

Clinical manifestations, course, and outcome of patients with neutralizing anti-interferon- γ autoantibodies and disseminated nontuberculous mycobacterial infections

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Abstract

Neutralizing anti-interferon- γ autoantibody (nAIGA)-associated immunodeficiency is an emerging medical issue worldwide. In the present study, we describe and discuss the clinical features and outcomes of patients with nAIGAs and disseminated infections by nontuberculous mycobacteria (dNTM).

We thoroughly reviewed the medical records of all patients. Microorganisms and nAIGAs were identified using previously described methods with modifications. All data were calculated and analyzed using SPSS software.

Among 46 adult patients with dNTM infections, we identified 45 cases (97.8%) with nAIGAs. The average patient age was 58.6 years, and there was no sex predominance. Cervical lymphadenitis (81.8%) was the most common clinical manifestation. Endocrine disorder was the leading comorbidity (7 cases). Malignancies were found in 4 patients, and all of the malignancies originated from the T-cell/macrophage lineage. More than half of the identifiable isolates were slow-growing NTMs. Twenty-eight (62.2%) and 18 (40.0%) patients had a history of zoster and salmonellosis, respectively. A high proportion of patients with recurrent episodes of NTM infection or a history of zoster and dNTM infection had initial nAIGA titers $\geq 10^{-5}$ dilution ($P < 0.05$). Twenty-seven patients (60.0%) required long-term antimycobacterial therapy and had at least 1 episode of recurrent NTM disease. No mortality was related to dNTM infection.

In Taiwan, nAIGAs are a recently recognized mechanism of dNTM infection. Long term of antibiotic treatment and adherence to medical advice are necessary to improve the clinical outcome of patients with nAIGAs.

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Abbreviations: AHIGA = antihuman IFN- γ antibody, AST = antimicrobial susceptibility testing, ATS = American Thoracic Society, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HBsAg = hepatitis B surface antigen, HIV = human immunodeficiency virus, HZ = herpes zoster, IDSA = Infectious Diseases Society of America, IFN = interferon, IL = interleukin, MAC = *Mycobacterium avium* complex, MSMD = Mendelian susceptibility to mycobacterial disease, nAIGAs = anti-interferon- γ autoantibodies, ND = neutrophilic dermatosis, NTM = nontuberculous mycobacteria, NTS = nontyphoidal salmonella, RGNTM = rapid-growing NTM, RT = room temperature, RTX = rituximab, SGNTM = slow-growing NTM, SPSS = Statistical Package for the Social Sciences, TB = tuberculosis, VZV = varicella-zoster virus, WBC = white blood cell.

Keywords: autoantibody, interferon-gamma, nontuberculous mycobacterium, Taiwan

1. Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment and are regarded as less virulent than *Mycobacterium tuberculosis* to humans. Most clinical NTM infections are localized, but under certain conditions, these infections can become disseminated. A majority of disseminated NTM (dNTM) infections occur in patients with a compromised immune status, often due to a malignancy or due to infection with human immunodeficiency virus (HIV). In the past few decades, however, investigators found that children with genetic defects in the interleukin (IL)-12/interferon- γ (IFN- γ) axis are predisposed to severe NTM infections. Such children are considered to have a Mendelian susceptibility to mycobacterial disease (MSMD).^[1] In the past decade, a group of adult patients with MSMD-like clinical manifestations were reported in the literature.^[2–14] Instead of genetic defects in the IL-12/IFN- γ axis, neutralizing anti-IFN- γ autoantibodies (nAIGAs) were found to be the cause of severe and dNTM infections. Although numerous reports of this recently identified disease/syndrome have been published, no large-scale case-series study focusing on the detailed clinical information of this unique patient population can be found in the literature. Therefore, the purpose of this study was to describe the clinical manifestations, disease course, therapeutic regimens, and outcomes of patients with nAIGAs and dNTM infection.

2. Methods

2.1. Patients and definitions

From December 2009 to April 2014, we screened for the presence of nAIGAs in adult patients (age ≥ 18 years) with dNTM infections and those with nAIGAs who were enrolled in the present study. The medical charts of all of the patients were thoroughly reviewed and analyzed. All of the patients were HIV-negative and had no history of malignancy before the identification of nAIGAs. The diagnosis of pulmonary NTM infection was based on criteria proposed by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA).^[15] Extrapulmonary NTM disease was diagnosed on the basis of clinical history, specified pathology, and a positive culture of the specific pathogen from aspirate or tissue biopsy. Tuberculosis (TB) was defined as a positive culture for *M tuberculosis* from clinical specimens. Disseminated mycobacterial infection was defined by the isolation of a mycobacterial species from more than 1 body site (noncontiguous) or from the blood or bone marrow. Patients with a serum creatinine level >1.5 mg/dL were considered to have renal insufficiency. If microorganisms other than NTM were isolated from a patient during the course of active dNTM infection, we diagnosed the patient with a coinfection. We considered patients, with or without treatment, who had no clinical evidence of active NTM disease, to be in a clinically stable condition. The clinical course of the patients was divided into the following 2 categories: cured (no recurrence of

NTM infection for at least 6 months after discontinuation of antimycobacterial therapy) and persistent infection. The recurrence frequency of NTM infection in each patient was also recorded. This study was approved (DMR98-IRB-261 and 102–3985B) by the Institutional Review Board of China Medical University Hospital and Chang-Gung Memory Hospital. Informed written consent was obtained from all of the patients in accordance with the Declaration of Helsinki.

2.2. Microbiological and molecular methods

All of our methods were based on our previous study with some modifications.^[4] For the detection and titration of nAIGAs, a 96-well microplate was precoated with 100 μ L of antihuman IFN- γ antibody/well (AHIGA; BD Biosciences, 1:250) and incubated overnight at 4°C. The plate was washed 3 times with phosphate buffer saline (PBS)-Tween 0.05% and then blocked by incubation with PBS-10% fetal bovine serum (Gibco) for 1 hour at room temperature (RT). In another microplate, plasma from patients and donors was serially diluted (10^{-1} to 10^{-6}) and incubated with 200 pg/mL recombinant human IFN- γ (BD) for 1 hour at 37°C. After blocking, the AHIGA-precoated plate was thoroughly washed, and a mixture of recombinant human IFN- γ and diluted plasma from patients or donors (100 μ L/well) was added. The plate was then incubated for 2 hours at RT and washed again, and the detection antibody (BD, 1:250) was added. After incubation for 1 hour at RT, the plate was washed 7 times, and substrate solution was added. The plate was then incubated for 5 to 10 minutes at RT. The defined titer of nAIGAs was based on the optical density value (450 nm). In the blocking assay, the plasma was diluted from 10^{-1} to 10^{-6} , and the blocking index was defined as the maximum dilution of plasma that blocked 50% of the IFN- γ concentration measurement. All molecular experiments were performed in duplicate.

2.3. Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 17.0; SPSS, Chicago, IL). Continuous variables are presented as the means \pm standard deviation or medians and were compared using the Mann-Whitney *U* test. Categorical variables are expressed as percentages and were analyzed using the chi-square test or Fisher exact test if any expected value was below 5. A 2-tailed *P* value <0.05 was considered significant.

3. Results

3.1. Demographics of patients with nAIGAs and dNTM infection

We screened 46 adult patients with dNTM infection for the presence of nAIGAs, and 45 of the patients (97.8%) had such autoantibodies (17 of them had been included in our prior

Table 1

Demographic data and outcome of 45 patients with anti-interferon γ autoantibodies and disseminated nontuberculous mycobacterial infections.

Parameters	Number of patients, %
Age, yrs (median, IQR)	56 (50–67)
Sex (male)	21/45 (46.7)
Hometown (Minnan)*	40/45 (88.9)
Comorbid diseases	
Asthma	1/45 (2.2)
Chronic obstructive pulmonary disease	2/45 (4.4)
Diabetes mellitus	4/45 (8.9)
Hypertension	6/45 (13.3)
Heart failure	1/45 (2.2)
Renal insufficiency	2/45 (4.4)
Liver cirrhosis	0/45 (0)
Endocrine disorder [†]	3/45 (6.7)
Autoimmune disease [‡]	4/45 (8.9)
Malignancy [§]	4/45 (8.9)
Zoster history	28/45 (62.2)
Salmonellosis history	18/45 (40.0)
Concomitant skin lesion	10/44 (22.2)
Coinfection	8/44 (17.8)
Outcome	
Cured	9/45 (20.0)
Persistent infection	27/45 (60.0)
Unknown	9/45 (20.0)

IQR=interquartile range.

* One patient was mainland, 2 patients were aborigine, and 2 patients were Hakka. Minnan population is the major group of Han Chinese in Taiwan.

[†] One patient had primary hypothyroidism, 1 patient had Hashimoto thyroiditis, and the other had autoimmune thyroiditis.

[‡] Sjögren syndrome in 1 patient and Beçhet disease in the other. The other 2 patients had Hashimoto thyroiditis and autoimmune thyroiditis, respectively.

[§] Three patient had peripheral T-cell lymphoma and 1 patient had Langerhan cell histiocytosis X.

^{||} Infection with pathogens other than salmonella and zoster during the course of NTM disease.

study)^[4] (Table 1). The median age at the time of nAIGA identification was 56 years (range: 37–87 years), and more than half of the patients (53.3%) were female. Most patients (88.9%) were Minnan (the major group of Han Chinese in Taiwan). Comorbid diseases were identified in 21 patients (46.7%); endocrine disorder was the leading comorbidity, followed by hypertension, malignancy, and autoimmune disease. Regarding endocrinopathy, only diabetes mellitus (4 cases) and thyroid disease (3 cases) were recorded. Four cases had autoimmune diseases that were diagnosed before or after the first NTM infection (range: –157 to 2284 days). Malignancies were found in 4 patients, and all malignancies originated from the T-cell/macrophage lineage (Table 1). Among those patients with malignancy, 2 cases received traditional chemotherapy. Another case was only treated with steroids, and no recurrence of the malignancy was reported during the follow-up period. The remaining patient received chemotherapy and a transplant of autologous peripheral stem cells. The nAIGA titers obtained from the last case decreased from the 10⁻⁶ to 10⁻² dilution during the course of chemotherapy and stem cell transplantation. Anti-mycobacterial drugs were discontinued during the bone marrow recovery process. Eight months after the end of antibiotic therapy, no recurrence of NTM infection was reported for this patient. In summary, in Taiwan, an extremely high prevalence rate of nAIGAs was found in dNTM patients, and endocrine/exocrine-associated diseases were the most common comorbidities among these patients.

Table 2

Distribution of nontuberculous mycobacterial species* and site of involvement[†] in patients with anti-interferon γ autoantibodies.

Species and sites	Number of patients (%)
Species	
Rapid-growing	16/52 (30.8)
<i>Mycobacterium abscessus</i>	14
<i>Mycobacterium fortuitum</i>	1
<i>Mycobacterium chelonae</i>	1
Slow-growing	22/52 (42.3)
<i>Mycobacterium avium</i> complex	13
<i>Mycobacterium kansasii</i>	3
<i>Mycobacterium scrofulaceum</i>	2
<i>Mycobacterium gordonae</i>	2
<i>Mycobacterium terrae</i> complex	1
<i>Mycobacterium szulgai</i>	1
Unidentified	14/52 (26.9)
Site of involvement	
Lymph node	36/44 (81.8)
Bone	27/44 (61.4)
Joint	9/44 (20.5)
Lung	28/44 (63.6)
Skin	12/44 (27.3)
Muscle	2/44 (4.5)
Spleen/liver/peritoneum	4/44 (9.1)
Genitourinary system	2/44 (4.5)
Central nervous system	1/44 (2.3)
Pericardium	1/44 (2.3)

* More than 1 isolate may be isolated from the same case.

[†] Proven by isolation of pathogen or characteristic pathological findings and negative polymerase chain reaction for tuberculosis.

3.2. Causative/coinfected pathogens and associated infections

Both rapid-growing and slow-growing NTMs were isolated from the patients included in this study (Table 2). *Mycobacterium abscessus* was the most common rapid-growing NTM (RGNTM), whereas *Mycobacterium avium* complex (MAC) was the most common slow-growing NTM (SGNTM). A history of TB was found in 4 cases, and all of these events occurred before the first episode of dNTM disease (range: –425 to –32 days). Consistent with our previous observation,^[4] a considerable proportion of patients had a history of varicella–zoster virus (VZV) reactivation (herpes zoster [HZ]) (62.2%) and salmonellosis (40.0%). Twelve patients (26.7%) had a history of HZ and salmonellosis. Eleven cases (24.4%) had neither of these 2 infections. In both instances, HZ and salmonellosis could occur before or after the first dNTM infection. Single dermatome involvement was the major clinical presentation of HZ, but 2 cases presented involvement of more than 2 dermatomes. All salmonellosis cases were caused by nontyphoidal salmonella (NTS) species, and all were invasive infections (bacteremia). A similar clinical course and therapeutic response to those of the general population were observed in our patients with HZ and/or salmonellosis, and recurrence was not observed in these cases despite the persistence of nAIGAs.

Nine patients were coinfecting with pathogens other than Salmonella and HZ during the course of dNTM infection, and *Penicillium marneffe* (4 cases) was the most common clinical isolate (Supplementary Table 1, ST1, <http://links.lww.com/MD/B37>). In view of the clinical course and therapeutic response, no difference was observed between these patients and the general population. The status of chronic viral infections was also

evaluated in some of our patients (ST2, <http://links.lww.com/MD/B37>). Most patients exhibited positive serological tests for herpes simplex virus 1 (92.9%), cytomegalovirus (94.1%), Epstein-Barr virus (90%), and VZV (100%). However, none of the tested patients presented any serological evidence of chronic hepatitis B virus infection (positive hepatitis B surface antigen [HBsAg]).

3.3. Clinical manifestations and inflammatory markers

Lymph nodes were the most common sites of involvement (81.8%), followed by the lungs, bones, and joints (63.6, 61.4, and 20.5%, respectively) (Table 2). Cervical lymphadenopathy was the most common clinical presentation (ST3, <http://links.lww.com/MD/B37>). With regard to osteomyelitis and arthritis (ST4, <http://links.lww.com/MD/B37> and ST5, <http://links.lww.com/MD/B37>), axial bones and joints were the major sites of involvement and were usually multifoci. In addition to cutaneous mycobacterial infection (12 cases), we also observed several types of dermatoses in 10 patients during the course of dNTM infection (ST6, <http://links.lww.com/MD/B37>). A few dermatoses, such as morbilliform eruption and acute generalized exanthematous pustulosis, were related to therapeutic agents and disappeared after discontinuation of the offending drugs. We also checked the inflammatory markers (white blood cell [WBC] count, erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]) of patients during active NTM disease and in a clinically stable condition (ST7, <http://links.lww.com/MD/B37>). During the episode of active infection, the WBC count, ESR, and CRP values were significantly higher ($P < 0.001$) than those observed in the clinically stable condition. In summary, lymphadenopathy and bone/joint infections were the most common clinical manifestations, and elevated inflammatory markers indicated disease activity.

3.4. Titers of anti-interferon- γ autoantibodies

The distribution of the initial nAIGA titers according to the types of infections, the recurrence frequency of NTM infections, and the patient outcomes is shown in Fig. 1. Most cases (95.6%) had an initial nAIGA titer $\geq 10^{-4}$ dilution (Fig. 2A). In terms of pathogens and histories of infection, a significantly higher proportion of patients with a history of HZ and dNTM infection had an initial nAIGA titer $\geq 10^{-5}$ dilution compared with the proportion of those with dNTM infection alone (Fig. 2B; $P < 0.05$). A higher proportion of patients with recurrent episodes, particularly those with >5 episodes, had an initial nAIGA titer $\geq 10^{-5}$ dilution (Fig. 2C). Patients with persistent NTM infection tended to have higher initial nAIGA titers ($\geq 10^{-5}$ dilution) than the cured cases, but the difference was not significant (Fig. 2D). In brief, a high proportion of patients with recurrent episodes of NTM infection or a history of HZ and dNTM infection had initial nAIGA titers $\geq 10^{-5}$ dilution.

3.5. Clinical courses, treatment, and outcome

Despite intensive treatment, more than half of the patients (27/45, 60.0%) had a persistent NTM infection and required long-term antimycobacterial therapy (Tables 1–3). Various combinations of antibiotics were used to suppress the activity of NTM infection. A macrolide-based combination was the most commonly used regimen. Fluoroquinolones and several standard anti-TB drugs (ethambutol, rifampin, and rifabutin) were the other major components of the maintenance-therapy regimens. Tetracyclines or linezolid were used in a few cases, and ceftibuten, a third-generation cephalosporin, was prescribed for 3 patients to treat the NTM infection (Table 3). All patients with persistent infections experienced at least 1 episode of recurrent NTM disease (range: 1–17 times; median: 2.5 times). Nonadherence to antibiotic therapy was the major cause for recurrent NTM

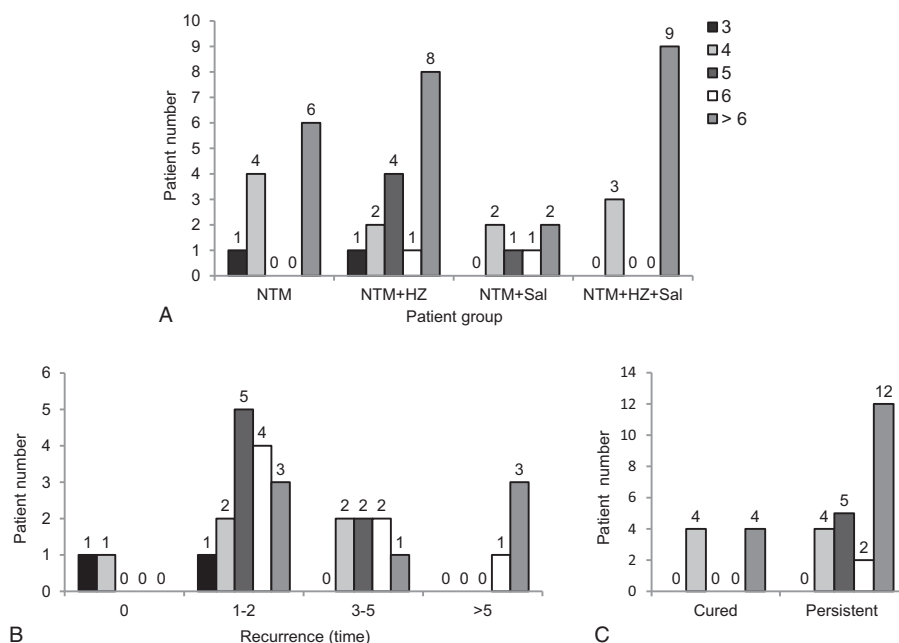


Figure 1. Titers of neutralizing anti-IFN- γ autoantibodies in various clinical conditions: A, different types of microbial infections; B, frequency of NTM infection recurrence; and C, outcome of patients. HZ=herpes zoster, NTM=nontuberculous mycobacteria, Sal=salmonellosis.

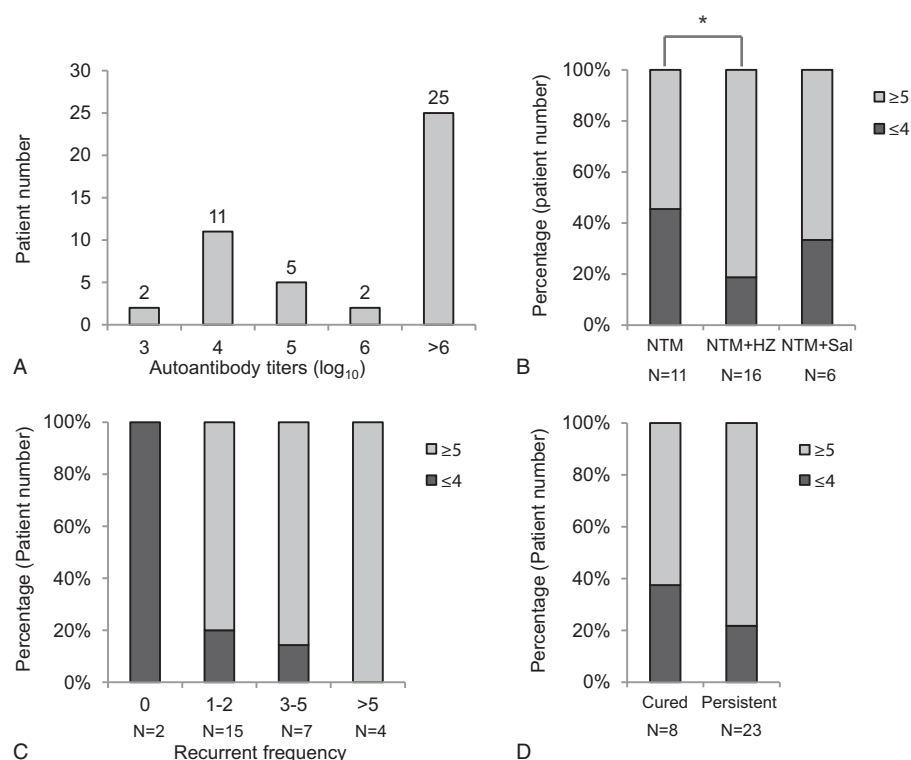


Figure 2. A, Number of patients with different titers of nAIGA. B, Patients with NTM infection and a history of HZ had a significantly higher initial nAIGA titer ($\geq 10^{-5}$ dilution) than those with NTM infection alone. C, Patients with recurrent NTM infections, particularly those with ≥ 5 episodes, had a higher initial nAIGA titer. D, Patients with persistent infection tended to have a higher initial nAIGA titer ($\geq 10^{-5}$ dilution). HZ = herpes zoster, nAIGA = neutralizing anti-interferon- γ autoantibodies, NTM = nontuberculous mycobacteria, Sal = salmonellosis. * $P < 0.05$.

infection. The elapsed time from the self-discontinuation of antibiotic therapy to the recurrence of NTM infection was approximately 1 to 2 months. However, 3 patients (cases 2, 10, and 13) who were regularly treated with effective antimycobacterial drugs also experienced recurrent episodes of NTM infections. During the recurrent episodes, all 3 cases experienced self-reported psychological or physical stress events. Only 9 patients (20.0%) were free from NTM disease after the end of antimycobacterial therapy (the median follow-up time: 729 days). Among these 9 patients, the duration of treatment ranged from 206 to 1439 days (median: 546 days). Recurrent NTM infection was also observed in these cured patients (once in 3 patients and twice in 1 patient), but the frequency of recurrence was significantly lower than that observed in patients with persistent NTM infections. Lymph nodes were the most common recurrent sites of NTM disease. During the study period, no mortality related to NTM infection was reported. In summary, antibiotic therapy alone was inadequate to control or eradicate NTM infection in more than half of the cases. Long-term antimycobacterial therapy, medical compliance, and stress avoidance were necessary to control the activity of NTM infection.

4. Discussion

In this study, we present detailed clinical information of 45 patients with nAIGAs. First, an extremely high prevalence rate (97.8%) of nAIGAs was found in patients with dNTM infection, and endocrine/exocrine-associated diseases were the most common comorbidities. Second, *M abscessus* and MAC were

the most common identifiable mycobacteria, and lymphadenopathy (81.8%) was the most common clinical manifestation. Third, patients with recurrent episodes of NTM infection or a history of HZ and dNTM infection tended to have a higher initial nAIGA titer ($\geq 10^{-5}$ dilution). Finally, antibiotic therapy alone was not an effective strategy for controlling or eradicating NTM infection in over half of the cases. Long-term antimycobacterial therapy and medical compliance were found to be necessary to control the activity of NTM infection.

Immunodeficiency caused by nAIGAs with severe/disseminated mycobacterial infection is a recently emerging medical issue, particularly in Southeast Asia. In the past decade, approximately 190 individuals (including those described in our study) with nAIGAs have been reported in the literature.^[2-14,16] Most are of Asian descent^[2-8,10-14,16] and are primarily from Thailand and Taiwan. In agreement with the prevalence rate (81%–96%) reported by Browne et al,^[3] a considerable proportion of our patients (97.8%) with dNTM infection, with or without another opportunistic infection, had nAIGAs. Among these patients, both RGNTMs and SGNTMs were isolated as the causative microorganisms; however, the distribution of the NTM species was different from that described in other reports.^[3,16] In the present study, more SGNTMs were isolated from the clinical specimens, whereas RGNTMs were more commonly isolated in the other studies.^[3,16] NTM are environmental microorganisms, and their distribution is dependent on the geographic location, particularly in Asian countries. For example, in Hong Kong, South Korea, and Taiwan, SGNTMs are the most frequently reported clinical isolates.^[17,18] However, RGNTMs are the main clinical isolates in Iran, Saudi Arabia, and India. Such geographic differences in

Table 3**Antibiotic regimens (used and maintain) in patients with anti-interferon γ autoantibodies and disseminated nontuberculous mycobacterial infections.**

Patient	Species of NTM	Used antibiotics	Maintenance therapy	Outcome
1	<i>M scrofulaceum</i> , <i>M abscessus</i>	AZ, CIP, CLA, EMB, LVX, RFB	CLA + LVX	Persistent infection
2	MAC	CLA, EMB, RFB, RMP	CLA + EMB	Persistent infection
3	<i>M gordonae</i> , <i>M abscessus</i>	AN, CLA, CIP, EMB, FOX, MXF, RMP, TE, TG	CLA + RMP + TG	Persistent infection
4	<i>M abscessus</i>	AN, CIP, CLA, EMB, INH, RMP	—	Cured
5	<i>M abscessus</i>	AZ, CIP, FOX, MIN, TG	AZ + CIP	Persistent infection
6	<i>M terrae</i> complex	AZ, CLA, EMB, INH, PZA, RMP	—	Cured
7	Unidentified	CLA, E, EMB, INH, RMP	—	Cured
8	<i>M scrofulaceum</i>	CLA, EMB, INH, LVX, RMP	—	Cured
9	MAC	AZ, CLA, CIP, EMB, LVX, MIN, RMP	MIN + RFB	Persistent infection
10	Unidentified	AN, AZ, CLA, EMB, FOX, INH, PZA, RFB, RMP	AZ + EMB + INH + RFB	Persistent infection
11	<i>M kansasii</i>	AN, CLA, EMB, FOX, INH, LZD, MXF, RMP, TG	—	Cured
12	Unidentified	CLA, EMB, INH, MXF, PZA, RMP	CLA + MXF	Persistent infection
13	<i>M abscessus</i>	AN, AZ, CIP, CLA, EMB, INH, IPM, LVX, MIN, MXF, RMP	AZ + CEF + CIP	Persistent infection
14	Unidentified	EMB, INH, PZA, RMP	—	Cured
15	MAC	CLA, EMB, INH, PZA, RMP	NA	Unknown
16	<i>M abscessus</i>	AN, AZ, CEF, CLA, IPM, LVX, MIN, TG	AZ + CEF + LVX	Persistent infection
17	<i>M abscessus</i> , <i>M szulgai</i>	AN, CIP, CLA, EMB, FOX, INH, IPM, LVX, RMP	Unknown	Persistent infection
18	<i>M abscessus</i>	CLA, EMB, INH, MIN, MXF, RMP	CLA + MIN	Persistent infection
19	<i>M gordonae</i>	AN, CLA, EMB, RMP	CLA + EMB	Persistent infection
20	MAC	CLA, EMB, LVX, RMP	AZ + RMP	Persistent infection
21	<i>M abscessus</i>	CLA, EMB, INH, PZA	CEF + CLA + DOX	Persistent infection
22	Unidentified	CLA, EMB, RMP	Unknown	Persistent infection
23	MAC	CLA, EMB, INH, LVX, MXF, PZA, RMP	CLA + EMB + LVX + RMP	Persistent infection
24	<i>M fortuitum</i>	CLA, INH, RMP, SXT	—	Cured
25	MAC	AZ, DOX, EMB, IPM, MXF, RFB, SXT	AZ + EMB + MXF + RFB	Persistent infection
26	Unidentified	AZ, CIP, EMB, INH, PZA, RFB, RMP	AZ + EMB	Persistent infection
27	MAC	CIP, CLA, EMB, RFB, RMP	INH + RMP	Persistent infection
28	<i>M abscessus</i>	AN, AZ, CLA, DOX, TG	CLA	Persistent infection
29	<i>M abscessus</i>	AN, CIP, CLA, IPM, LZD, MIN, MXF	AZ + DOX + LVX	Persistent infection
30	MAC	AN, CLA, EMB, FOX, IPM, MXF, RFB, TG	NA	Unknown
31	MAC	CEF, CLA, EMB, LVX, MXF, RMP, SXT	CLA + EMB + RMP	Persistent infection
32	MAC	AN, CLA, EMB, INH, RFB, RMP, TG	CLA + EMB + RFB	Persistent infection
33	Unidentified	CLA, EMB, MXF, RMP	CLA + MXF + RMP	Persistent infection
34	Unidentified	NA	NA	Unknown
35	<i>M abscessus</i>	INH, RMP, EMB, AZ, CIP	NA	Unknown
36	Unidentified	NA	NA	Unknown
37	Unidentified	NA	NA	Unknown
38	Unidentified	NA	NA	Unknown
39	<i>M abscessus</i>	IPM, AN, CLA, MXF, LVX, MIN, AZ, SXT, LZD	CLA + LZD + MXF	Persistent infection
40	MAC, <i>M abscessus</i> , <i>M kansasii</i> , <i>M chelonae</i>	IPM, AN, CLA, EMB, RMP, INH, LVX, MIN, MXF	—	Cured
41	MAC	NA	NA	Unknown
42	Unidentified	NA	NA	Unknown
43	MAC, <i>M kansasii</i>	RFB, DOX, CLA, LZD, SXT, LVX, IPM, AN	RFB + DOX + CLA	Persistent infection
44	Unidentified	CLA, EMB, INH, RMP, TG, LZD, SXT, CIP	—	Cured
45	Unidentified	INH, RMP, EMB, CLA	INH + RMP + EMB + CLA	Persistent infection

AN = amikacin, AZ = azithromycin, CEF = ceftibuten, CIP = ciprofloxacin, CLA = clarithromycin, DOX = doxycycline, EMB = ethambutol, E = erythromycin, FOX = cefoxitin, INH = isoniazid, IPM = imipenem, LVX = levofloxacin, LZD = linezolid, *M* = *Mycobacterium*, MAC = *M avium* complex, MIN = minocycline, MXF = moxifloxacin, NA = not available, NTM = nontuberculous mycobacterium, PZA = pyrazinamide, RFB = rifabutin, RMP = rifampin, SXT = trimethoprim-sulfamethoxazole, TE = tetracycline, TG = tigecycline.

the distribution of NTM species, rather than the presence of nAIGAs, may explain why over half of the identifiable NTM species from our patients were SGNTMs.

Consistent with the findings described in other reports,^[3,16] in addition to the NTM species, NTS was the most common bacterial coinfection in our patients with nAIGAs. In an earlier 3-year population-based study in Taiwan (23 million residents),^[19] a total of 13,264 patients with NTS infections were identified, and 6.3% of those infections were caused by septicemia. Among our patients, however, NTS bacteremia was recorded in 40% of cases. A similar high susceptibility to invasive NTS has also been observed in MSMD patients.^[20] Zoster was the most commonly

reported viral infection in the present study and others.^[3,4,16] In comparison to prior reports (4%–28.9%),^[3,16] a greater proportion of our patients (62.2%) experienced a history of HZ. In Taiwan, the lifetime risk of HZ in the general population is 32%,^[21] which is far less than the risk observed in our study. Regarding the persistence and latency of HZ, we also compared the serological statuses of other chronic viral infections (not clinically active, ST2, <http://links.lww.com/MD/B37>). A wide range of positive serological results (17.2%–100%) were noted for all tested viruses except hepatitis B. According to the HBsAg result from official 1982 Taiwanese data, approximately 15% to 20% of the general population were hepatitis B carriers.^[22] All of

our patients were born before 1982; thus, the estimated number of hepatitis B carriers in our patient population should be approximately 4 to 6 cases. It is unclear whether the presence of nAIGAs influences the serological result of the HBsAg test. In summary, patients with nAIGAs had a higher tendency to have a history of HZ or salmonellosis than the general population.

Similar to the observations made by Wongkulab et al,^[16] lymph nodes were the most common sites of organ involvement by NTM species. Neutrophilic dermatoses (NDs) are another clinical feature that can occur in patients with nAIGAs and dNTM infection.^[13,8,23] Similar skin lesions were also observed in our patients (ST6, <http://links.lww.com/MD/B37>). As described by Chan et al,^[23] most of the NDs appeared while patients were having an active NTM infection. IL-17 has been linked to certain autoimmune diseases and skin disorders,^[24] and an increased percentage of IL-17⁺ cells was observed in the ND lesion site.^[25] Thus, these observations suggest that Th17 cells may play an important role in the pathogenesis of ND in patients with nAIGAs and dNTM infection. Another intriguing observation was that all of the malignancies reported in our cohort originated from the T-cell/macrophage lineage. This clinical observation suggests that IFN- γ might play a role in the surveillance of T-cell/macrophage-associated malignancies in humans. However, a long-term observation of patients with nAIGAs is required to determine the relationship between IFN- γ and T-cell/macrophage lineage-associated malignancies.

The antimycobacterial agents used with our patients are primarily based on the recommendations proposed by the ATS and IDSA.^[15] However, poor therapeutic responses and disease recurrences were not uncommon in the present study. There are several possible explanations for this clinical observation, including nAIGA-induced immunodeficiency, medication non-adherence, and drug resistance. In the context of antimicrobial susceptibility testing (AST) of NTM isolates, the results of AST are distinct among different pathogens and various geographic regions.^[18,26] Not all patients in the present study received an initial AST, and potentially resistant isolates may be a cause of recurrent NTM disease. Various adjuvant therapies have been used to improve the clinical outcome of patients with nAIGAs,^[2,5,9,27,28] and B-cell depletion therapy with rituximab (RTX) has attracted much attention in recent years. Due to economic considerations and the restrictions of the Taiwan National Health Insurance, none of our patients received these therapies. Furthermore, these adjuvant therapies have their own problems. For example, concerns regarding the usage of RTX include its high cost, a recovery of the nAIGA titer after the end of RTX therapy, and associated side effects.^[29] According to our limited experience, chemotherapy with subsequent autologous stem cell transplantation is another option to overcome the undesired effects of nAIGAs. In the future, a more inexpensive, more durable, and safer adjuvant therapy will likely be required to modify the effects of nAIGAs.

The present study has some limitations. First, the number of cases was limited. However, our study provides the first detailed clinical picture of patients with dNTM infection and nAIGAs. Second, considering the inclusion criteria and the rarity of dNTM infections among relatively healthy individuals, only 1 dNTM case without nAIGAs was identified in our study; thus, no comparison between dNTM patients with nAIGAs and those without nAIGAs could be performed using the current data. A further long-term study is required to elucidate the difference in clinical manifestations between these 2 patient groups. Third, adjuvant therapies were not used in our cases, and the efficacy of

these agents could not be evaluated based on the present results. Despite these limitations, our results still offer valuable clinical information of patients with dNTM infection and nAIGAs to physicians dealing with such cases.

In conclusion, nAIGA-associated immunodeficiency is a common etiology in Taiwanese patients with dNTM infection with or without other opportunistic infections. When treating patients with an unusual clinical presentation of NTM infection, such as dissemination or frequent recurrence, physicians should be aware of the presence of nAIGAs, particularly in patients with a history of HZ or salmonellosis. The adherence to medical advice, an AST to screen for baseline drug resistance, and adjuvant therapy are necessary to improve the clinical outcome of patients with nAIGAs. Additional investigations are required to elucidate the trigger of nAIGAs and develop a more effective treatment strategy for these patients.

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