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Clinical characteristics of acquired anti-IFN-γ autoantibodies in patients infected with *non-tuberculous mycobacteria*: a prospective cohort study

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Abstract

Background Patients with positive anti-IFN-γ autoantibodies (AIGAs) are characterized by susceptibility to disseminated infection by multiple pathogens. The clinical characteristics of *non-tuberculous mycobacterial* (NTM) infection with AIGAs positivity remain unclear.

Methods A prospective cohort study was conducted at the First Affiliated Hospital of Guangxi Medical University from January 2021 to January 2024. A total of 93 patients diagnosed with NTM infection were divided into two groups: AIGAs-positive with NTM infection and AIGAs-negative with NTM infection. The clinical manifestations, laboratory data, imaging examination, and pathogens were analyzed to characterize the disease.

Results A total of 44 AIGAs-positive and 49 AIGAs-negative patients with NTM infection were enrolled. Disseminated infections were significantly more common among AIGAs-positive patients ($P < 0.001$), with frequent co-infections involving *Talaromyces marneffei* (TM) and viruses. Additionally, AIGAs-positive patients exhibited elevated inflammatory markers and immunoglobulins. In the AIGAs-positive group, lymph nodes, bones, skin, and blood were the most frequently affected sites. Chest CT scans exhibited a range of findings. Over a mean follow-up period of 36 months, 56.82% of patients with AIGAs positivity experienced exacerbations despite undergoing regular anti-NTM therapy.

Conclusions AIGAs-positive patients with NTM infection exhibit elevated inflammatory markers, abnormal immune indicators, and coagulation function. Disseminated infections involving multiple organs are common, with frequent co-infection with TM and viruses. These patients may have unique symptoms, signs, and imaging findings compared to AIGAs-negative patients. Recurrence is common among these patients, highlighting the need for timely identification and intervention.

Keywords Anti-interferon-γ autoantibodies, *Non-tuberculous mycobacteria*, Clinical characteristics

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Introduction

Non-tuberculous mycobacteria (NTM) are human opportunistic pathogens whose source of infection is the environment. NTM infection has been increasingly diagnosed worldwide over recent decades. NTM species occur in a wide range of environments, including slow-growing and fast-growing species [1–4].

Adult-onset immunodeficiency (AOID) due to anti-interferon-γ autoantibodies (AIGAs) is characterized by a variety of opportunistic infections, such as recurrent and refractory NTM and *Talaromyces marneffei*(TM) [5]. Similar to *Mendelian susceptibility to mycobacterial disease* (MSMD), its clinical manifestations are diverse and include infections caused by pathogens within macrophages [6]. It has been observed that AIGAs-positive patients with NTM infection still experience recurrence after antibacterial treatment. Most AIGAs-positive cases have been reported in Thailand, Taiwan, southern China, and other Southeast Asian countries, mainly in specific regions of the globe [7]. The region we are located in, Guangxi, in southern China, is a high-incidence area.

High levels of AIGAs are produced by effector B cells. Previous studies have reported abnormal immune indices in AIGAs-positive patients, including elevated globulin (GLB) and immunoglobulin G (IgG) levels, decreased $CD4^+$ T cells [6–10]. AIGAs with neutralizing ability can disrupt the binding of IFN-γ to its receptor, thus inhibiting the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway and STAT-1 phosphorylation [5, 11]. As a result, these patients were prone to severe or fatal multiple intracellular pathogens infections. AIGAs in adults with disseminated NTM infections is strongly associated with two specific HLA class II alleles: *HLA-DRB1*16:02/ DQB1*05:02* and *HLA-DRB1*15:02/DQB1*05:01* [6, 12, 13]. However, there is a lack of systematic observation and detailed description of changes in the composition of immunocytes in the NTM patients with neutralizing AIGAs.

In this study, we systematically analyzed the clinical characteristics, immunological features, and survival outcomes of 93 patients with NTM infection and compared the differences between AIGAs-positive ($n=44$) and AIGAs-negative ($n=49$) subgroups. This study might provide the new recognition of NTM infection with AIGAs for the clinician and contribute to early diagnosis and treatment of these diseases.

Methods

Study subjects

This study was approved by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University (IRB Protocol Number: 2022-KT-Guike-127).

Study design and oversight

A 36-month prospective clinical study was conducted at the First Affiliated Hospital of Guangxi Medical University from January 2021 to January 2024. The inclusion criteria for all subjects were infections caused by NTM (with or without other opportunistic infections), necessitating hospitalization for treatment.

For diagnosing NTM infections, high-quality specimens including bronchoalveolar lavage fluid, lymph nodes, skin, purulent exudates, blood, sputum, and other clinical samples are required. These must demonstrate the presence of NTM pathogens, either individually or in combination, using culture and/or metagenomic next-generation sequencing (mNGS) with a significant copy number [14]. Additionally, the diagnosis must be supported by concurrent clinical and radiological symptoms of infection.

Disseminated infection implies the involvement of two or more non-contiguous organ sites, whereas localized infection indicates the involvement of a single organ site. Organ involvement is confirmed through biopsy, culture, mNGS, and/or characteristic imaging findings, and there is improvement following treatment of the primary disease.

Exclusion criteria included a history of HIV infection or acquired immune deficiency syndrome (AIDS). The subjects were divided into AIGAs-positive and AIGAs-negative groups based on their serum AIGAs titers and neutralization ability.

Exacerbation refers to a worsening of a patient's clinical condition, characterized by the recurrence of symptoms, signs, or worsening of laboratory findings after improvement of initial treatment, necessitating hospitalization. This includes those who suffered recurrent NTM infections or subsequently developed other opportunistic infections within the AIGAs-positive group. Alternatively, patients who initially stabilize after treatment but then experience a worsening due to not completing the course of therapy are also considered to be exacerbation. And the progression-free survival refers to the time from the initial treatment until the patient experiences an exacerbation or death, with death being included as an endpoint.

AIGAs-positive patients were followed up at regular intervals of 1, 3, 6, 9 months, and 1 year after the treatment. If patients did not recover within 1 year, the follow-up period was extended until their condition stabilized. At these time points, clinical and laboratory data, including titers of AIGAs, were recorded.

Detection of AIGAs and case definition

We identified the positive or negative AIGAs through indirect enzyme-linked immunosorbent assay (ELISA) on serially diluted plasma from healthy donors and patients. Recombinant human IFN-γ was coated on the well plate using carbonate-coated buffer (pH 9.5). Samples with optical density (OD) values above 0.5 were considered to be AIGAs-positive. The AIGAs-positive results were further divided into three titers based on different sample dilutions of 1:100, 1:500, and 1:2500.

Western blot (WB) analysis was performed to evaluate the function to neutralize the IFN-γ-induced STAT-1 phosphorylation in THP-1 cells. The patients' serum was incubated with recombinant human IFN-γ to stimulate the adherent macrophages induced from THP-1 cells by PMA (Phorbol 12-myristate13-acetate), which simulate the human immune environment. Samples of AIGAs-positive patients showed the ability of AIGAs to neutralize interferon, which inhibited the activation of the STAT1 pathway. The p-STAT1 protein detected in the AIGAs-positive group was low or absent. Normal and AIGAs-negative patients had activated expression of the p-STAT1 protein. Protein signal intensity was quantified by ImageJ software.

Indirect ELISA positive (OD > 0.5 in 1:100 dilution) and WB showed the presence of neutralizing capacity were considered as AIGAs-positive group. Negative results in indirect ELISA indicated negative AIGAs [15].

Clinical, laboratory, and outcome data

Clinical and laboratory data were collected at baseline, and patients were followed up for 36 months through a prospective, protocol-mandated approach. Data on clinical processes and outcomes were collected at different times during the visits. Progression-free survival (PFS), and overall survival (OS) were also recorded during the follow-up period.

Quantitative data were analyzed using measures such as mean, standard deviation, median, minimum, and maximum values. Categorical data were presented as absolute number and percentage. Subgroups were compared using statistical tests, such as t test for measurement data, Chi-square ($\chi 2$) or Fisher's exact probability test for count data, and Wilcoxon's rank-sum test for ordinal data. Statistical analysis and graph generation are conducted using SPSS (Version 27.0), R (Version 4.3.0), and GraphPad Prism (Version 10.2.1). A two-tailed P value less than 0.05 is considered statistically significant.

Results

Demographic, clinical characteristics, and laboratory examination

A total of 93 patients with NTM infection were enrolled in the study and divided into AIGAs-positive ($n=44$) and AIGAs-negative ($n=49$) subgroups according to the serum anti-IFN-γ autoantibodies. AIGAs-positive group included 21 females (47.7%) and 23 males (52.3%), with an average age of 52.66 years. There were no significant differences in sex, age, and BMI between the two groups ($P > 0.05$; Table 1).

Among the 44 AIGAs-positive patients, 33 (75%) were diagnosed with NTM infection by mNGS, 4 (9%) by culture, and 7 (16%) by both methods. In the AIGAs-negative group, 44 (89.8%) were diagnosed by mNGS, 2 (4.1%) by lung tissue pathology, 1 (2%) by lung lavage fluid NGS and lung tissue pathology, 1 (2%) by a combination of lung lavage fluid and lymph node mNGS with culture, and 1 (2%) by lymph node pathology and blood culture.

A higher proportion of patients in the AIGAs-negative group had underlying diseases ($P=0.007$; Table 1), with structural lung diseases, malignant tumors, and cardiovascular diseases (including hypertension) being more commonly observed (Supplementary Fig. 1). A higher percentage of patients in the AIGAs-positive group are from rural areas ($P=0.006$; Table 1). The median number of pathogens in the AIGAs-positive group was higher than that in the AIGAs-negative group ($P=0.017$; Table 1). The proportion of disseminated infection in AIGAs-positive group was 95.5%, which was markedly higher than that in AIGA negative group ($P<0.001$; Table 1).

Clinical symptoms of fever, chill, hypodynamia, poor appetite, osteodynia, nausea, dizziness and headache, and signs of superficial lymphadenopathy, anemic face, skin eruption and skin abscess, were more common in AIGAs-positive NTM-infected patients compared with AIGAs-negative NTM-infected patients ($P<0.05$; Table 1). Among them, 81.8% of AIGAs-positive patients had fever, mainly high fever, with an average body temperature of 39.23 ± 0.75℃ (Table 1).

The AIGAs-positive group presented with elevated levels of white blood cell (WBC), neutrophil (Neu), lymphocyte (Lym), eosinophil (Eos), monocyte (Mon), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Procalcitonin (PCT), Prothrombin Time (PT), D-dimer, Fibrinogen (FIB) compared with the AIGAs-negative group ($P<0.05$; Table 2). The AIGAs-positive group had lower levels of hemoglobin (HGB), cholinesterase (CHE), prothrombin activity (PTA) than the AIGAs-negative group ($P<0.001$; Table 2).

For immunological indicators, AIGAs-positive group showed elevated levels of CD8 + T cell, globulin (GLB), IgG, IgE, compared with the AIGAs-negative group ($P<0.05$). The AIGAs-positive group had lower levels of albumin (ALB) than the AIGAs-negative group ($P<0.001$; Table 2). The percentages of total T lymphocyte cells (T cell %) and CD4 + T lymphocyte cells (CD4 + T cells%)

Table 1 Comparison of clinical information and laboratory data between AIGAs-positive and AIGAs-negative patients with NTM infection

Variables	AIGAs-positive group($n=44$)	AIGAs-negative group($n=49$)	*P* value
General characteristics			
Gender, male n (%)	23(52.3)	33(67.3)	0.203
Average age (years)	52.66 ± 12.77	52.90 ± 17.14	0.939
BMI (kg/m^2)	21.09 ± 2.64	20.98 ± 4.16	0.879
Underlying diseases, yes n (%)	27(61.4)	42(85.7)	0.007
No. of underlying diseases	1[0–2]	2[1-3]	0.007
Residence, rural n (%)	34(77.3)	24(49.0)	0.006
No. of infective pathogens	4.00[2.25–7.75]	3.00[1.00–5.50]	0.017
Disseminated infection, yes n (%)	42(95.5)	27(55.1)	< 0.001
Clinical symptoms, n (%)			
Fever	36(81.8)	20(40.8)	< 0.001
Cough	37(84.1)	40(81.6)	0.754
Sputum	37(84.1)	34(69.4)	0.096
Emaciation	24(54.5)	17(34.7)	0.054
Chill	20(45.5)	6(12.2)	< 0.001
Hypodynamia	21(47.7)	10(20.4)	0.005
Poor appetite	20(45.5)	3(6.1)	< 0.001
Dyspnea	16(36.4)	14(28.6)	0.422
Dizziness and Headache	14(31.8)	4(8.2)	0.009
Osteodynia	14(31.8)	3(6.1)	0.003
Chest pain	11(25.0)	10(20.4)	0.597
Chest distress	8(18.2)	6(12.2)	0.424
Hemoptysis	7(15.9)	15(30.6)	0.096
Night-sweat	5(11.4)	2(4.1)	0.350
Nausea	5(11.4)	0(0.0)	0.021*
Abdominal pain	2(4.5)	3(6.1)	1.000
Clinical features, n (%)			
Superficial lymphadenopathy	36(81.8)	13(26.5)	< 0.001
Anemic face	18(40.9)	2(4.1)	< 0.001
Skin eruption	14(31.8)	4(8.2)	0.009
Moist rales	9(20.5)	5(10.2)	0.276
Skin abscess	7(15.9)	0(0.0)	0.004*
Hepatomegaly	4(9.1)	1(2.0)	0.296
Splenomegaly	5(11.4)	1(2.0)	0.160
Subcutaneous nodule	4(9.1)	1(4.3)	0.296
Highest temperature(℃)	39.23 ± 0.75	39.01 ± 0.61	0.270

* Fisher exact probability

were lower in the AIGAs-positive group, while that of IgG4, IgM were higher (Table 2).

Organ involvement

AIGAs-positive with NTM infection can involve multiple organs throughout the body. Involvement of lymph nodes, bone, skin, blood, spleen, liver, marrow and nasopharynx is more common in AIGAs-positive patients compared with AIGAs-negative patients ($P<0.05$; Table 3).

81.8% of AIGAs-positive patients with NTM infection had more than or equal to 3 organs involved, and the proportion of disseminated infection (involvement of at least two non-adjacent organs) in the AIGAs-positive group reached 95.5%, which were higher than those in the AIGAs-negative group. In addition, the median number of affected organs in the AIGAs-positive group

Table 2 Comparison of laboratory data between AIGAs-positive and AIGAs-negative patients with NTM infection

Variables	AIGAs-positive group($n=44$)	AIGAs-negative group($n=49$)	*P* value
WBC (x10^9cells/L)	15.58[10.97–19.41]	6.53[5.00–8.47]	< 0.001
Neu (x10^9cells/L)	11.10[7.88–16.67]	4.37[2.90–6.09]	< 0.001
Lym (x10^9cells/L)	1.78 ± 0.72	1.41 ± 0.65	0.012
Eos (x10^9cells/L)	0.46[0.22–0.91]	0.12[0.05–0.22]	< 0.001
Mon (x10^9cells/L)	0.83[0.51–1.1]	0.54[0.41–0.70]	0.001
HGB (g/L)	85.05[71.83–104.38]	119.30[111.80–127.50]	< 0.001
CRP (mg/L)	89.67[39.88–169.75]	5.20[1.10–26.79]	< 0.001
ESR (mm/h)	88.50[74.00–105.00]	24.00[9.75–54.00]	< 0.001
PCT (ng/mL)	0.33[0.11–0.83]	0.06[0.03–0.09]	< 0.001
CHE (U/L)	4133.00[3187.00–5342.00]	7507.00[6562.00–8985.00]	< 0.001
PT (s)	12.95[11.93–14.05]	11.60[11.10–12.50]	< 0.001
PTA (%)	80.95 ± 15.00	93.39 ± 17.39	< 0.001
FIB (g/L)	5.16 ± 1.21	4.01 ± 1.24	< 0.001
D-dimer (mg/L)	209.10[64.10–519.75]	52.90[22.40–151.57]	< 0.001
CD4 + T cell (cells/μL)	583.00[385.00–1042.00]	618.00[373.75–843.00]	0.775
CD8 + T cell (cells/μL)	551.00[313.00–696.00]	390.50[201.25–512.75]	0.006
T cell %	66.17 ± 11.90	70.77 ± 9.66	0.065
CD4 + T cells%	35.41 ± 10.38	42.01 ± 7.94	0.002
CD8 + T cells%	28.65 ± 9.99	25.20 ± 9.58	0.125
CD4/CD8	1.15[0.82–2.04]	1.78[1.47–2.46]	0.009
IgG (g/L)	21.38[16.77–29.61]	12.70[11.26–15.58]	< 0.001
IgE (g/L)	184.55[32.52–601.63]	46.70[19.50–161.70]	0.007
IgA (g/L)	2.78 ± 1.15	2.64 ± 1.21	0.573
IgM (g/L)	1.13[0.72–1.50]	0.94[0.57–1.65]	0.482
IgG4 (g/L)	1.11[0.62–2.71]	0.76[0.52–1.66]	0.064
GLB (g/L)	42.05[36.18–48.33]	30.5[27.85–36.40]	< 0.001
ALB (g/L)	30.62 ± 5.09	37.67 ± 5.98	< 0.001

was 4, which was significantly greater than that in the AIGAs-negative group (*P < 0.001*; Table 3).

Superficial lymph nodes and deep lymph nodes were respectively involved in 81.8% and 77.3% of AIGAs-positive NTM-infected patients, significantly higher than the AIGAs-negative group (*P < 0.001*; Supplementary Table S1). Among superficial lymph nodes, cervical lymph nodes and axillary lymph nodes were mostly common involved; among deep lymph nodes, mediastinal lymph nodes were most frequently involved (Supplementary Table S1).

Infection of pathogens

Figure 1 demonstrates species and affected proportions of NTM as well as co-infected fungi, viruses, and common bacteria between AIGAs-positive group and AIGAs-negative group.

The NTM infected by the AIGAs-positive patients include *M. avium* ($n=11$; 25.0%; Supplementary Table S2), *M. abscessus* ($n=10$; 22.7%; Supplementary Table S2), *M. colombiense* ($n=7$; 15.9%; Supplementary Table S2), *M. intracellulare* ($n=7$; 15.9%; Supplementary Table S2), *M. fortuitum* ($n=5$; 11.4%; Supplementary Table S2), *M. gordonae* ($n=2$; 4.5%; Supplementary Table S2), *M. kansasii* ($n=2$; 4.5%; Supplementary Table S2), *M. triviale* (n = 1; 2.3%; Supplementary Table S2), *M. aurum* ($n=1$; 2.3%; Supplementary Table S2), *M. asiaticus* ($n=1$; 2.3%; Supplementary Table S2), other NTMs ($n=2$; 4.5%; Supplementary Table S2), Rapidly growing mycobacteria and nonchromogens belonging to the slowly growing mycobacteria are more popular. However, there was no significant difference in the types of NTM between the AIGAs-positive group and AIGAs-negative (Supplementary Table S2).

AIGAs-positive patients with NTM infection were prone to merging with other opportunistic pathogens. For fungi, the proportion of AIGAs-positive NTM-infected patients co-infected with TM was significantly higher compared with the AIGAs-negative group (*P < 0.05*; Supplementary Table S2). Regarding viruses,

Table 3 Comparison of involved organs between AIGAs-positive and AIGAs-negative patients with NTM infection

Variables	AIGAs-positive group($n=44$)	AIGAs-negative group($n=49$)	*P* value
Involved organs, n (%)			
Lung	41(93.2)	49(100)	0.102*
Lymph nodes	40(90.9)	25(51.0)	< 0.001
Bone	30(68.2)	3(6.1)	< 0.001
Skin	11(25.0)	1(2.0)	0.003
Blood	10(22.7)	0(0.0)	< 0.001*
Pleura	3(6.8)	2(4.1)	0.902
Spleen	7(15.9)	0(0.0)	0.004*
Soft tissue	6(13.6)	1(2.0)	0.085
Liver	5(11.4)	0(0.0)	0.021*
Marrow	5(11.4)	0(0.0)	0.021[a]
Nasopharynx	7(15.9)	0(0.0)	0.004*
Brain	3(6.8)	0(0.0)	0.102*
Pericardium	2(4.5)	1(2.0)	0.924
Number of organs involved ≥ 3, yes, n (%)	36(81.8)	4(8.2)	< 0.001
Disseminated infection, yes, n (%)	42(95.5)	27(55.1)	< 0.001
Number of organs involved, yes, n (%)	4[3–5]	2[1-2]	< 0.001

* Fisher exact probability

Torque teno virus (TTV), *Varicella-zoster virus* (VZV), *Cytomegalovirus* (CMV), *Epstein-Barr virus* (EBV), and some other herpes viruses were more frequently detected in the AIGAs-positive group, and were significantly different from those in the AIGAs-negative group ($P<0.05$; Supplementary Table S2). *Adenovirus* (ADV) and other viruses have also been detected in patients with NTM infection (Supplementary Table S2). Common bacteria that cause co-infection include *tuberculosis* (TB), *Streptococcus pneumoniae* (SP), *Staphylococcus aureus* (S. aureus), *Klebsiella pneumoniae* (KP), *Acinetobacter baumannii* (A. baumannii), *Stenotrophomnas maltophilia* (S. maltophilia), and *Haemophilus parainfluenzae* (HPi). However, no significant differences in the types of bacterial infections were observed between the two groups (Supplementary Table S2).

Computed tomography (CT) scan

In this analysis, most patients demonstrated bilateral lung compromise in both the AIGAs-positive and AIGAs-negative groups. Lung involvement was indicated by consolidation, nodules or masses, cavitation, pulmonary atelectasis, bronchiectasis, interstitial lung disease, pleural effusion, and mediastinal lymphadenopathy. Compared with the AIGAs-negative group, AIGAs-positive patients more often demonstrated mediastinal lymphadenopathy, pleural effusion, and bronchiectasis ($P<0.05$; Supplementary Table S3). Right lung involvement was more common in the AIGAs-positive group (Supplementary Table S4).

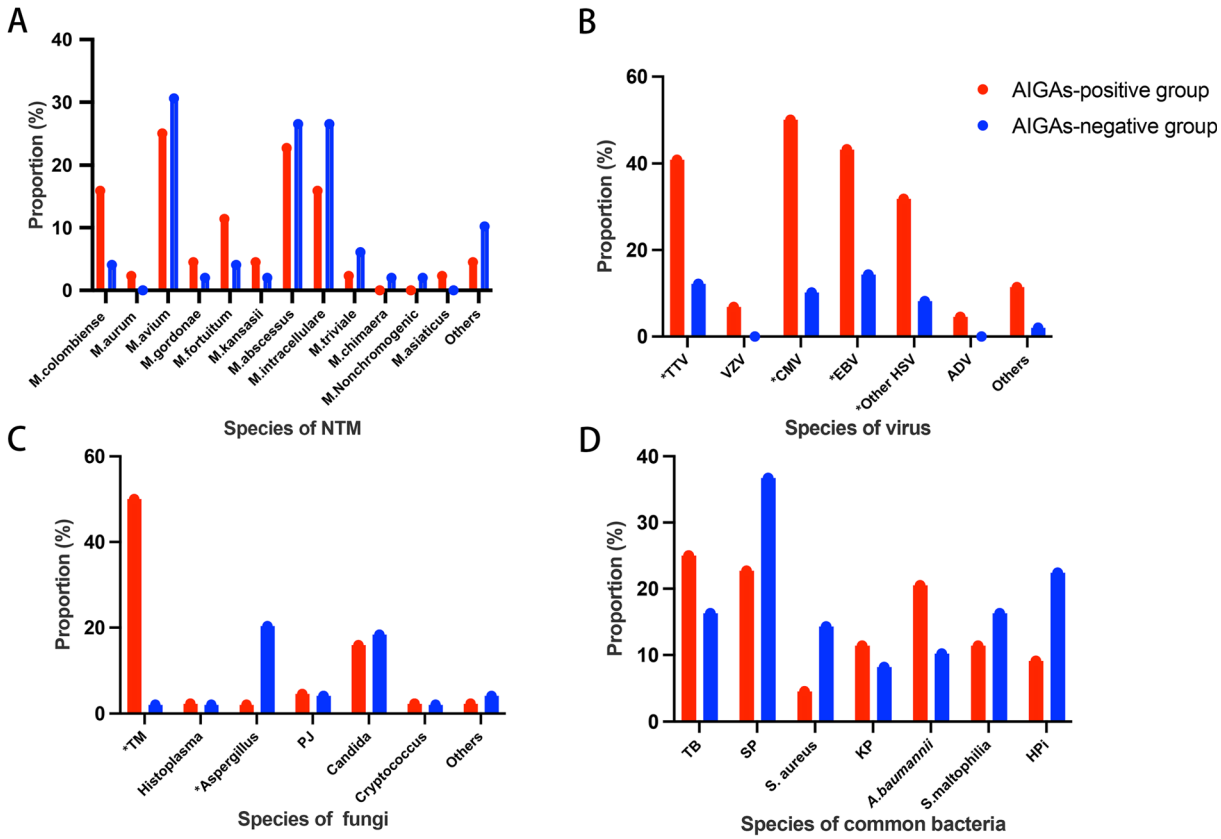
Outcomes of participants

We conducted a long-term follow-up for 36 months on all 93 enrolled patients. Of 44 AIGAs-positive NTM-infected patients, 37 (84.1%) completed a course of regular anti-NTM treatment for more than one year. 3 died after antimicrobial treatment, and 25 (56.82%) experienced exacerbations. In the AIGAs-negative group after 36 months follow-up, 48 patients survived, 1 died, and 16 (32.65%) experienced exacerbations.

The AIGAs-positive and AIGAs-negative groups showed 32.7% (95% CI: 29.89%-35.51%) and 65.3% (95% CI: 60.14%-70.46%) PFS rate, respectively (Fig. 2). The hazard ratio (HR) for recurrence in the AIGAs-positive group was 2.181(95% CI: 1.146–4.419), which is higher than that in the AIGAs-negative group, and the difference was statistically significant ($P=0.017$, Fig. 2). The OS rates were 84.0% (95% CI: 78.88%–89.12%) in the AIGAs-positive group and 87.3% (95% CI: 82.50%–92.10%) in the AIGAs-negative group. The risk of death was not significantly different between the two groups ($P=0.421$).

Discussion

In this study, we conducted a comprehensive analysis of the clinical and immunological characteristics, as well as survival and prognosis, in AIGAs-positive patients with NTM infection. Our findings revealed that these patients exhibited elevated infection markers and abnormal immune indicators. Common clinical manifestations of these patients include fever, chill, hypodynamia, poor



**P<0.05*

Fig. 1 Species and affected proportions of pathogens between AIGAs-positive group and AIGAs-negative group. (**A**) Comparison of species and affected proportions of NTM between AIGAs-positive group and AIGAs-negative group. (**B**) Comparison of species and affected proportions of virus between AIGAs-positive group and AIGAs-negative group. (**C**) Comparison of species and affected proportions of fungi between AIGAs-positive group and AIGAs-negative group. (**D**) Comparison of species and affected proportions of common bacteria between AIGAs-positive group and AIGAs-negative group. *, proportion between the two groups has significant difference, $P < 0.05$. Abbreviation: M., Myobacterium; TM, Talaromyces mameffei; PJ, Pneumocystis jiroveci; TTV, Torque teno virus; VZV, Varicella-zoster virus; CMV, Cytomegalovirus; EBV, Epstein-Barr virus; ADV, Adenovirus; TB, tuberculosis; E. coli, Escherichia coli; KP, Klebsiella pneumoniae; HPi, Haemophilus parainfluenzae

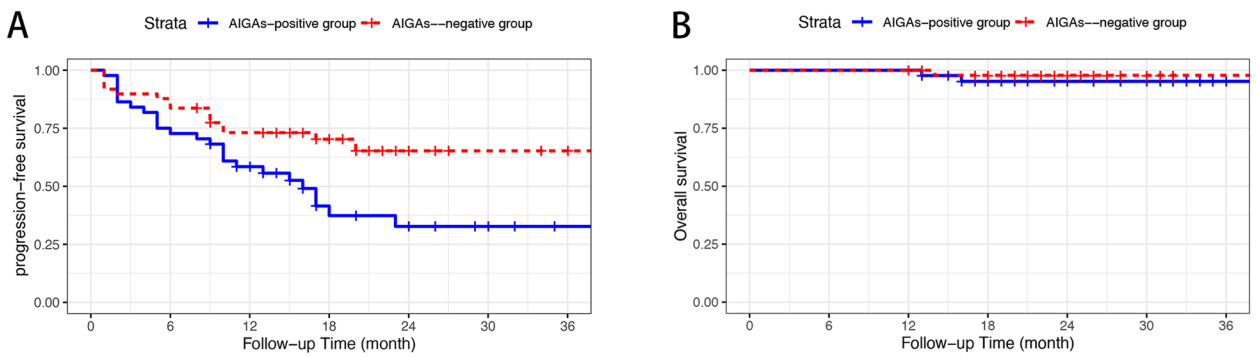


Fig. 2 Kaplan–Meier curves of PFS and OS of the whole population (0 means when admitted to hospital; 6, 12, 18, 24,30 and 36 indicate follow up for 6, 12, 18, 24,30 and 36 months)

appetite, osteodynia, nausea, dizziness and headache, and superficial lymphadenopathy, anemic face, skin eruption, skin abscess. Disseminated infections involving multiple organs were frequently observed, with TM and various types of viruses being the main co-infections. Moreover, the incidence of lymph node, bone, and skin involvement, as well as bloodstream infections, is relatively high. Additionally, 7 (15.9%) patients developed skin abscesses that were not seen in the AIGAs negative group. It was found that the infection, clinical characteristics and prognosis of NTM diseases are closely related to anti-IFN-γ autoantibodies with neutralizing ability [7, 15, 16]. It is worth noting that AIGAs-positive patients are more prone to recurrence or worsening after receiving regular anti-NTM treatment. Prompt identification and management of AIGAs-positive individuals with NTM infection may better improve clinical outcomes.

AIGAs-negative patients with NTM infection showed similar distributions of gender, age, and BMI, but the AIGAs-positive patients are more commonly found in rural areas. However, since the study hospital is in a tropical area and is an area inhabited by ethnic minorities, geographical distribution bias cannot be ruled out. Additionally, the living environment and nutritional status can affect immune function, resulting in an amplification of immunodeficiency issues [17, 18].And the subsequent research should enlarge the sample size and conduct multicenter studies.

In AIGAs-negative patients with NTM infection, there is a higher proportion and number of underlying diseases, particularly structural lung diseases and malignant tumors. Although these patients may not have immune deficiencies, they still experience more severe NTM infections, possibly due to these underlying diseases increasing their susceptibility to NTM infection [19]. Among them, structural lung disease is a common underlying disease in patients with AIGAs-negative NTM infection. Previous studies have shown that the prevalence of NTM lung disease is higher in patients with bronchiectasis, and factors such as nodular bronchiectasis are independently associated with NTM infection [20]. Therefore, the underlying airway structural abnormalities and impaired clearance functions may be important factors contributing to the increased risk of NTM infection.

More than 95% of AIGAs-positive patients with NTM infection involve disseminated infections in multiple organs, accompanied by a greater diversity of pathogens and affected organs. These severe infections may be induced by neutralizing AIGAs. AIGAs prevent IFN-γ binding to its receptor by neutralizing IFN-γ and inhibits STAT1 phosphorylation. This disrupts cytokine production and increases susceptibility to intracellular pathogens, causes dispersal of infection in body, especially opportunistic pathogens such as NTM [6].

Interestingly, we observed that some specific symptoms may not be related to infection, such as skin rash which is also common in AIGAs-positive patients, maybe it's related to immune damage. In our previous study, we also found AIOD due to AIGAs with immune damage in the eyes and skin after infection control, which was relieved by treatment with glucocorticoids [10, 21].

Skin eruptions can arise from both infectious and non-infectious etiologies. Infectious causes may include bacteria such as TM and NTM or viruses like the VZV. Non-infectious causes can stem from immune-mediated skin damage, and despite negative results from repeated biopsies, mNGS testing, and cultures, symptoms often improve with corticosteroid treatment [15, 21]. Regardless of the cause, whether infectious or non-infectious, the clinical presentations of rashes are diverse and not highly specific. Symptoms of rashes can manifest as ulcers, erythema, vesicles, nodules, and other dermatological findings. However, skin manifestations are a frequent feature of this kind of syndrome, including skin infections and immune damage such as *Sweet* syndrome [21, 22].

There was no significant difference in the types of NTM and bacteria infected between the two groups, indicating that the immune deficiency does not have an impact on the pathogen types of NTM and bacteria. However, it is relatively common for AIGAs-positive patients to be susceptible to TM [5]. Additionally, many types of viruses were more frequently detected in the AIGAs-positive group. This may also be related to the neutralization of IFN-γ by AIGAs. IFN-γ plays a crucial role in viral infections, especially retroviruses, by preventing viral replication and promoting innate and adaptive immune responses. At the same time, IFN-γ is also the core of eliminating viruses in the central nervous system [23, 24]. Further research is needed on the susceptibility of AIGAs to viruses.

We must note that the clinical manifestations of AIGAs syndrome often result from damage to the entire body due to multiple pathogen infections, not just a single pathogen. Research indicates that AIGAs patients can be infected with up to 7 different pathogens, either sequentially or simultaneously [25]. However, our assessment of co-infections in patients cannot rely solely on mNGS and other test results. If patients lack relevant clinical manifestations and radiological findings, or if the mNGS sequence count is low, consider the possibility of colonization or contamination rather than a true disease.

Notably, this study found that AIGAs-positive patients had elevated levels of GLB and immunoglobulins including IgG, IgE, and IgG4. Elevated globulin and IgG levels

may be associated with the presence of AIGAs, while increased IgG4 levels may be associated with the subtype of AIGAs present [5]. Another point that caught our attention was the elevated IgE and Eos levels in AIGAs-positive patients. IgE is usually elevated in pathological states with low healthy levels and plays an important role in the regulation of allergic reactions [26]. Increase in Eos is generally associated with allergies, parasitic infections, blood system diseases, and rheumatic diseases [27]. The elevated IgE and Eos levels in these patients may be related to allergic reactions, pathogenic infections, or even IgE subtype AIGAs, which requires further exploration. Abnormal coagulation function of patients in the positive group may also indicate prognosis. A study on COVID-19 showed that the coagulation status of critically ill and deceased patients was worse than that of patients with mild infection, including increased D-dimer, and prolonged PT [28].

In addition, during the follow-up process, we observed that these patients experienced acute exacerbations during the infection phase. Once the infection was controlled, they entered a stable phase. However, even in this stable phase, they remain susceptible to recurrent infections due to various reasons, such as incomplete therapy leading to a relapse, or the development of a new co-infection with a different pathogen, which can trigger a return to exacerbation. This aligns with our previous cohort study on AIGAs syndrome [15].

56.8% suffered recurrent NTM infections or subsequently developed other opportunistic infections after regular anti-NTM treatment in the AIGAs-positive group. For patients with neutralizing AIGAs, antibiotic treatment only was prone to relapse. Until now, apart from anti-infectious therapy, no standardized approach has been established to treat adult-onset immunodeficiency patients with anti-IFN-γ autoantibodies. Rituximab, exogenous IFN, plasma exchange, cyclophosphamide, and glucocorticoids have been used to treat refractory infections [10, 13, 29–31].

Understanding the clinical characteristics of AIGAs-positive patients with NTM infection can help clinicians in identification and diagnosis. Patients who were previously healthy but developed multiple organ involvement, recurrent fever, anemia, lymph node and skin involvement, abnormal infection indicators and immunoglobulin, and chest CT showing mediastinal lymphadenopathy and pleural effusion, should be tested for AIGAs. AIGAs-positive patients exhibit abnormalities in infectious indicators and non-infectious immune indicators (elevated WBC, neutrophils, C-reactive protein, etc.) as well as abnormalities in non-infectious indicators (elevated IgE, IgG, CD4+T cell, etc.). Research by Nasikarn Angkasekwinai suggests that ESR and CRP are auxiliary means for the clinical assessment of disease activity, while changes in AIGAs levels are significantly associated with treatment outcomes [16]. Studies by Ye Qiu indicate that high globulin and IgG levels, low CD4+T cell levels, dual or multiple infections, and disseminated infections are potential effective predictive factors for AIGAs positivity in HIV-negative patients with TM and/or NTM infections [25]. Our team's research shows that elevated AIGAs, IgG, IgG4, and IgE in AIGAs-positive patients suggest an abnormal immune damage, and patients with increased AIGAs titers and immune indices may benefit from glucocorticoid therapy [15]. In summary, monitoring these indicators may be related to prognosis, and our future research will explore specific intervention measures.

The pathogenesis and treatment of the AIGAs-related syndrome are still unclear. Future research should expand the sample size and conduct multi-center studies.

Conclusion

AIGAs-positive patients with NTM infection showed elevated inflammatory markers, abnormal immune indicators and coagulation function. Disseminated infections involving multiple organs are predominant, co-infecting with TM and viruses might be most frequent. Symptoms, signs, and imaging examinations have special manifestations compared to AIGAs-negative patients. These patients are prone to recurrence, Timely identification and intervention are important.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
HL, SL, YN contributed equally to this work. ZH designed the study, ensuring data accuracy, while NC and XH conducted experiments. RN, PY, HW, LH, SW, QZ, ZL, DQ and XL gathered clinical data and followed up with patients. HL and SL analyzed data statistically and assisted in manuscript drafting, YN prepared the figures and tables. ZH also revised the manuscript, which was read and approved by all authors.

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Data availability
The information presented has not been shared before. Data are available upon request from the corresponding authors.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University (IRB Protocol Number: 2022-KT-Guike-127) and adhered to the Declaration of Helsinki. Informed consent was obtained from all patients.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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