis, tumor immunity, and autoimmune responses.[27,28] The key components in the signal transduction pathway of IFN-γ are its receptors, which consist of two different subunits, namely IFN-γ receptor 1 (IFN-γ R1) and IFN-γ receptor 2 (IFN-γ R2). These receptors work in conjunction with JAKs. When IFN-γ binds to its receptors, homodimers are formed, activating the JAK-STAT1 signaling pathway. Additionally, research suggests the involvement of other signaling pathways that cooperate with or run parallel to the JAK-STAT pathway, including mitogen-activated protein kinases (MAPK), phosphoinositide 3-kinase (PI3K), calcium–calmodulin-dependent protein kinase II (CaMKII), and nuclear factor-κB (NF-κB).[29] Once activated, phosphorylated STAT1 homodimers translocate into the nucleus, where they bind to gamma-activated sequences to regulate the expression of IFN-γ-responsive genes.

Within the intracellular environment, IFN-γ enhances resistance to microbial infections by positively regulating toll-like receptor (TLR) signaling pathways, activating guanosine triphosphate-binding proteins, and inducing the generation of reactive oxygen species (ROS) and reactive nitrogen intermediates(RNI). It also enhances antigen presentation by increasing the expression of MHC class I and II molecules, and amplifies IFN-γ signaling by promoting interleukin-12 (IL-12) production.[30] These mechanisms strengthen Th1-type immune responses, which are essential for combating intracellular pathogens. However, when the autoantibodies against IFN-γ are present in high titers, they inhibit signal transduction, including STAT1 phosphorylation, and IL-12 production, leading to severe impairment of Th1 responses.[31] This AOID syndrome caused by AIGA is closely associated with opportunistic infections in HIV-negative adults.[32] Patients with AOID typically exhibit increased susceptibility to pathogens, particularly intracellular organisms such as NTM, MAC, and salmonella species. Disseminated infections are common in these patients, leading to prolonged illness, delayed diagnosis, and poor prognosis.[21,33,34] The pathogenicity of mycobacteria primarily depends on their ability to colonize mucosal surfaces in the respiratory or gastrointestinal tracts, evade protective barriers, and survive within macrophages. In healthy individuals, such infections are rare, but in patients with compromised immune systems or underlying conditions, the risk of infection increases significantly. Pulmonary MAC infection is the most prevalent form of NTM infection, typically presenting as a localized infection. However, it can progress to the submucosal tissue, enter the bloodstream, and spread to other organs and tissues, leading to disseminated MAC infection.[35] Studies have shown

that patients with systemic immune deficiencies are more prone to disseminated NTM infections.[36] In this study, patients with MAC infections frequently exhibited disseminated disease. Furthermore, research has consistently demonstrated that persistent NTM infection is a c hallmark of AOID caused by AIGA.[37] In a separate retrospective study of 810 patients with positive anti-IFN-γ autoantibodies, 676 were found to have NTM infections.[38] Similarly, in this study of 30 patients with concurrent mycobacterium infections, 20 were diagnosed with NTM.

Although the unique clinical features of patients with AIGA-positive infections have been reported multiple times, the comprehensive understanding of this syndrome remains limited, and research into its pathological mechanisms has been relatively scarce. Besides, treatment strategies and management for this patient population present significant challenges, such as determining the most effective antibiotics, the appropriate duration of therapy, and the potential role of immunomodulatory therapy. This study systematically reviews and analyzes the clinical manifestations of patients with positive anti-IFN-γ autoantibodies and concurrent mycobacterial infections. Through this research, we aimed to enhance understanding of the disease's characteristics, diagnostic challenges, and treatment outcomes for this specific patient population, further guiding clinical practice, optimizing treatment strategies, and improving patient prognosis. Among the 30 patients included in this study, 13 cases (about 43.3%) involved NTM infection, highlighting the prevalence of NTM in AIGA-positive patients. This finding underscores the importance of recognizing and appropriately managing NTM infections in this population. Additionally, most patients (25 cases) experienced varying degrees of anemia, possibly due to the effect of chronic inflammation on red blood cell production or survival. Other common conditions included hypoproteinemia, hepatic dysfunction, and renal insufficiency, which could be attributed to malnutrition, protein loss, drug toxicity, or direct pathogen damage. Notably, one case involved multiple organ failure and combined with schistosomiasis japonica infection, underscoring the clinical importance of recognizing the diversity and complexity of TB-related complications.

In this study, elevated total white blood cell (WBC) and C-reactive protein (CRP) levels usually indicated the presence of an inflammatory response. During bronchoscopy, granulation tissue formation was observed. Granulomas are pathological markers of the host's response to TB infection, and their formation is rooted in innate inflammatory processes.[39] Granulation tissue consists primarily of newly formed, capillary-rich fibrous connective tissue, which develops in response to tissue damage to fill wounds or encapsulate foreign bodies. In the case of TB infection, granulation tissue formation represents the body's reparative response to the infection, indicating a direct indication of host-pathogen interaction. This observation aligns with previous hematological indications.

Although a comprehensive analysis of hematological indicators across the three groups was conducted, no significant differences were found. This suggests a degree of commonality in the physiological responses of patients with different types of infections regarding these specific hematological markers. It could reflect that certain immune and inflammatory responses are universal across various pathogens. However, this highlights the limitations of current hematological indicators in distinguishing between different types of infections. To more accurately assess the impact of different infection types on patients' physiological conditions, future research should explore new biomarkers or employ more advanced diagnostic technologies to enhance the specificity and sensitivity of diagnosis.

Consequently, assessing CD3+ T cells is crucial for evaluating and monitoring immune health. CD4+ T cells, typically associated with helper immune responses, showed increased levels in these patients, suggesting a heightened need for immune regulation to combat the infection. Conversely, CD8+ T cells, which are usually associated with cytotoxic responses, were relatively lower in patients with dual infections. This may indicate CD8+ T cell exhaustion, a phenomenon that can occur in certain infections. Moreover, the mean level of eosinophils was $0.56 \pm 0.37 \times 10^9$/L. Among the 30 patients studied, 20 demonstrated a significant increase in eosinophils at disease onset, indicating a potential trend toward allergic reactions or immunopathological mechanisms. Despite these inflammatory markers, patients with NTM and TB dual infections demonstrated lower levels of neutrophils, and total leukocytes, revealing the complex immune dysregulation caused by the diversity of infections.

In this study, all enrolled cases underwent thorough imaging examinations. The data revealed that, compared to patients with normal immune function, infections of TB in the lungs of immunocompromised individuals tend to exhibit more extensive dissemination and diffuse lesions.[40] In such patients, weakened defense mechanisms allow the microorganism to spread unrestrictedly in lung tissues, forming multiple infectious foci. This results in greater variability in

clinical responses to treatment and highlights the need for cautious, personalized treatment plans. Timely identification and management of infections are critical to prevent further deterioration of the condition or transmission to others.

Based on the analysis of laboratory data from 80 patients, we identified a series of laboratory indicators that reflect the co-infection status of AOID with mycobacteria, including CRP, WBC, and hematocrit.[41] These parameters provide important diagnostic references for clinicians to detect the status of mycobacterial infections. Increased levels of CRP, WBC, and ESR typically indicated the presence of an inflammatory response, which aligns with the bronchoscopy findings, further confirming active inflammatory in the body as a direct reaction to infection. Notably, the increased levels of CD3+ T lymphocytes, CD4+ T lymphocytes, and eosinophils in patients with multiple infections may reflect diverse immune responses and varying levels of inflammation in dual infections. These findings are significant for understanding the severity and dynamics of the disease. Based on these findings, we recommend that in clinicians closely monitor extrapulmonary mycobacterial infections in patients with anti-IFN-γ autoantibodies. Laboratory indicators such as CRP, WBC, and ESR should be routinely tracked to assess disease activity and inflammatory state. Additionally, detailed analysis of CD3+, CD4+, and CD8+ T lymphocytes, and eosinophils should be conducted to understand the immune response to infection and determine the need for immunomodulatory treatments. Finally, given the risk of multiple organ failure in these patients, clinicians should regularly assess organ function and adjust treatment plans promptly to optimize patient outcomes.

The diagnosis of anti-INF-γ autoantibody-positive immunodeficiency diseases primarily relies on laboratory tests, such as ELISA, which detects anti-INF-γ autoantibodies in the blood. It also requires a detailed assessment of the patient's clinical history, including recurrent infections and physical examinations. Among the 30 patients observed in our hospital, the diagnostic period ranged from 6 to 12 months. All cases were diagnosed after identifying opportunistic infection pathogens, which prompted subsequent testing for anti-IFN-γ autoantibodies. These cases underscore the importance of screening for anti-IFN-γ autoantibodies in patients repeatedly infected with opportunistic pathogens who test negative for HIV. At present, there are no specific therapies for AOID, and treatment focuses on symptomatic management and infection control. This typically involves long-term antibiotic therapy to prevent or treat infections and immunomodulatory treatments, such as corticosteroids or other immunosuppressants, aimed at reducing the levels of anti-INF-γ antibodies. Unfortunately, the prognosis for patients with co-infections remains poor. In the AOID patient population, even after targeted therapy, there is little evidence of a reduction in IFN-γ antibody titers, particularly in patients infected with TM, who often face a poor prognosis.[42] Case reports with small sample sizes further suggest that patients with AOID infected with mycobacteria, frequently develop disseminated mycobacterial disease, further exacerbating the severity of the their condition and leading to unfavorable outcomes.[43–45] Some studies have indicated that plasma exchange therapy can significantly improve clinical symptoms and may increase the function of immunoglobulins in the patients with immune deficiencies.[38,41] Besides, intravenous immunoglobulin (IVIG) therapy has also shown potentially beneficial in some case reports, although further research is needed to verify its effectiveness.[46,47] In this study, despite the use of treatments such as glucocorticoids, IVIG, and plasma exchange, the clinical outcomes were limited. Browne et al (2012) reported a successful case of treating NTM infection associated with anti-IFN-γ autoantibodies using rituximab.[48] In 2014, another AOID case was reported in which a patient received conventional treatment for mycobacterial infection in combination with rituximab. This therapy successfully reduced the patient's B-cell count, eradicated autoantibodies, and achieved sustained relief from infection.[49]

With ongoing research, rituximab is emerging as a promising immunomodulatory therapy for treating opportunistic infections in patients with anti-IFN-γ autoantibodies. However, due to the rarity of AOID cases, large-scale clinical trial data remain limited. Further studies are needed on evaluate the long-term efficacy and safety of rituximab, as well as its optimal integration into existing treatment regimens. Future research should focus on identifying the most efficacy and indications treatment protocols for rituximab in different populations. In addition to rituximab, other therapies have shown potential. Cyclophosphamide, rituximab, bortezomib, abatacept, and daratumumab have achieved partial success in treating similar conditions.[10] Recent studies have found that the combination of bortezomib and rituximab is significantly effective in preventing the production of new autoantibodies,[50] offering hope for new treatments for AOID patients.

The treatment of AOID combined with MAC presents many challenges, especially in managing patients undergoing long-term therapy. Due to the recurrent nature of the disease, some patients discontinue treatment shortly after

experiencing brief recovery periods. This makes it difficult for medical teams to track their treatment outcomes and health status, thus increasing the rate of loss to follow-up. A high proportion of lost-to-follow-up patients poses a significant challenge to effective disease management. Without continuous medical supervision, the health condition of these patients may deteriorate further, leading to a higher risk of poor prognosis. To address this issue, improving patient adherence to treatment plans is evident. This could involve enhancing patient education, providing increased social support, and strengthening medical tracking systems. These measures may help patients maintain treatment continuity, reducing recurrence and mortality rates and improving overall treatment outcomes.

The findings of this study provide valuable decision-making support for clinical physicians in the diagnosis and treatment of AOID. Additionally, they offer a scientific foundation for future in-depth research into the pathophysiological mechanisms of the disease and the development of new therapeutic strategies.

The limitations of this study are mainly reflected in three aspects, such as small sample size, incomplete patient records, and observational study design. Firstly, the small sample size reduces statistical power, increases the likelihood of random results, and limits the generalizability and reliability of the conclusions. It also fails to fully represent the diversity of the target population.

Secondly, incomplete records from some patients hinder the accurate assessment of treatment effectiveness and the accuracy of correlation analysis. This complicates data processing and increases the uncertainty of the results. Finally, as an observational cohort study, this research is unable to establish causal relationships. Confounding factors may influence the results, and the underlying mechanisms of complex biological processes, such as immune responses, limiting the ability to comprehensively understand disease mechanisms and therapeutic action pathways.

For future studies, we expand the sample size and adopt multicenter research designs to improve statistical power and the representativeness of results. We also need to refine data collection processes, enhance data review and quality control, and improve the training and awareness of medical staff to ensure the completeness and accuracy of data. For the challenge of determining causal relationships, we can employ more rigorous statistical methods, design prospective studies, and utilize instrumental variables and causal discovery algorithms to enhance the accuracy of causal inference. These approaches will help reveal the underlying mechanisms of immune responses and disease progression, providing a more comprehensive understanding of AOID and potential therapeutic interventions.

Conclusion

The immune deficiency caused by positive anti-IFN-γ autoantibodies closely resembles that seen in late-stage HIV/AIDS, rendering affected individuals highly susceptible to opportunistic infections. Among these infections, NTM are the most frequently identified pathogens, followed by MTB and TM. These findings highlight a novel form of immune deficiency that predisposes patients to a wide spectrum of opportunistic infections, posing new challenges to public health.

To address these risks, enhanced monitoring and management are essential for patients with positive anti-IFN-γ autoantibodies. Early detection and timely treatment of infections can significantly improve patient outcomes and mitigate the burden of these potentially life-threatening conditions.

Ethics Approval and Informed Consent

The Ethics Committee of Human Research Ethics Committee of the Fourth People's Hospital of Nanning (Approval No: [2023]24). All patients and legal guardians provided informed consent. This study complied with the principles of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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