Journal of Clinical Immunology (2025) 45:93
https://doi.org/10.1007/s10875-025-01885-z

REVIEW

Deepening Understanding of the Clinical Features and Diagnostic Approaches to Anti-Interferon-Gamma Autoantibody Associated Adult-Onset Immunodeficiency in the Last 20 Years: A Case Report and Literature Review

Liyan Zhao[1] · Jindi Ma[1] · Ying Sun[1] · Xiaopeng Yu[1] · Yingfeng Lu[1] · Haijiang Qian[2] · Ren Yan[1] · Yimin Zhang[1,2]

Received: 26 October 2024 / Accepted: 30 April 2025

Abstract

Anti-interferon-gamma autoantibody (AIGA)-associated adult-onset immunodeficiency (AOID) is an emerging disease that can lead to serious opportunistic infections, which has a history of 20 years since it was first reported in 2004. It's a hard-detected AOID caused by AIGA. In recent years, there has been an increasing number of reports on the disease, but there is still a lack of consensus on the diagnosis and treatment. We here report a case of a 70-year-old Chinese male who had had AIGA in serum and suffered from recurrent pyothorax. Although his condition improved with antimicrobial therapy each time, his pyothorax frequently relapsed, requiring repeated hospitalizations. A literature review of AIGA-associated AOID was conducted. We searched PubMed, Web of Science, Embase, and the Chinese literature database for manuscripts concerning AIGA. Cases detected with AIGA and met our criteria were included. A total of 502 patients were retrospectively analyzed, with 256 (51.0%) males and 246 (49.0%) females. The majority of patients are from Southeast Asia (98.2%). Lymph node (83.7%) is the most commonly involved organ, followed by the lung (60.6%). Nontuberculous mycobacteria (NTM) was identified as the predominant pathogen reported in 77.49% of the patients. The clinical manifestations are diverse and non-specific for the disease often presenting with multi-organ involvement and multiple infections. Timely identification of patients with AIGA, appropriate diagnosis, and individualized treatment are critical; thus, we propose a reasonable diagnostic criterion and a structured diagnostic and treatment process based on our findings to provide clinicians with comprehensive information for clinical practice.

Keywords Anti-interferon-gamma autoantibody · Adult-onset immunodeficiency · Nontuberculous mycobacteria · *Talaromyces marneffei* · Pyothorax

Introduction

Anti-interferon-gamma autoantibody (AIGA)-associated adult-onset immunodeficiency (AOID) is an acquired immunodeficiency resulting from the presence of anti-cytokine autoantibodies and is an emerging disease that can cause serious diffused opportunistic infections. It was first reported in 2004 [1, 2]. Patients often present with complex, long-lasting, recurrent opportunistic infections that resemble the clinical features of Acquired Immune Deficiency Syndrome (AIDS) [3]. It is also similar to Mendelian susceptibility to mycobacteria disease (MSMD), which can cause congenital genetic defects in the IL-12/interferon-gamma (IFN-γ) pathway and result in genetic immunodeficiency [4, 5]. Due to the intricate and non-specific nature of clinical

Liyan Zhao and Jindi Ma authors contributed equally to this work.

Yimin Zhang is the Leading contact.

✉ Ren Yan
1514090@zju.edu.cn

✉ Yimin Zhang
1307020@zju.edu.cn

[1] State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

[2] Department of Infectious Diseases, Haining People's Hospital, Haining, China

Published online: 13 May 2025

manifestations, coupled with insufficient clinical awareness, the incidence of AIGA-associated AOID is likely significantly underestimated. Here, we report a case of recurrent pyothorax associated with the presence of AIGA. The diagnosis of AIGA-associated AOID was established despite the patient's atypical clinical presentation and infecting pathogens. The case was thoroughly discussed to illustrate the diagnostic approach. Moreover, we conducted a literature review, through which we systematically summarized the clinical characteristics of AIGA-associated AOID. Based on the findings, we proposed a diagnostic criterion and a clinical evaluation process aimed at improving clinical awareness and diagnostic accuracy among healthcare providers. This study was approved by the Medical Ethics Committee of Haining People's Hospital [Approval No. 2022(23)], following the principles of the Declaration of Helsinki.

Case Presentation

A 70-year-old man from China was admitted to our hospital with a 1-week history of chills, fever, and epigastric pain of unclear origin. Prior to referral, he had received treatment at a local health center with piperacillin-tazobactam, cefotiam, and azithromycin, but his condition showed minimal improvement.

Upon admission, the patient still had a low-grade fever (temperature 37.3 ℃). Laboratory investigations revealed a white blood cell count of 5.7×10^9/L (neutrophil 85.9%, lymphocyte 7.1%), hemoglobin 125 g/L, C-reactive protein (CRP) 229.6 mg/L, and immunoglobin G (IgG) 17.27 g/L (upper normal level: 17.4 g/L). A cardiothoracic CT scan revealed a left-sided encapsulated pleural effusion. He was diagnosed with"pyothorax". The patient was initiated on empiric anti-infective therapy with cefoperazone sulbactam and moxifloxacin. Ultrasound-guided thoracentesis was performed to relieve symptoms. The pleural fluid was dark and turbid. Biochemical analysis of the pleural fluid showed a total protein concentration of 0.5 g/L, adenosine deaminase level of 96.9U/L, lactate dehydrogenase level of 12744 IU/L, and ultrasensitive CRP level of 10.3 mg/L. Routine examination of the pleural fluid showed a positive Levantine test, a white blood cell count of $36{,}891 \times 10^6$/L (neutrophil 87%, lymphocytes 6%, monocytes 6%, mesothelial cells 1%), and an erythrocyte count of $110{,}000 \times 10^6$/L. The diagnosis of pyothorax was confirmed. Acid-fast staining and culture were performed in pleural fluid. The results of acid-fast staining were all negative while culture revealed an anaerobic infection but was reported negative for mycobacterial infection after 42 days of culture. To identify the specific pathogens and guide targeted treatment, a Metagenomics Next-Generation Sequencing (mNGS) examination of the pleural effusion was performed and revealed human *Roseburia hominis* species (sequence number 4015, confidence level of 99.0%) and *Clostridium bolteae* species (sequence number 5622, confidence level of 99.0%) as the causative agents. Postoperatively, he received anti-infective therapy with imipenem-cilastatin, which was later switched to piperacillin-tazobactam. His symptoms and inflammatory markers gradually improved, and he was discharged following the removal of the drainage catheter. After discharge, he continued treatment with oral amoxicillin-clavulanate. Unfortunately, the pyothorax recurred. Over the six months following disease onset, he was hospitalized three more times for similar symptoms (Table 1). His primary treatment course and key examinations are summarized in Fig. 1.

The patient exhibited the following three key characteristics: 1) recurrent pyothorax caused by opportunistic pathogens; 2) a negative HIV test; and 3) no known history of immunodeficiency. Based on a review of the relevant literature, AIGA-associated AOID was suspected.

An interferon-γ release assay (IGRA) for *Mycobacterium tuberculosis* (MTB) was subsequently performed. The assay utilized whole blood and had a detection range for IFN-γ concentrations of 1 pg-5000 pg/mL, according to manufactory's instruction. The patient's IFN-γ concentration was extremely low (below 1 pg/ml) and was therefore interpreted as negative. The patient's blood sample was then sent for AIGA qualitative testing. The assay was conducted using the Cusabio Human interferon γ (IFN-γ) antibody ELISA kit (Cusabio, Wuhan, China, CSB-E14210 h). Briefly, serum was diluted 1:2000 and added to IFN-γ antigen-precoated microplate wells, along with negative and positive controls, in accordance with the manufacturer's standard protocol. A sample was defined as positive for AIGA if its optical density (OD) value exceeded 2.1-fold that of the negative control. The OD value of the patient's sample was 0.643, while the OD values of the negative and positive controls were 0.24 and 0.681, respectively. Therefore, the test result was interpreted as positive.

Thus, AIGA-associated AOID was diagnosed. Although his condition improved following each round of antimicrobial and symptomatic treatment, his pyothorax continued to recur frequently, significantly impairing his quality of life.

Literature Review

We systematically searched PubMed, Web of Science, and Embase for articles on AIGA-associated AOID published in English between January 1, 2004 and August 31, 2024, using the keywords "anti-interferon-gamma autoantibody" OR "adult-onset immunodeficiency". Titles and abstracts of all identified articles were screened, and the full-texts of relevant articles were retrieved for data collection and analysis. Additionally, Chinese literature databases were

Table 1 Main clinical information of the patient's three hospitalizations

Time	Chief complaint	Symptoms	Signs	Diagnosis	Laboratory data	pathogen
d0-d28	Fever for 1 week	1. Fever with chills 2. Upper abdominal pain	Pulse: 105 times/min Blood pressure: 132/85 mmHg Temperature: 37.3℃	Pyothorax without a fistula	WBC 5.7 × 10^9/L N% 85.9% CRP 229.6 mg/L Hb 125 g/L	mNGS: human *Roseburia hominis* species, *Clostridium bolteae* species
d87-d106	Repeated fever for over 2 months	1. Fever with chills 2. Upper abdominal pain	Pulse: 121 times/min Blood pressure: 113/69 mmHg Temperature: 37.8℃	Pyothorax without a fistula	WBC 7.3 × 10^9/L N% 77.1% CRP 157.3 mg/L Hb 115 g/L ESR 82.0	Blood and pleural fluid cultures showed no bacterial growth
d163-d178	Diagnosed pleural effusion for more than 5 months, recurrence of chest tightness for 2 weeks	Chest tightness	Pulse: 104 times/min Blood pressure: 109/74 mmHg Temperature: 36.4℃ There is a sinus formation on the left chest wall. In the sinus, there is a prolapse of adipose tissue and a small amount of purulent discharge	Pyothorax with a fistula	WBC 5.7 × 10^9/L N% 81.1% CRP 98.2 mg/L Hb 132 g/L	Blood and pleural fluid cultures showed no bacterial growth

WBC white blood cell; *N%* neutrophil percentage; *CRP* C-reactive protein; *Hb* Hemoglobin; *ESR* erythrocyte sedimentation rate; *mNGS* Metagenomics Next-Generation Sequencing; *d* day

searched using the same strategy. Studies were included if they met the following criteria: 1) Published in English or Chinese within the specified time frame; 2) Case reports and case series describing patients' demographic characteristics, sites of infection, and identified pathogens; and 3) Original articles focusing on diagnostics, immunology, or reviews pertaining to AIGA-associated AOID containing the aforementioned information. Studies were excluded if they met any of the following criteria: 1) Not related to the subject; 2) Case reports or case lacking complete patient information; 3) Retrospective studies; and 4) Conference abstract. The detailed search strategy is illustrated in Fig. 2.

A total of 502 patients were included in this study, comprising 256 males (51.0%) and 246 females (49.0%). The median age at presentation was 51 years old (range: 10–87 years). Juvenile patients accounted for only 1.3% (4/304) of the cases. Among adults, the 45–59 age group constituted the largest proportion (Fig. 3). As for regional distribution, the vast majority of patients were from Southeast Asia (98.2%, 493/502), including 60.6% (304/502) from China, 28.7% (144/502) from Thailand, and 5.2% (26/502) from Japan (Fig. 4). Notably, there is a clear concentration trend in regional distribution, and most of the patients are Asian. This suggests that the disease is closely related to race and genetics. Pithukpakorn et al. found that the allelic polymorphism of this clinical syndrome is very limited when comparing HLA gene typing between patients and healthy controls. They found AOID is associated with HLA-DRB1 and DQB1 alleles, particularly HLA-DRB1 * 15:01, DRB1 * 16:02, DQB1 * 05:01, and DQB1 * 05:02 [6]. However, no further genetic studies on AIGA-associated AOID have been conducted since then.

The lymph nodes were the most commonly affected organs (83.7%, 420/502), followed by the lungs (60.6%, 304/502), skin/soft tissue (48.0%, 241/502), bone/joints (42.2%, 212/502), and blood/bone marrow (27.9%, 140/502) (Fig. 5a). Notably, 92.1% (374/406) of patients exhibited infections in either the lymph nodes or lungs, a feature that should be emphasized during clinical evaluation.

The distribution of involved organs may correlate with specific pathogens. Our data indicated that the most prevalent pathogens were Nontuberculous mycobacteria (NTM), identified in 77.49% (389/502) of patients (Fig. 6). Within this group, *Mycobacterium avium* complex (MAC) (34.19%, 133/389) and *M. abscessus* (31.62%, 123/389) were the most frequently reported species. *Talaromyces marneffei* (TM) was the second most common pathogen (31.87%, 160/502). Other notable pathogens included *Salmonella* (20.32%, 102/502), varicella-zoster virus (VZV) (13.15%, 66/502), and MTB (6.77%, 34/502). The predominant pathogens, NTM and TM, frequently affect the lymph nodes, lungs, and skin [7, 8]. In cases of disseminated infections, the liver, spleen, bones, nervous system, and other sites may

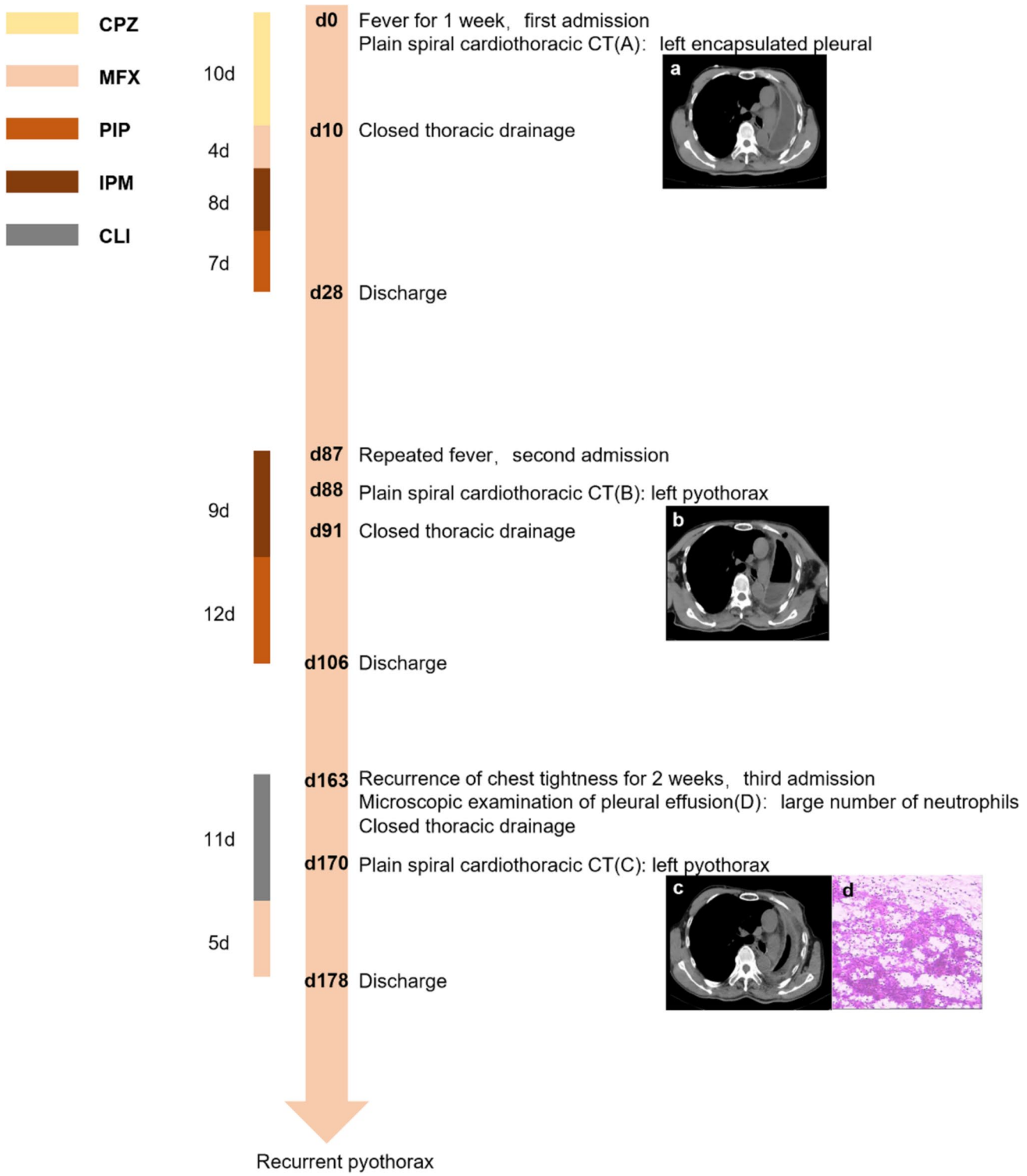


Fig. 1 Clinical course of antibiotic use and main examinations. **a**-**c** Plain spiral cardiothoracic CT: Repeated pyothorax in the same area; postoperative changes of the left lung, right lung compensatory emphysema, right lung fibroproliferative focus, pleural thickening, and adhesion on both sides. **d** Microscopic examination of pleural effusion: a large number of neutrophils. CPZ: Cefoperazone; MFX: Moxifloxacin; PIP: Piperacillin; IPM: Imipenem; CLI: Clindamycin; CT: Computed Tomography; d: day

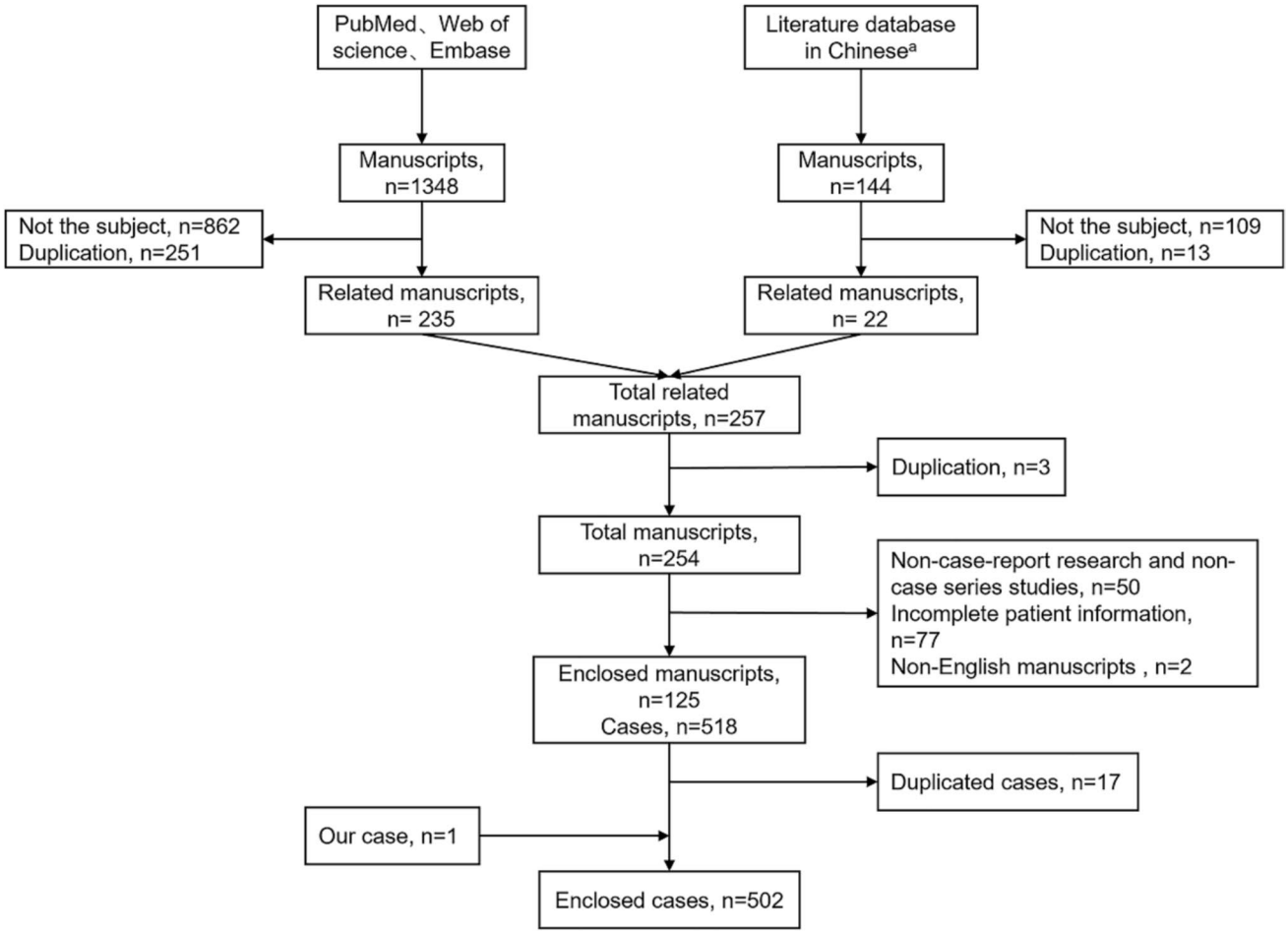


Fig. 2 Flow chat of literature review process. [a] Including: CNKI, Wanfang, SinoMed

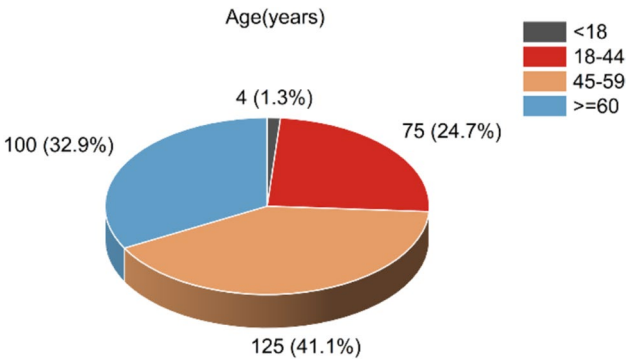


Fig. 3 Age distribution of patients (Number of cases that can be included in the statistics: $n = 304$; "n" in the following figure legends has the same meaning)

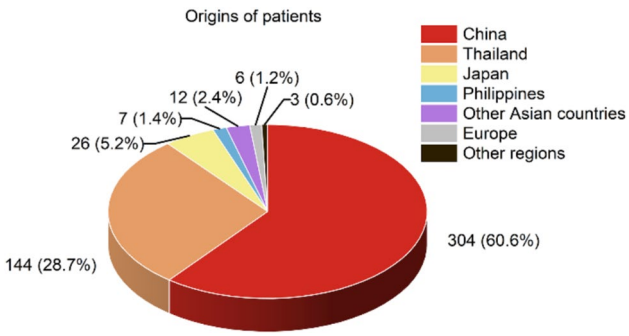


Fig. 4 Distribution of patient regional sources ($n = 502$)

also be involved. Therefore, common infection sites are largely determined by the distribution of major pathogens. Additionally, treatment strategies for the five most prevalent pathogen types are listed in Table 2.

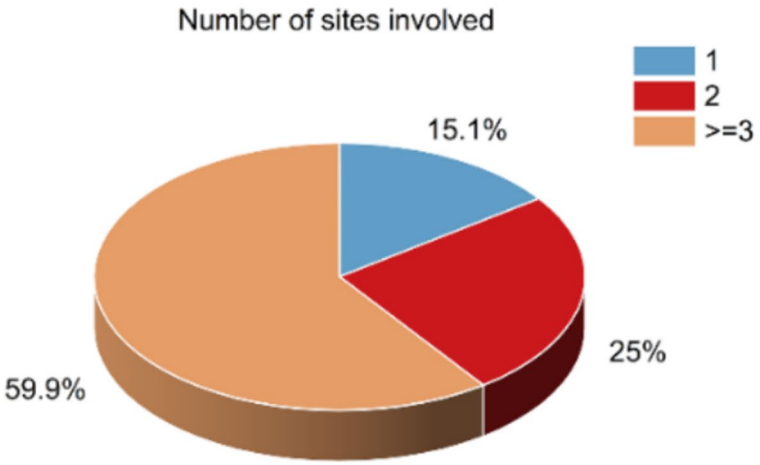
It's also noteworthy that only 15.1% of patients presented with a single-organ involvement, while 25.0% had infections involving two anatomical sites. The remaining 59.9% had infections affecting three or more sites (Fig. 5b). Multiple organ involvement is particularly prevalent in patients with AIGA-associated AOID, contributing to the complex and

Fig. 5 Characteristics of affected sites. **a** Types and proportions of organs involved ($n = 502$); **b** Figure: Number of involved organs ($n = 312$)

a

Affected sites	Number of cases	Percentage (%)
Lymphnode	420	83.7
Lung	304	60.6
Skin and soft tissue	241	48.0
Bone and joint	212	42.2
Blood and marrow	140	27.9
Liver and spleen	64	12.7
Nervous system	22	4.4
Other parts	58	11.6

b



heterogeneous clinical presentation. However, this feature may also serve as an important diagnostic clue.

Currently, the incidence of AIGA-associated AOID is likely significantly underestimated due to limited clinical awareness among physicians. As a result, improving the ability to recognize this condition has become increasingly important [13]. However, no standardized diagnostic guidelines or expert consensus currently exist for AIGA-associated AOID. Based on the characteristics of the disease and the practicality for physicians, five dimensions of features were summarized from these 502 cases (Table 3). The suggested diagnostic criteria are as follows:1) Suspected cases should meet the first four criteria, regardless of whether the fifth criterion is fulfilled; 2) Confirmed cases must meet criterion 1 and have a positive serum AIGA result. Furthermore, we have outlined the complete diagnostic and treatment pathway in Fig. 7.

Discussion

AIGA-associated AOID is characterized by the presence of AIGA, leading to a state of immunodeficiency in affected individuals. It typically presents in adulthood, with reported ages ranging from 10 to 87 years and a median age of 51 years, though Liew et al. previously reported cases in a 10-year-old boy and a 16-year-old girl. However, only a limited number of juvenile cases have been documented over the past 20 years [14, 15]. AIGA-associated AOID predominantly affects adults.

The incidence of the AIGA-associated AOID is strongly related to ancestry, with most of the cases reported so far involving individuals of Asian descent. Among Asian countries, China and Thailand are the most frequently

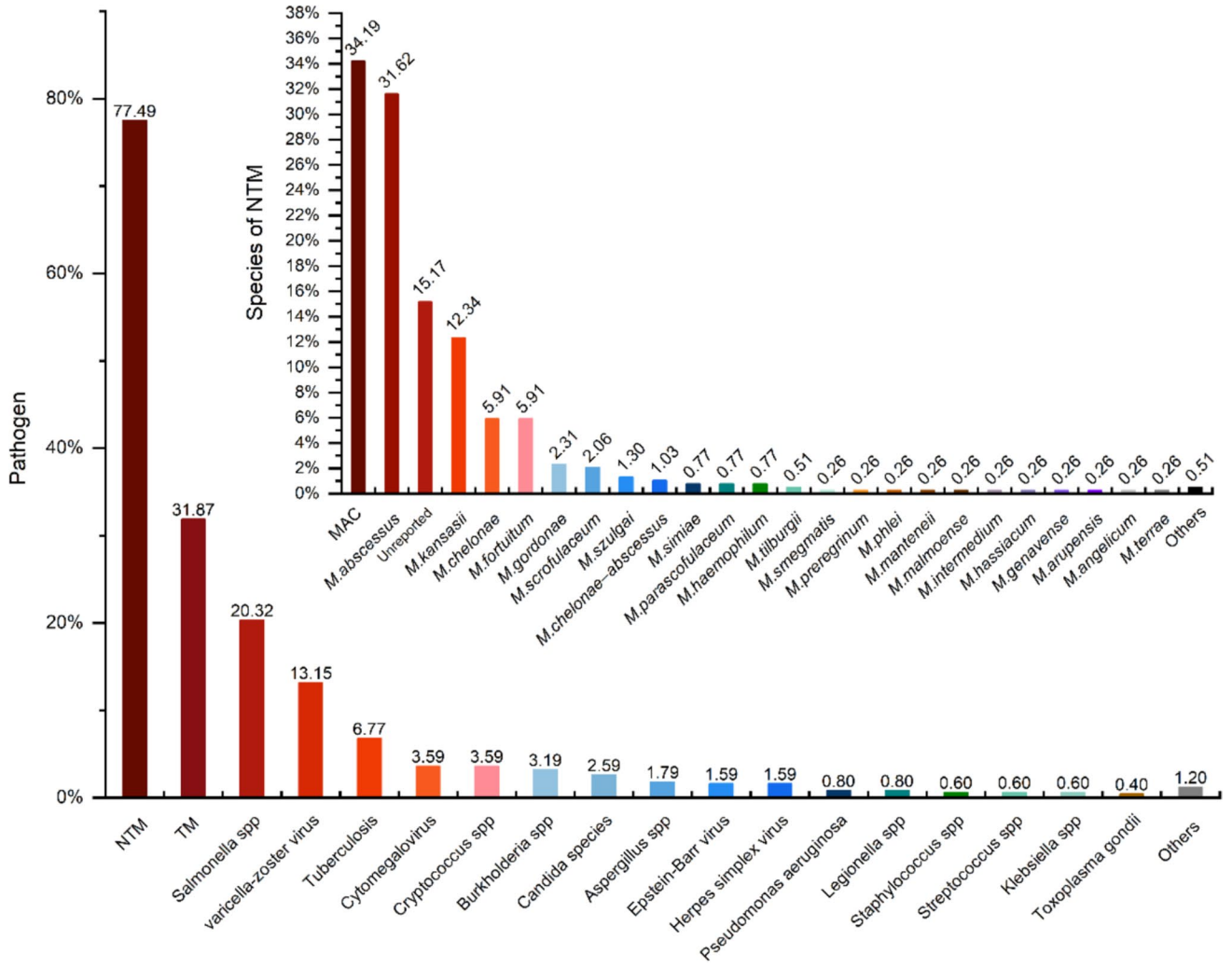


Fig. 6 Types and proportions of pathogens. All the cases ($n = 502$) we enclosed report the types of pathogens they infected with, of which 389 patients are infected with NTM. The frequency of each pathogen is labeled in the figure. NTM: Nontuberculous mycobacteria; TM: *Talaromyces marneffei*; MAC: *Mycobacterium avium* complex

Table 2 Therapeutic regimens for common pathogens

Pathogen		Antibacterial/Antiviral protocols
NTM	*M. avium complex*	susceptibility based treatment for macrolides and amikacin over empiric therapy [9]
	M. abscessus	multidrug regimen that includes at least three active drugs (including macrolides and amikacin), guided by in vitro susceptibility [9]
	M. kansasii	rifampicin + ethambutol + either isoniazid or macrolide [9]
TM		liposomal amphotericin B (induction therapy) + itraconazole (consolidation therapy), followed by itraconazole (maintenance therapy or secondary prophylaxis). [10]
Salmonella		ciprofloxacin or levofloxacin (if not infected in Asia) [11]
VZV		acyclovir, valacyclovir or famciclovir [11]
MTB		Recommended 4-mo Rifapentine-Moxifloxacin–Containing Regimen: isoniazid + rifampicin + pyrazinamide + moxifloxacin. More regimens detailed in the reference [12]

NTM Nontuberculous mycobacteria, *TM Talaromyces marneffei*, *VZV* Varicella-zoster virus, *MTB Mycobacterium tuberculosis*

Table 3 Parameters for diagnosis

Diagnostic parameters
1. Patient belongs to Asian ancestry
2. Recurrent opportunistic infections and polymicrobial infection (especially those caused by NTM or co-infected with NTM, TM, or *Salmonella*)
3. Patient tested negative for HIV and does not exhibit any congenital immunodeficiencies or other secondary immunodeficiencies
4. The involved sites conform to the following conditions: a. Single site involvement, affecting the lymph nodes; b. Two sites involvement, affecting the lymph nodes and another commonly affected site, or involving any two of the lung, bones and joints, skin and soft tissue, or blood and bone marrow; c. Three or more sites involvement
5. Laboratory examination reveals elevated inflammatory markers and/or IgG levels

NTM Nontuberculous mycobacteria, *TM Talaromyces marneffei*, *HIV* Human Immunodeficiency Virus, *IgG* immunoglobulin G

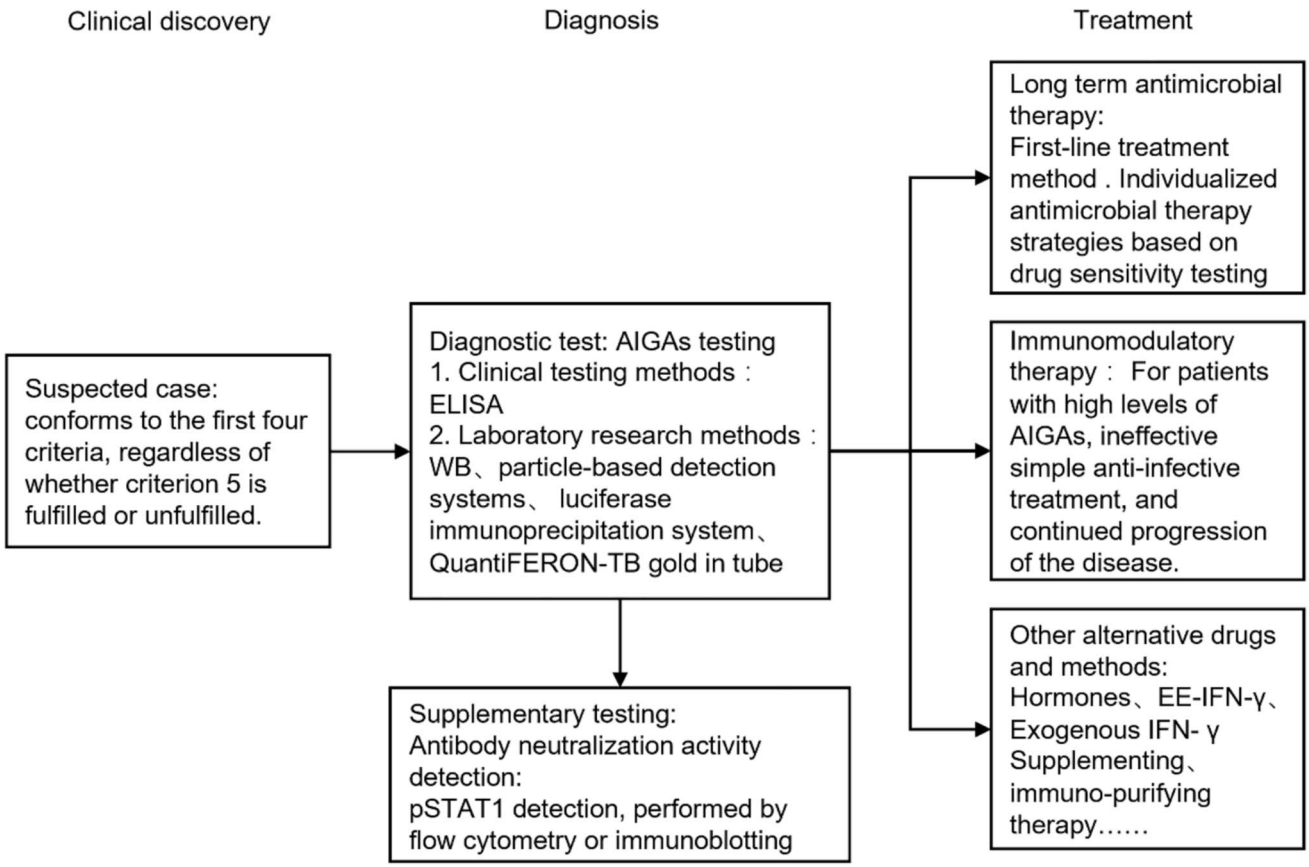


Fig. 7 Flow chat of recommended diagnosis and treatment process. ELISA: enzyme-linked immunosorbent assay; WB: Western Blot; pSTAT1: phosphorylation signal transducer and activator of transcription 1; IFN-γ: interferon-gamma; EE-IFN-γ: epitope-erased variant of IFN-γ

cited locations for the disease. The racial relevance of AIGA-associated AOID has been attributed to HLA typing. People who carry the alleles HLA-DRB*15:02/16:02 and DQB*05:01/05:02 are more susceptible to AIGA-associated AOID [6]. Although AIGA-associated AOID is not typically regarded as familial, a recent conference abstract reported three affected individuals from the same household, raising the possibility of shared environmental or genetic predisposition (2023 Annual Scientific Meeting American College of Allergy, Asthma & Immunology, abstract M283) [16]. Most patients are previously healthy prior to disease onset [3]. "Previously healthy" here refers to individuals without known immunodeficiency, or an underlying condition capable of causing transient immune suppression.

Clinically, AIGA-associated AOID is characterized by recurrent opportunistic infections. Patients' clinical manifestation always begin with symptoms of infection. NTM,

TM, *Salmonella*, and VZV are common opportunistic pathogens in the AIGA-associated AOID. Among these, NTM is the most prevalent, with *M. abscessus* and MAC being the major species [17, 18]. Yamaguchi et al. and Hanitsch et al. have reported cases of *Toxoplasma gondii* infection, but in general, parasitic infections are rare [19, 20].

The variation in infection rates among different pathogens is likely related to distinct immune response mechanisms and varying degrees of dependency on IFN-γ in defending against different microbial infections [21]. It's also reported that geographical distribution of microorganisms and environmental exposures can lead to differences in pathogen species across various countries and regions [22]. Multiple infections are quite common, affecting almost half of all patients [17, 23, 24]. Browne et al. reported that neutralizing AIGA was detected in 88% of Asian adults with multiple opportunistic infections. This suggests that we need to be highly suspicious of the existence of AIGA in patients with multiple opportunistic infection [3, 25].

In our case, anaerobic Gram-negative bacilli were detected in pleural fluid culture, although species identification failed. Subsequent mNGS of pleural fluid identified two types of rare anaerobic species: human *Roseburia hominis* and *Clostridium bolteae*. Though anerobic bacterial infection is limited to identified for previously reported AIGA-associated AOID cases, there are two cases also detected with anaerobic bacteria via mNGS [26, 27]. The difficulty for anerobic bacterial incubation may explain the limited record in AIGA-associated AOID patients [28–30]. This suggests anaerobic infections may be underestimated in these patients and mNGS may be suitable for additional identification.

The role of AIGA in host immune responses to anaerobic bacteria remains unclear, and direct evidence is currently lacking. This represents a valuable direction for future research. However, research for bacterial infection has presented the following valuable clues for the potential role of AIGA in anaerobic bacteria infection. The causative agents of pyothorax were identified as anaerobic bacteria which are recognized as commensal organisms colonizing the human intestinal tract [31, 32]. IFN-γ plays a crucial role in both innate and adaptive immune responses against bacterial infections and pathological inflammatory processes, including activating macrophage bactericidal functions [33], enhancing antigen presentation and inflammatory signaling [34], and promoting the formation of immune memory [35]. In the context of AIGA-associated AOID, the neutralization of IFN-γ significantly diminishes its bactericidal activity, including against anaerobic bacteria [36, 37]. Specifically, anaerobic bacteria are major resident microorganisms in the gut, and IFN-γ plays a key role in maintaining the integrity of the intestinal epithelial barrier [38, 39]. Therefore, AIGA may impair the ability of IFN-γ to preserve the intestinal epithelial barrier, increasing the translocation of anaerobic bacteria.

The clinical presentation of AIGA-associated AOID is incredibly varied and encompasses systemic symptoms (e.g., fever, weight loss, malaise), localized or generalized lymphadenopathy, skin manifestations (e.g., erythema, rash, nodules, pustulosis, SWEET's syndrome), pulmonary symptoms (e.g., cough, dyspnea, hemoptysis, imaging abnormalities), abscess formation (e.g., skin and muscle abscess, deep abscesses, fistula formation), bloodstream infections, and bone marrow infections [40–42]. Infections most commonly affect lymph nodes, followed by the lungs, skin/soft tissues, and bones/joints. In addition, infections of the liver, nervous system, gastrointestinal tract, gland, etc. have also been documented [26, 43, 44]. Through our review, we found that the vast majority of patients experience lymph nodes and/or lung infections, and it is helpful for the clinical detection and diagnosis of patients with AIGA. Furthermore, we found a high rate of multi-organ involvement among AIGA-associated AOID patients, which is consistent with the study of Zhang et al., and it also provides clues for patient identification [17].

mNGS is increasingly recognized as a valuable tool for pathogen identification. However, it should be very carefully confirmed whether mNGS-identified pathogens are responsible for infection in AIGA-associated AOID patients especially for NTM. NTM often exists as colonization bacteria in the respiratory duct which will show positive results in bronchoalveolar lavage fluid (BALF) mNGS testing. Furthermore, acid-fast staining and mycobacterial culture are still essential for mycobacterial infection differentiation [9, 45]. In enrolled AIGA-associated AOID cases with NTM infection, 98/389 acid-fast staining was positive while 237/389 also showed positive results for mycobacterial culture. The combination of these methods with the clinical information especially imaging and histopathological examination can enhance diagnostic accuracy for NTM infection in these patients.

To confirm a diagnosis of AIGA-associated AOID, either qualitative or quantitative detection of autoantibodies against interferon gamma is essential [18, 46]. The enzyme-linked immunosorbent assay (ELISA) is the most commonly used method. In our case, qualitative ELISA testing showed relatively confident positive results for AIGA. However, this method only reflects the binding capacity between antigen and antibody, and does not directly assess the neutralizing activity of autoantibodies. Evaluating neutralizing function requires complementary techniques such as flow cytometry-based functional assays or competitive ELISA [47–49]. Due to the unavailability of quantitative and neutralizing assays for AIGA in domestic laboratories (including our center), these evaluations were not performed in this case.

Other additional laboratory techniques for AIGA-associated AOID diagnosis include particle-based detection systems, Western Blot (WB), luciferase immunoprecipitation system, and QuantiFERON-TB gold in-tube (QFT-GIT) assays [50–53]. Previous research has shown that QFT-GIT can be used to screen for AIGA-associated AOID patients which based on the presence of neutralizing AIGA in these patients will lead to the undetectable or extremely low IFN-γ level. In our IGRA of MTB, which is similar to QFT-GIT, the level of IFN-γ was extremely low (blow the lower detecting line, 1.0 pg/mL) for patient blood. It is in accordance with the previous research conclusion [54].

In clinical practice, elevated IgG levels may serve as potential predictive factors for AIGA positivity in HIV-negative patients for most AIGA have been identified as belonging to the IgG class [20, 46, 55]. This characteristic was also reflected in our case, the serum IgG level (17.27 g/L) is very close to the upper normal level (17.4 g/L). As for the possible reason that the IgG level in our case did not exceed the upper limit of normal, it may be only one case and not get the series results of IgG level during the whole course of the disease.

The triggers for the elevation of pathogenic antibodies remain unclear, but it is believed that genetic and environmental factors may play a role in their production. The molecular mimicry mechanism is considered one of the possible causes because the amino acid sequence of IFN-γ that binds to antibodies is highly homologous to the Aspergillus ribosome assembly protein Noc2, which may lead to the production of autoantibodies in individuals infected with Aspergillus [56].

Antimicrobial therapy is the first-line treatment for AIGA-associated AOID, and many patients require a long course of antimicrobial therapy [57]. For patients with high levels of AIGA, ineffective simple anti-infective treatment, and ongoing disease progression, immunomodulatory therapy can be considered. Commonly used drugs include rituximab (RTX) and cyclophosphamide [58, 59]. Daratumumab (anti-CD38 monoclonal antibody), bortezomib, intravenous immunoglobulin, and plasma exchange, have also been used in refractory cases [60, 61]. Other treatments, such as glucocorticoids, EE-IFN-γ, exogenous IFN-γ, and immune-purifying therapy, have been reported [62]. The research of therapeutic methods acting on IFN-γ and AIGA may play an important role in managing the disease. However, the optimal regimens and durations for these therapeutic approaches remain undetermined, the treatment regimen should be tailored for different patients.

Due to insufficient understanding of the disease among clinicians and the absence of specific, sensitive treatment methods, patients have to endure prolonged opportunistic infections [63, 64]. There have been significant increases in reports related to the AIGA after 2012 and 2019, indicating that the disease is attracting the attention of clinicians. Establishing robust expert consensus and clinical diagnosis and treatment guidelines is essential for improving patient conditions.

Conclusions

In conclusion, we present a case of AIGA-associated AOID that is difficult to diagnose. For similar patients, it is important to be aware of the possibilities of AIGA-associated AOID. Through a comprehensive literature review, we have summarized the clinical features of the disease and present our insights on the diagnosis of the disease. Timely and accurate diagnosis can drive improvements in treatment. In the future, developing and advancing the disease's standardized diagnostic and treatment protocols in clinical practice is crucial.

Author Contributions Liyan Zhao: Writing Original Draft, Methodology, Data curation, Visualization. Yimin Zhang: Conceptualization, Methodology, Supervision, Writing-Reviewing and Editing. Jindi Ma and Ying Sun: Resources, Data curation. Xiaopeng Yu, Yingfeng Lu and Haijiang Qian: Resources. Ren Yan: Methodology, Writing-Reviewing and Editing. The final manuscript was approved by all authors.

Funding This study was supported by Key R&D Program of Zhejiang (2022 C03125), the Fundamental Research Funds for the Central Universities (grant No. 2022ZFJH003).

Data Availability Data is provided within the manuscript or supplementary information files.

Declarations

Ethical Approval and Consent to Participate This study was approved by the Medical Ethics Committee of Haining People's Hospital [approval no. 2022(23)], following the principles of the Declaration of Helsinki. Written informed consent for research and the publication with patient's information was obtained from the patient in case report.

Competing interests The authors declare no competing interests.

References

1. Döffinger R, Helbert MR, Barcenas-Morales G, Yang K, Dupuis S, Ceron-Gutierrez L, et al. Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. Clin Infect Dis. 2004;38(1):e10–4. https://doi.org/10.1086/380453.
2. Höflich C, Sabat R, Rosseau S, Temmesfeld B, Slevogt H, Döcke WD, et al. Naturally occurring anti-IFN-gamma autoantibody and severe infections with Mycobacterium cheloneae and Burkholderia cocovenenans. Blood. 2004;103(2):673–5. https://doi.org/10.1182/blood-2003-04-1065.
3. Browne SK, Burbelo PD, Chetchotisakd P, Suputtamongkol Y, Kiertiburanakul S, Shaw PA, et al. Adult-onset immunodeficiency in Thailand and Taiwan. N Engl J Med. 2012;367(8):725–34. https://doi.org/10.1056/NEJMoa1111160.
4. Butel-Simoes GI, Kiss C, Kong K, Rosen LB, Hosking LM, Barnes S, et al. Disseminated tuberculosis, CMV viraemia & haemophagocytic-lymphohistiocystosis syndrome in an adult patient with anti- IFNγ autoantibodies - case report and brief review. Clin Immunol Commun. 2023;4:55–9. https://doi.org/10.1016/j.clicom.2023.08.001.
5. Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-γ immunity. Semin Immunol. 2014;26(6):454–70. https://doi.org/10.1016/j.smim.2014.09.008.
6. Pithukpakorn M, Roothumnong E, Angkasekwinai N, Suktitipat B, Assawamakin A, Luangwedchakarn V, et al. HLA-DRB1 and HLA-DQB1 are associated with adult-onset immunodeficiency with acquired anti-interferon-gamma autoantibodies. PLoS ONE. 2015;10(5):e0128481. https://doi.org/10.1371/journal.pone.0128481.
7. Ratnatunga CN, Lutzky VP, Kupz A, Doolan DL, Reid DW, Field M, et al. The rise of non-tuberculosis mycobacterial lung disease. Front Immunol. 2020;11. https://doi.org/10.3389/fimmu.2020.00303.
8. Cao C, Xi L, Chaturvedi V. Talaromycosis (Penicilliosis) due to Talaromyces (Penicillium) marneffei: insights into the clinical trends of a major fungal disease 60 years after the discovery of the pathogen. Mycopathologia. 2019;184(6):709–20. https://doi.org/10.1007/s11046-019-00410-2.
9. Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ, Andrejak C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis. 2020;71(4):905–13. https://doi.org/10.1093/cid/ciaa1125.
10. Infections in Adults and Adolescents with HIV— A Working Group of the Office of AIDS Research Advisory Council (OARAC). Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV 2024. Available from: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-oi/guidelines-adult-adolescent-oi.pdf. Accessed 6 Apr 2025.
11. Gilbert DN, Chambers HF, Saag MS, Pavia AT, Boucher HW, Black D, et al. The Sanford guide to antimicrobial therapy 2023. 53rd ed. Sperryville, VA: Antimicrobial Therapy, Inc.; 2023.
12. Saukkonen JJ, Duarte R, Munsiff SS, Winston CA, Mammen MJ, Abubakar I, et al. Updates on the treatment of drug-susceptible and drug-resistant tuberculosis: an official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med. 2025;211(1):15–33. https://doi.org/10.1164/rccm.202410-2096ST.
13. Wu UI, Wang JT, Sheng WH, Sun HY, Cheng A, Hsu LY, et al. Incorrect diagnoses in patients with neutralizing anti-interferon-gamma-autoantibodies. Clin Microbiol Infect. 2020;26(12):1684.e1-.e6. https://doi.org/10.1016/j.cmi.2020.02.030.
14. Chetchotisakd P, Anunnatsiri S. Linezolid in the treatment of disseminated nontuberculous mycobacterial infection in anti-interferon-gamma autoantibody-positive patients. Southeast Asian J Trop Med Public Health. 2014;45(5):1125–31.
15. Nie YD, Pan SQ, Wang H, Wang TY, Feng YY, Zhang Y, et al. Adult-onset immunodeficiency induced by anti-interferon-γ autoantibodies: report of 13 cases. Zhonghua Jie He He Hu Xi Za Zhi. 2023;46(2):144–50. https://doi.org/10.3760/cma.j.cn112147-20220725-00625.
16. Hirsch W, Megna B, Adeyi O, Lim N. Macrophage activation syndrome with acute hepatitis in a patient with adult-onset immunodeficiency with anti-interferon gamma antibodies: a case report. J Med Case Rep. 2024;18(1). https://doi.org/10.1186/s13256-023-04245-w.
17. Zhang B, Fan J, Huang C, Fan H, Chen J, Huang X, et al. Characteristics and outcomes of anti-interferon gamma antibody-associated adult onset immunodeficiency. J Clin Immunol. 2023;43(7):1660–70. https://doi.org/10.1007/s10875-023-01537-0.
18. Shih HP, Ding JY, Yeh CF, Chi CY, Ku CL. Anti-interferon-γ autoantibody-associated immunodeficiency. Curr Opin Immunol. 2021;72:206–14. https://doi.org/10.1016/j.coi.2021.05.007.
19. Yamaguchi E, Tanaka H, Fukuoka T, Ohbayashi Y, Sato M, Yokoi T. A case of disseminated nontuberculous mycobacteriosis and cerebellar toxoplasmosis with autoantibody to interferon-γ. Sarcoidosis Vasc Diffuse Lung Dis. 2013;30(4):312–6.
20. Hanitsch LG, Löbel M, Müller-Redetzky H, Schürmann M, Suttorp N, Unterwalder N, et al. Late-onset disseminated Mycobacterium avium intracellulare Complex Infection (MAC), cerebral toxoplasmosis and Salmonella sepsis in a German Caucasian patient with unusual anti-interferon-Gamma IgG1 autoantibodies. J Clin Immunol. 2015;35(4):361–5. https://doi.org/10.1007/s10875-015-0161-5.
21. Kampitak T, Suwanpimolkul G, Browne S, Suankratay C. Anti-interferon-γ autoantibody and opportunistic infections: case series and review of the literature. Infection. 2011;39(1):65–71. https://doi.org/10.1007/s15010-010-0067-3.
22. Hong GH, Ortega-Villa AM, Hunsberger S, Chetchotisakd P, Anunnatsiri S, Mootsikapun P, et al. Natural history and evolution of anti-interferon-γ autoantibody-associated immunodeficiency syndrome in Thailand and the United States. Clin Infect Dis. 2020;71(1):53–62. https://doi.org/10.1093/cid/ciz786.
23. Zeng W, Qiu Y, Tang SD, Zhang JQ, Pan ML, Zhong XN. Characterization of anti-interferon-γ antibodies in HIV-negative patients infected with disseminated Talaromyces marneffei and Cryptococcosis. Open Forum Infect Dis. 2019;6(10). https://doi.org/10.1093/ofid/ofz208.
24. Qiu Y, Feng X, Zeng W, Zhang H, Zhang J. Immunodeficiency disease spectrum in HIV-negative individuals with talaromycosis. J Clin Immunol. 2020;41(1):221–3. https://doi.org/10.1007/s10875-020-00869-5.
25. Guo J, Ning XQ, Ding JY, Zheng YQ, Shi NN, Wu FY, et al. Anti-IFN-γ autoantibodies underlie disseminated Talaromyces marneffei infections. J Exp Med. 2020;217(12). https://doi.org/10.1084/jem.20190502
26. Zheng JH, Wu D, Guo XY. Intracranial infection accompanied sweet's syndrome in a patient with anti-interferon-γ autoantibodies: a case report. World J Clin Cases. 2023;11(32):7926–34. https://doi.org/10.12998/wjcc.v11.i32.7926.
27. 谭洁, 詹森林, 邓国防, 张培泽, editors. 抗干扰素γ自身抗体综合征导致播散性哥伦比亚分枝杆菌感染的一例病例. 中国防痨协会第33届全国学术大会暨中国防痨科技奖颁奖大会; 2021; 中国山东青岛.

28. Tang M, Zeng W, Qiu Y, Fang G, Pan M, Li W, et al. Clinical features of rare disseminated Mycobacterium colombiense infection in nine patients who are HIV-negative in Guangxi. China Int J Infect Dis. 2023;128:321–4. https://doi.org/10.1016/j.ijid.2023.01.002.
29. Xing F, Hung DLL, Lo SKF, Chen S, Lau SKP, Woo PCY. Next-generation sequencing-based diagnosis of bacteremic Listeria monocytogenes meningitis in a patient with anti-interferon gamma autoantibodies: a case report. Infect Microbes Dis. 2022;4(1):44–6. https://doi.org/10.1097/IM9.0000000000000080.
30. Nagy E, Urbán E, Sóki J, Terhes G, Nagy K. The place of molecular genetic methods in the diagnostics of human pathogenic anaerobic bacteria. A minireview. Acta Microbiol Immunol Hung. 2006;53(2):183–94. https://doi.org/10.1556/AMicr.53.2006.2.5.
31. Machiels K, Joossens M, Sabino J, De Preter V, Arijs I, Eeckhaut V, et al. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut. 2014;63(8):1275–83. https://doi.org/10.1136/gutjnl-2013-304833.
32. Zhang Y, Luo K, Peters BA, Mossavar-Rahmani Y, Moon JY, Wang Y, et al. Sugar-sweetened beverage intake, gut microbiota, circulating metabolites, and diabetes risk in Hispanic Community Health Study/Study of Latinos. Cell Metab. 2025;37(3):578-91.e4. https://doi.org/10.1016/j.cmet.2024.12.004.
33. Boehm U, Klamp T, Groot M, Howard JC. Cellular responses to interferon-gamma. Annu Rev Immunol. 1997;15:749–95. https://doi.org/10.1146/annurev.immunol.15.1.749.
34. Boxx GM, Cheng G. The roles of type I interferon in bacterial infection. Cell Host Microbe. 2016;19(6):760–9. https://doi.org/10.1016/j.chom.2016.05.016.
35. Badovinac VP, Tvinnereim AR, Harty JT. Regulation of antigen-specific CD8+ T cell homeostasis by perforin and interferon-gamma. Science. 2000;290(5495):1354–8. https://doi.org/10.1126/science.290.5495.1354.
36. Crisler WJ, Lenz LL. Crosstalk between type I and II interferons in regulation of myeloid cell responses during bacterial infection. Curr Opin Immunol. 2018;54:35–41. https://doi.org/10.1016/j.coi.2018.05.014.
37. Browne SK. Anticytokine autoantibody-associated immunodeficiency. Annu Rev Immunol. 2014;32:635–57. https://doi.org/10.1146/annurev-immunol-032713-120222.
38. McElrath C, Espinosa V, Lin JD, Peng J, Sridhar R, Dutta O, et al. Critical role of interferons in gastrointestinal injury repair. Nat Commun. 2021;12(1):2624. https://doi.org/10.1038/s41467-021-22928-0.
39. de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. Gut. 2022;71(5):1020–32. https://doi.org/10.1136/gutjnl-2021-326789.
40. Tungphaisal V, Phinyo P, Rujiwetpongstorn R, Kiratikanon S, Tovanabutra N, Chaiwarith R, et al. Reactive neutrophilic dermatoses in adult-onset immunodeficiency due to interferon-gamma autoantibody and their associated factors. Dermatology. 2023;239(2):248–54. https://doi.org/10.1159/000528064.
41. Pattanaprichakul P, Leeyaphan C, Angkasekwinai N, Bunyaratavej S, Senawong S, Sereeaphinan C, et al. Prevalence and clinical manifestations of cutaneous findings in patients with adult-onset immunodeficiency due to anti-interferon gamma autoantibodies: an eight-year retrospective study. Int J Dermatol. 2023;62(12):1506–10. https://doi.org/10.1111/ijd.16870.
42. Qiu Y, Fang G, Ye F, Zeng W, Tang M, Wei X, et al. Pathogen spectrum and immunotherapy in patients with anti-IFN-γ autoantibodies: a multicenter retrospective study and systematic review. Front Immunol. 2022;13:1051673. https://doi.org/10.3389/fimmu.2022.1051673.
43. Trisirirat K, Phannikul C, Patamatamkul S, Wijitpan S. Successful treatment of nasal and parotid Mycobacterium avium complex infection in adult-onset immunodeficiency: a case report with literature review. J Med Assoc Thailand. 2023;106(3):314–9. https://doi.org/10.35755/jmedassocthai.2023.03.13814.
44. Roerden M, Döffinger R, Barcenas-Morales G, Forchhammer S, Döbele S, Berg CP. Simultaneous disseminated infections with intracellular pathogens: an intriguing case report of adult-onset immunodeficiency with anti-interferon-gamma autoantibodies. BMC Infect Dis. 2020;20(1):828. https://doi.org/10.1186/s12879-020-05553-y.
45. Gu W, Miller S, Chiu CY. Clinical metagenomic next-generation sequencing for pathogen detection. Annu Rev Pathol. 2019;14:319–38. https://doi.org/10.1146/annurev-pathmechdis-012418-012751.
46. Qiu Y, Tang M, Zeng W, Feng X, Pan M, Li W, et al. Clinical findings and predictive factors for positive anti-interferon-γ autoantibodies in patients suffering from a non-tuberculosis mycobacteria or Talaromyces marneffei infection: a multicenter prospective cohort study. Sci Rep. 2022;12(1):9069. https://doi.org/10.1038/s41598-022-13160-x.
47. Aoki A, Sakagami T, Yoshizawa K, Shima K, Toyama M, Tanabe Y, et al. Clinical significance of interferon-γ neutralizing autoantibodies against disseminated nontuberculous mycobacterial disease. Clin Infect Dis. 2018;66(8):1239–45. https://doi.org/10.1093/cid/cix996.
48. Chen ZM, Yang XY, Li ZT, Guan WJ, Qiu Y, Li SQ, et al. Anti-interferon-γ autoantibodies impair T-lymphocyte responses in patients with Talaromyces marneffei infections. Infect Drug Resist. 2022;15:3381–93. https://doi.org/10.2147/idr.S364388.
49. Shalash AO, Azuar A, Madge HYR, Modhiran N, Amarilla AA, Liang B, et al. Detection and quantification of SARS-CoV-2 receptor binding domain neutralization by a sensitive competitive ELISA assay. Vaccines (Basel). 2021;9(12). https://doi.org/10.3390/vaccines9121493.
50. Burbelo PD, Browne SK, Sampaio EP, Giaccone G, Zaman R, Kristosturyan E, et al. Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. Blood. 2010;116(23):4848–58. https://doi.org/10.1182/blood-2010-05-286161.
51. Ding L, Mo A, Jutivorakool K, Pancholi M, Holland SM, Browne SK. Determination of human anticytokine autoantibody profiles using a particle-based approach. J Clin Immunol. 2012;32(2):238–45. https://doi.org/10.1007/s10875-011-9621-8.
52. Khositnithikul R, Laisuan W, Setthaudom C, Sriwanichrak K, Kunakorn M, Srikhirin T, et al. Application of QuantiFERON ELISA for detection of interferon-gamma autoantibodies in adult-onset immunodeficiency syndrome. Lab Med. 2022;53(1):12–7. https://doi.org/10.1093/labmed/lmab039.
53. Yasamut U, Thongkum W, Moonmuang S, Sakkhachornphop S, Chaiwarith R, Praparattanapan J, et al. Neutralizing activity of anti-interferon-γ autoantibodies in adult-onset immunodeficiency is associated with their binding domains. Front Immunol. 2019;10:1905. https://doi.org/10.3389/fimmu.2019.01905.
54. Wu UI, Chuang YC, Sheng WH, Sun HY, Jhong YT, Wang JY, et al. Use of QuantiFERON-TB Gold In-tube assay in screening for neutralizing anti-interferon-γ autoantibodies in patients with disseminated nontuberculous mycobacterial infection. Clin Microbiol Infect. 2018;24(2):159–65. https://doi.org/10.1016/j.cmi.2017.06.029.
55. Wipasa J, Chaiwarith R, Chawansuntati K, Praparattanapan J, Rattanathammethee K, Supparatpinyo K. Characterization of anti-interferon-γ antibodies in HIV-negative immunodeficient patients infected with unusual intracellular microorganisms. Exp Biol Med (Maywood). 2018;243(7):621–6. https://doi.org/10.1177/1535370218764086.
56. Chawansuntati K, Rattanathammethee K, Wipasa J. Minireview: insights into anti-interferon-γ autoantibodies. Exp Biol Med

(Maywood). 2021;246(7):790–5. https://doi.org/10.1177/1535370220981579.
57. Matono T, Suzuki S, Yamate R, Nakamura K, Sakagami T. Diagnostic and therapeutic challenges in disseminated Mycobacterium colombiense infection caused by interferon-γ neutralizing autoantibodies. Open Forum Infect Dis. 2023;10(2):ofad035. https://doi.org/10.1093/ofid/ofad035.
58. Koizumi Y, Sakagami T, Nishiyama N, Hirai J, Hayashi Y, Asai N, et al. Rituximab restores IFN-γ-STAT1 function and ameliorates disseminated Mycobacterium avium infection in a patient with anti-interferon-γ autoantibody. J Clin Immunol. 2017;37(7):644–9. https://doi.org/10.1007/s10875-017-0425-3.
59. Saba M, Greene JN. Refractory mycobacterium avium complex pneumonia and anti-interferon-γ autoantibodies: a case report. Infect Dis Clin Pract. 2019;27(2):110–3. https://doi.org/10.1097/IPC.0000000000000698.
60. Angkasekiwinai N, Suputtamongkol Y, Tantibhedhyangkul W, Onlamoon N, Phoompoung P, Pithukpakorn M, et al. Efficacy of bortezomib for treating anti-interferon-gamma autoantibody-associated adult-onset immunodeficiency (AOID) syndrome. Clin Infect Dis. 2023. https://doi.org/10.1093/cid/ciad676.
61. Ochoa S, Ding L, Kreuzburg S, Treat J, Holland SM, Zerbe CS. Daratumumab (Anti-CD38) for treatment of disseminated nontuberculous mycobacteria in a patient with anti-interferon-γ autoantibodies. Clin Infect Dis. 2021;72(12):2206–8. https://doi.org/10.1093/cid/ciaa1086.
62. Lin CH, Chi CY, Shih HP, Ding JY, Lo CC, Wang SY, et al. Identification of a major epitope by anti-interferon-γ autoantibodies in patients with mycobacterial disease. Nat Med. 2016;22(9):994–1001. https://doi.org/10.1038/nm.4158.
63. Temsangsukmanee J, Laisuan W, Thadanipon K, Pisitkun P, Ngamjanyaporn P, Suangtamai T, et al. Health related quality of life in anti interferon γ autoantibody associated immunodeficiency syndrome measured with EQ5D5L and SF36. Sci Rep. 2023;13(1):14346. https://doi.org/10.1038/s41598-023-41340-w.
64. Hidekawa C, Yoshimi R, Kishimoto D, Kato H, Mitsuhashi M, Sakurai N, et al. Anti-interferon-γ antibody-seropositive disseminated nontuberculous mycobacterial infection mimicking POEMS and TAFRO syndromes. Intern Med. 2022;61(15):2377–85. https://doi.org/10.2169/internalmedicine.8366-21.