Diagnostic Microbiology and Infectious Disease 88 (2017) 308–315

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Mycobacteriology

Patient ethnicity and causative species determine the manifestations of anti-interferon-gamma autoantibody-associated nontuberculous mycobacterial disease: a review

Isano Hase [a,b,*], Kozo Morimoto [c], Takuro Sakagami [d], Yoshiki Ishii [b], Jakko van Ingen [e]

[a] Department of Respiratory Medicine, National Hospital Organization Utsunomiya Hospital, 2160 Shimo-Okamoto, Utsunomiya-shi, Tochigi, 329-1193, Japan
[b] Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi, 321-0293, Japan
[c] Respiratory Disease Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association, 3-1-24 Matsuyama, Kiyose-shi, Tokyo, 204-0022, Japan
[d] Department of Respiratory Medicine and Infectious Disease, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata-shi, Niigata, 951-8510, Japan
[e] Department of Medical Microbiology, Radboud University Medical Center, P.O. Box 9101, 6500HB, Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form 21 April 2017
Accepted 16 May 2017
Available online 18 May 2017

Keywords:
Anti-interferon-gamma autoantibody
Nontuberculous mycobacterium
Clinical manifestation
Ethnicity
Adult-onset immunodeficiency

ABSTRACT

Nontuberculous mycobacteria (NTM) infections involving anti-interferon-gamma (IFN-γ)-neutralizing autoantibodies have been described in previously immunocompetent adults. To investigate the factors underlying various disease manifestations, we reviewed 35 articles published between January 2004 and November 2016 and identified 111 NTM patients with anti-IFN-γ autoantibodies. Rapidly growing mycobacteria (RGM) accounted for 53% of the isolated species. RGM were predominant among the NTM species isolated from Thai (73%), Chinese (58%) and Filipino (56%) patients, whereas *M. avium* complex (MAC) was predominant among Japanese (58%) and non-Asian (80%) patients. The commonly involved organs included the lymph nodes (79%), bones/joints (34%) and lungs (32%). Compared with the patients with MAC, the patients with RGM had a higher incidence of lymph node lesions ($P < 0.05$) and a lower incidence of bone/joint ($P < 0.01$), lung ($P < 0.01$), soft tissue ($P < 0.01$), bronchus ($P < 0.01$) and muscle ($P < 0.05$) lesions. Clinical manifestations of NTM disease with anti-IFN-γ-neutralizing autoantibodies differ across ethnicities and NTM species.

Contents

* Corresponding author. Tel.: +81-282-87-2151; fax: +81-282-86-5080.
E-mail address: isanotaki@gmail.com (I. Hase).

http://dx.doi.org/10.1016/j.diagmicrobio.2017.05.011
0732-8893/

1. Introduction

Nontuberculous mycobacteria (NTM)-associated diseases encompass a broad spectrum of clinical manifestations driven by exposure, host immune status and bacterial virulence (Fig. 1). In affected immunocompetent individuals, common manifestations are pulmonary and skin lesions in adults and lymphadenitis in children. However, individuals with disseminated infections exhibit varied organ involvement, including the lungs, skin, blood, lymph nodes and bone. These infections mainly affect immunocompromised individuals, such as post-transplant patients, individuals with acquired immune deficiency syndrome (AIDS), and individuals with genetic defects that impart a Mendelian susceptibility to mycobacterial disease (MSMD) (e.g., deficiencies in the interferon-γ receptor 1 (IFN-γR1), the IL-12 receptor β1 (IL-12Rβ1), IL-12p40 and STAT1).

NTM infections involving anti-IFN-γ-neutralizing autoantibodies in Asian-born individuals were first described in 2004 and have since been reported worldwide (Döffinger et al., 2004; Höflich et al., 2004). Because these patients were previously immunocompetent adults, most of whom had presented with disseminated NTM infections, this entity became known as "adult-onset immunodeficiency" (Browne et al., 2012a). The anti-IFN-γ-neutralizing antibodies showed neutralizing capacity against IFN-γ and blocked the IFN-γ-IL-12 pathway, which plays an important role in the host immune system against mycobacterial pathogens (Fig. 2). Similar to patients with MSMD, patients with neutralizing anti-IFN-γ autoantibodies also demonstrated opportunistic infections other than NTM, such as infections with *Salmonella* species and Varicella zoster virus (Browne et al., 2012a). The coexistence of reactive dermatitis was also reported in these patients (Browne et al., 2012a).

We performed a literature review to assess correlations among disease manifestations, causative NTM species and ethnicity in patients with NTM infections involving anti-IFN-γ-neutralizing autoantibodies.

2. Methods

2.1. Literature review

We reviewed the English-language literature describing anti-IFN-γ autoantibody-positive cases with NTM infections and without other apparent immunocompromising conditions such as HIV infection, transplantation, malignant disease, primary immunodeficiency or immunosuppressive therapy administration. These cases were retrieved via a PubMed search conducted using the free text terms "disseminated nontuberculous mycobacteria", "adult-onset immunodeficiency", and "autoantibody, interferon γ".

The following essential data were abstracted for all subjects included in this review: ethnicity, gender, age, NTM species, NTM infection sites and outcomes. Additional data were also gathered if available, including symptoms, co-infective organisms other than NTM, reactive skin lesions and treatments. When no information was available regarding the ethnicity of the patient, the country of the reporting institution was considered the patient's "ethnicity". When several figures were reported for the age of a patient, we chose the age when the patient first experienced an NTM disease episode. If that age was unavailable, we chose the age of onset. "Symptoms" were defined as the chief complaints related to anti-IFN-γ autoantibody-associated diseases on admission, including symptoms other than NTM infections. "Location" referred to the NTM-infected organs, including the site diagnosed by the physical exam and radiology, providing no other etiologies was apparent. NTM infection involving synovium or manifesting a pleural effusion were described as "joint" or "pleura", respectively. "Lung" included NTM from sputum without apparent bronchial lesions. "Bronchus" included subglottic lesions and "bone" included spine lesions. The distributions of the infected sites were classified as disseminated disease or local disease. Disseminated disease was defined as organ involvement of 2 or more noncontiguous sites, or NTM-positive cultures from the blood or bone marrow. We grouped the reactive dermatitides associated with anti-IFN-γ autoantibody-related diseases as follows: Sweet's syndrome, pustular psoriasis, acute generalized exanthematous pustulosis (AGEP), erythema nodosum, and pyoderma gangrenosum. According to the pathological examination, "mature granuloma" included granuloma or granulomata, granulomatous lymphadenitis, or specimens with granuloma-specific findings such as multinucleated giant cells, whereas "immature or no granuloma" included granulomatous inflammation, granulation tissue, or specimens without granuloma-specific findings. "Treatments" excluded the corticosteroids that were prescribed for reactive dermatitis or subglottic stenosis. Secondary prophylaxis was

	Allergy	Local infection			Disseminated infection		
Location	Lung	Lung	Skin and soft tissue	Lymph node	Any organs (including blood)		
Age	Adults	Adults/children		Children	Adults/children	Adults	Children
Immune status	Hypersensitivity	Any status		Immunocompetent	Any status	Immunocompromised	
Underlying condition	None	Bronchiectasis Cystic fibrosis COPD Old TB e.t.c Unknown (middle aged women)	Trauma Surgery Tatoo Foreign body	None (1-5 years old)	Foreign body (Heart valve replacement, VP shunt, e.t.c)	Low CD4 AIDS Impairment of IFN-γ/ IL-12 pathway Anti-IFN-γ autoantibodies / MSMD Others Malignancy, post transplants, immnosuppressive drugs (Steroids, TNF-α inhibitor)	
Bacterial virulence	Unknown	Middle-high level		Unknown	Unknown	Any level	
Transmission route	Airway	Airway	Skin	Oral	Foreign body	Any route	

Fig. 1. NTM-related diseases. COPD = chronic obstructive disease; TB = tuberculosis; VP = ventriculoperitoneal; IFN-γ = interferon-gamma; IL-12 = interleukin-12; TNF = tumor necrosis factor; MSMD = Mendelian susceptibility to mycobacterial disease.