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Disseminated Nontuberculous Mycobacterial Infection in a Tertiary Referral Hospital in South Korea: A Retrospective Observational Study

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Purpose: Disseminated nontuberculous mycobacterial (D-NTM) disease occurs primarily in immunocompromised hosts. However, these cases have rarely been reported in South Korea. This study aimed to describe the clinical manifestations, disease course, and underlying immune deficiencies of patients with D-NTM disease.
Materials and Methods: We retrospectively reviewed the cases of D-NTM disease from January 2005 to December 2019 at a tertiary referral hospital in South Korea. D-NTM disease was defined as a bloodstream infection or infection of two or more non-contiguous body organs with species identification.
Results: Of the 53342 mycobacterial samples from 23338 patients, extrapulmonary NTM was detected in 104 patients, and 3 (2.9%) were diagnosed with D-NTM disease. *Mycobacterium avium* was isolated from two patients, while *M. abscessus* subspecies *abscessus* was identified in one. The patients were aged between 18 and 25 years, and two patients were male. All patients were immunocompromised – one received lung transplantation, one was diagnosed with anhidrotic ectodermal dysplasia with T-cell immune deficiency, and one had monocytopenia and mycobacterial infection syndrome associated with *GATA2* mutations. All patients underwent a standard macrolide-based regimen for >5 months, and their sputum tested negative. However, one patient died of bacterial sepsis, while the other two survived.
Conclusion: D-NTM disease is rare in a tertiary referral center in South Korea. They occur primarily in immunocompromised patients at a relatively young age. Careful investigation of the underlying immune status is required when treating patients with D-NTM disease.

Key Words: Immunocompromised host, immunity, nontuberculous mycobacteria

INTRODUCTION

Nontuberculous mycobacteria (NTM) is a collective name given to a group of over 197 mycobacterium species other than *Mycobacterium tuberculosis* or *M. leprae*.[1] NTM are ubiquitous in the environment, including air, soil, dust, plants, drinking water, biofilm, and wild animals.[2] With the increase in the incidence of NTM disease worldwide, interest in the disease has also been growing.[3] Recently, a rapid increase in the annual age-adjusted prevalence and incidence of NTM disease was reported in South Korea.[4]

NTM is most commonly associated with lung disease, while extrapulmonary NTM has been identified in approximately 5%–10% of patients with NTM disease.[5-7] Extrapulmonary diseases are classified as skin, lymph nodes, soft tissue, bone, ligaments, and disseminated disease.[8] Disseminated NTM (D-NTM) disease is serious and life-threatening. It occurs in people with advanced human immunodeficiency virus (HIV) infec-

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tion and uncommon in those without. [9-11]

Recently, D-NTM cases have been reported in non-HIV patients, such as those with a history of solid organ transplant (SOT) and defects of the interferon-gamma (IFN-γ)/interleukin (IL)-12 immune axis.[12] Immunocompromised patients with D-NTM disease are more commonly affected than immunocompetent patients.[13-16] With the emergence of advanced transplant technology and the utilization of immunosuppressive drugs, opportunistic infections, such as D-NTM disease, pose a substantial health burden in clinical practice. However, there is a paucity of data on D-NTM disease in South Korea. Therefore, the present study aimed to describe the clinical manifestations, disease course, and underlying immune deficiencies of patients with D-NTM disease.

MATERIALS AND METHODS

Study participants and design

We retrospectively reviewed the respiratory and non-respiratory mycobacterial culture results from January 2005 to December 2019 at Severance Hospital, a tertiary referral hospital in Seoul, South Korea. We examined the medical records and collected relevant clinical information.

Definitions

NTM disease was diagnosed according to the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines.[9] We defined D-NTM disease as a bloodstream infection or infection of two or more non-contiguous body organs with species identification.[16] If NTM was identified in only one organ and the others were positive for NTM polymerase chain reaction (PCR) or culture without identification, we classified it as presumptive D-NTM disease. We excluded extrapulmonary NTM disease involved in only one organ or two organs without any species identification.

The treatment outcome of D-NTM disease was assessed based on the NTM-NET consensus statement.[17] Culture conversion involved identifying at least three consecutive negative mycobacterial cultures from respiratory samples collected at least 4 weeks apart during antimycobacterial treatment. The initial date of negative culture was considered the culture conversion date. Both respiratory and non-respiratory specimens, including brain, stool, skin, liver, and lymph nodes, were stained according to the ATS/IDSA guidelines.[9] Reverse-hybridization line probe assay was used for identification of species.[18]

Ethical statement

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Severance Hospital (4-2022-1048). The need for patient consent was waived by the review board due to the study's retrospective design.

RESULTS

We screened 53342 non-respiratory mycobacterial samples from 23338 patients. Patients with negative culture results (n=22415) and extrapulmonary tuberculosis (n=819) were initially excluded (Fig. 1). After identifying 104 patients with extrapulmonary NTM isolation, we excluded patients with positive NTM culture results in one organ (n=88) or two non-contiguous organs without any identification of NTM species (n=13). Finally, three patients were diagnosed with D-NTM disease. Clinical information and treatment regimens are summarized as follows, and in Tables 1 and 2.

Patient 1

A 25-year-old male underwent lung transplantation for pulmonary graft-versus-host disease due to acute myeloid leukemia. He was hospitalized for 6 months due to recurrent pneumonia and underwent a second lung transplant for acute respiratory distress syndrome. *Mycobacterium abscessus* subspecies *abscessus* was identified in the donor lungs and isolated from the patient's bronchial alveolar lavage fluid 9 days after the second lung transplantation. There was no evidence of NTM disease on postoperative chest CT. However, *M. abscessus* subspecies *abscessus* was detected in the skin and blood of the patient after 8 months of the transplant, and a newly developed nodular lesion was observed on the chest CT. He was diagnosed with D-NTM disease and started treatment due to the immunocompromised state. He was treated with amikacin, imipenem, moxifloxacin, and azithromycin. Intravenous amikacin was discontinued after 60 days of treatment due to ototoxicity. The patient achieved sputum culture conversion after 22 days of treatment initiation, blood culture conversion after 60 days, and skin culture conversion after 90 days. However, the patient died of bacterial sepsis after 150 days of NTM treatment.

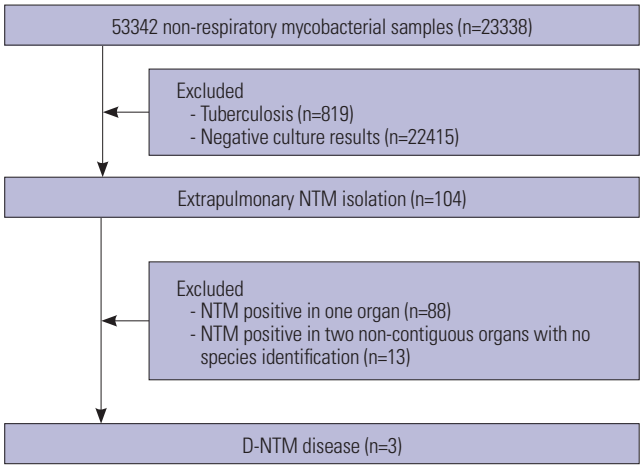

Fig. 1. Flowchart of the study participants. D-NTM, disseminated nontuberculous mycobacteria.

Table 1. Summary of Patients with Disseminated Nontuberculous Mycobacterial Infection

	Patient 1	Patient 2	Patient 3
Age, yr	25	18	22
Sex	Male	Male	Female
Signs and symptoms	General weakness, coarse crackles on chest auscultation	Fever, recurrent seizure	Sustained fever
Medical history	AML, PBSCT, GVHD, Lung transplantation	TB encephalitis	Latent tuberculosis
Culture or PCR results	BAL–*M. abscessus* Skin wound–*M. abscessus* Blood–*M. abscessus*	Sputum–*M. avium* Brain–NTM PCR +	Sputum–*M. avium*, *M. abscessus* sub. *abscessus* Blood–*M. avium* Liver–NTM PCR + SCN–NTM PCR +
Underlying disease	AML, Lung transplantation	Anhidrotic ectodermal dysplasia with T-cell immune deficiency	MonoMAC syndrome HLH
Final diagnosis	NTM bacteremia	NTM-PD NTM encephalitis (presumed)	NTM bacteremia
	D-NTM	Presumptive D-NTM	D-NTM

AIDS, acquired immunodeficiency syndrome; AML, acute myeloid leukemia; BW, bronchial washing; BAL, bronchoalveolar lavage; D-NTM, disseminated nontuberculous mycobacteria; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; MonoMAC, monocytopenia and mycobacterial infection syndrome; NTM, nontuberculous mycobacteria; NTM-PD, NTM pulmonary disease; PBSCT, peripheral blood stem cell transplantation; PCR, polymerase chain reaction; SCN, supraclavicular lymph node.

Table 2. Summary of Treatment Regimens and Prognosis

	Patient 1	Patient 2	Patient 3
Regimen (duration)	Amk (2 m)+Ipm+AZM+Mfx (5 m)	At age 18: INH+RIF+EMB+PZA+CLR (18 m) At age 20: INH+RIF+EMB+PZA+AZM (18 m) At age 22: CLR (9 m)+RIF+EMB+Mfx (12 m) At age 24: Amk (21 d)+EMB+RIF+AZM (on-going)	1st treatment: RIF+EMB+CLR+cefoxitin (2 m) 2nd treatment: Am (21 d)+AZM+Mfx+EMB (10 m)
Duration of culture conversion	BAL–unidentified Skin–90 days Blood–60 days Sputum–22 days	Sputum–50 days Brain–unidentified	Sputum–*M. avium*: 14 days –*M. abscessus*: 60 days Blood–unidentified Liver–unidentified
Status	Deceased	Alive	Alive

INH, isoniazid; RIF, rifampin; EMB, ethambutol; BW, bronchial washing; BAL, bronchial lavage; Amk, amikacin; Ipm, imipenem; Mfx, moxifloxacin; PZA, pyrazinamide; CLR, clarithromycin; AZM, azithromycin.

Patient 2

An 18-year-old male with a history of tuberculous (TB) encephalitis at 14 years of age was admitted for epilepsy. Brain MRI showed a recurrence of TB encephalitis. Brain biopsy was positive for NTM PCR, and *M. avium* was identified in his sputum. Chest CT showed multiple nodular consolidations, suggesting a mycobacterial infection. He was diagnosed with presumptive D-NTM disease, but the diagnosis of recurrent TB encephalitis could not be excluded. Therefore, he was treated for both *M. avium* and TB encephalitis for 18 months (isoniazid, rifampin, ethambutol, pyrazinamide, and clarithromycin). After 5 weeks of treatment, his sputum culture was negative for *M. avium*; however, the seizures persisted intermittently. After 4 years of modifying the medication, the patient was cured of D-NTM disease (Table 2). Despite ongoing treatment for D-NTM disease, the patient experienced repeated skin infections and pneumonia. We performed a genetic evaluation to identify the underlying disease for repeated infections at a young age. Next-generation sequencing panel revealed anhidrotic ectodermal dysplasia with T-cell immune deficiency due to nuclear factor-κB (NF-κB) sporadic mutation.

Patient 3

A 22-year-old female with a history of treated latent TB at the age of 7 years was referred for persistent fever for 2 weeks. Blood tests revealed pancytopenia and hyperferritinemia. Chest CT showed diffuse interstitial thickening and nodules in both lungs, suggesting mycobacterial infection or hematolymphangitic metastasis. Sputum culture was positive for *M. avium*. Supraclavicular lymph node biopsy revealed subacute necrotizing lymphadenitis, and NTM PCR was positive. *M. avium* was detected in subsequent blood cultures. Abdominopelvic CT indicated hepatosplenomegaly and a bone marrow biopsy revealed hemophagocytosis. The patient was diagnosed with D-NTM disease and secondary hemophagocytic lymphohistiocytosis.

The patient was treated with steroids, etoposide, clarithro-

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mycin, ethambutol, and rifampin. After 14 days of treatment, sputum culture converted to negative. On the 47th day of treatment, NTM medication was discontinued due to hepatotoxicity. Liver biopsy was positive for NTM PCR. The treatment regimen was changed to moxifloxacin, azithromycin, and ethambutol. On day 180 of treatment, *M. abscessus* subspecies *abscessus* was detected twice in the sputum cultures. Intravenous amikacin was administered for 2 months due to persistent fever and cough. On day 240 of treatment, the sputum culture tested negative for NTM. The patient was cured after 1 year of treatment.

Despite 6 months of treatment, the patient's sputum cultures results were positive for *M. abscessus* subspecies *abscessus*, and the symptoms persisted. Therefore, NGS was conducted to identify the underlying disease. She was diagnosed with *GATA2* deficiency and monocytopenia and mycobacterial infection (MonoMAC) syndrome. Allogeneic peripheral blood stem cells were transplanted without any complications.

DISCUSSION

We assessed the clinical characteristics and various underlying conditions of patients with D-NTM. To the best of our knowledge, this is the first study to investigate D-NTM disease in Korea. Among 104 patients with extrapulmonary NTM infection, three (2.9%) were diagnosed with D-NTM disease at relatively young ages, and all had acquired or congenital immune defects. Although the prevalence of D-NTM disease is low, it is important to define the underlying immune status when D-NTM is diagnosed, as it could play a key role in determining further treatment plan.

The IFN-γ/IL-12 axis is a critical pathway for the intracellular killing of mycobacteria.[12] When mycobacteria are ingested, mononuclear phagocytes express IL-12, which stimulates T cells and natural killer (NK) cells and induces the production of IFN-γ through the IL-12 receptor. IFN-γ induces macrophage activation and differentiation and IL-12 expression. It upregulates tumor necrosis factor α, which is essential for granuloma formation.[12] These events result in the activation of macrophages capable of destroying intracellular microorganisms.[12,19] If there is a flaw within the pathway or products of the effectors associated with cell-mediated immunity, it could increase susceptibility to mycobacterium.

D-NTM diseases are often reported in patients with acquired immune deficiency, such as those with advanced HIV infection. By the 1980s, disseminated *M. avium* complex (MAC) disease was frequently reported in patients with advanced HIV. However, its occurrence significantly decreased after the introduction of highly active antiretroviral therapy.[6,20] The precise mechanism of D-NTM disease in patients with advanced HIV remains unknown. According to a report,[9] it is generally assumed that the susceptibility to mycobacterium can be increased if the activity of specific T cells is reduced, which usually occurs when the level of cluster differentiation 4 (CD4) cells fall below 50 cells/mm^3.

With the advancements in the technology of transplantation and the use of immunosuppressants, the survival rate of organ transplantation has improved. However, problems, such as complications of graft rejection and infection, have emerged.[15] Immunosuppressive agents in SOT patients can reduce the activity of T cells and increase the risk of D-NTM disease.[14,21] Longworth, et al.[22] identified demographic factors associated with NTM disease in SOT recipients. They reported that NTM pulmonary disease was the most common (21/34 patients; 62%), followed by D-NTM (6/34 patients; 18%). They also reported that lung transplantation was significantly associated with the development of NTM pulmonary disease (15/19 lung transplant patients). Transplanted lungs are susceptible to NTM due to easy exposure to potential environmental pathogens and higher immunosuppression levels compared to other organ transplants.[22]

Deficiencies in genes related to innate immunity can increase the risk of having D-NTM disease. In patient 2, D-NTM disease was diagnosed with anhidrotic ectodermal dysplasia with T-cell immune deficiency. Anhidrotic ectodermal dysplasia with immunodeficiency is a primary immunodeficiency disease caused by a mutation in NF-κB activation or signaling pathway.[23] NF-κB is crucial in regulating the survival, activation, and differentiation of innate immune cells and inflammatory T cells, especially CD4+ T-helper cells.[24] In Patient 2 in our study, sporadic mutation of the NFkB1A gene increased the susceptibility to D-NTM disease.

MonoMAC syndrome is a rare disease caused by heterozygous mutations in *GATA2*, which results in loss of gene function that regulates various aspects of development from hematopoiesis to lymphatic, leading to immunodeficiency and bone marrow failure.[25,26] Mutations in the *GATA2* gene result in immune deficiency diseases that reduce the numbers of circulating monocytes, dendritic cells, NK cells, and B cells, resulting in increased opportunistic infections and increased risk of malignant blood cancer.[26] Patient 3 in our study showed decreased NK cells, B cells, and pancytopenia. This occurred due to *GATA 2* mutation, which may also be considered a factor responsible for increasing the susceptibility to D-NTM disease.

Besides the immune defects presented in this study, various conditions increase susceptibility to D-NTM disease. One well-known condition is mutations in IFN-γ receptors (IFNGR).[12] IFNGR consists of heterodimers of IFNGR1 and IFNGR2.[12] Recessive complete IFNGR1 deficiency has been related to severe Bacille Calmette-Guerin disease or mycobacterial disease presenting in infancy or early childhood.[27] Majority of the deaths occur due to severe NTM disease. The only curative treatment is hematopoietic stem cell transplantation, but its success rate is quite low due to impaired engraftment and the occurrence of severe complications.[12]

Another immune dysfunction to provoke D-NTM disease is the development of autoantibodies to IFN-γ.[28,29] According to Kampmann, et al.,[28] plasma IFN-γ levels were not detected in patients with severe NTM disease of unknown etiology, and IFN-γ neutralizing factors were isolated and identified as autoantibodies. Several studies have reported on D-NTM diseases associated with IFN-γ autoantibodies.[11,29] Aoki, et al.[30] reported that it could be detected in an immunocompetent patient. We checked for neutralizing antibodies of IFN-γ in Patients 2 and 3, but the results were negative. Since autoantibodies to IFN-γ are rare, further research is needed to identify the mechanisms of pathogenesis.[30]

Determining the etiology of D-NTM is important because varied treatment approaches can be employed. There is no definitive treatment for anhidrotic ectodermal dysplasia with T-cell immune deficiency. Infection can reoccur in these patients due to immunological abnormalities.[23] D-NTM caused by *GATA2* mutation was cured in our study with peripheral blood stem cell transplantation, and the patient survived without any infection. Therefore, efforts to determine the relationship between D-NTM disease and host immune factors may enable individual prophylaxis, family screening, and target therapy.[12]

This study had a few limitations. First, this was a retrospective cohort study performed at a single center. Second, we diagnosed patients with presumptive D-NTM based on positive NTM PCR results. For accurate diagnosis and treatment of D-NTM, samples should be cultured to obtain definitive results.

In conclusion, the prevalence of D-NTM disease was low in a tertiary referral hospital in Korea. If patients are diagnosed with an unknown cause of D-NTM disease, clinicians should investigate the underlying etiology of immune deficiency, including congenital and acquired diseases. This would help determine the fundamental treatment plan. Further studies determining the nature of D-NTM disease using prospective multicenter approaches are needed.

DATA AVAILABILITY STATEMENT

The datasets used in this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: Young Ae Kang and Youngmok Park. Data curation: Hyejin Park. Formal analysis: Hyejin Park. Investigation: Hyejin Park and Youngmok Park. Methodology: Young Ae Kang and Youngmok Park. Project administration: Youngmok Park. Supervision: Young Ae Kang and Youngmok Park. Validation: all authors. Visualization: Youngmok Park. Writing—original draft: Hyejin Park. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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