INTRODUCTION

The incidence rate of pulmonary nontuberculous mycobacterial disease (PNTMD) in Japan during 2014 was estimated to be 14.7 cases per 100,000 person-years, exceeding that of culture-positive pulmonary tuberculosis (TB) for the first time (1). This rate was the highest among major industrialized nations (2). Patients with PNTMD generally have a long disease course and the estimated PNTMD prevalence in Japan is greater than 110 cases per 100,000 persons, suggesting the increasing importance of cooperation between respiratory specialists and general physicians.

On the other hand, many physicians in Japan may lack knowledge about acid-fast bacteria (AFB) tests due to the decreasing number of tuberculosis (TB) patients. Furthermore, when physicians with little experience in treating TB patients provide medical care to patients with nontuberculous mycobacterium (NTM), they may confuse these mycobacterial diseases, leading to a diagnostic pitfall.

In addition, the general use of biological products for autoimmune and malignant diseases has led to an increase of mycobacterial diseases in patients whose immune response was altered by therapeutic agents. Therefore, physicians need to be reminded that they may encounter mycobacterial disease regardless of their specialty. This review describes the varying clinical presentations of NTM disease, and discusses the challenges of AFB tests and points to keep in mind when providing medical care to patients with NTM.

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DIAGNOSTIC CHALLENGES IN PULMONARY MYCOBACTERIAL DISEASES

The typical clinical course and radiological manifestations of PNTMD are different from those of PTB, and the differential diagnosis between these infections can be simplified by identifying the mycobacterial species detected from the patient and use of supplementary methods such as Mycobacterium tuberculosis (MTB) antigen specific interferon-γ release assay (IGRA) and measurement of antibodies to the glycopeptidolipid (GPL) core antigen specific to Mycobacterium avium complex (MAC) (3-5).

However, diagnostic pitfalls may cause physicians to make an incorrect initial diagnosis. Some of the diagnostic challenges of pulmonary mycobacterial diseases are as follows:

Erroneous diagnosis of multidrug-resistant tuberculosis (MDR-TB) caused by the presence of NTM

In Japan, MDR-TB, defined as the disease caused by MTB resistant to isoniazid and rifampicin, accounts for less than 1% of new TB cases (6, 7). As patients with MDR-TB are refractory to treatment, information about drug-susceptibility tests (DST) is important in clinical practice (6). However, the results of DST may not always reflect the subsequent clinical course. The diagnosis of MDR-TB was reported to be incorrect in 9 (13%) of 70 patients possibly due to laboratory-related errors (8). Situations that are considered to be laboratory-related errors include a good treatment course with standard regimens, disagreement with the DST results on resubmitted specimens, detection of MDR-TB from untreated inactive lesions, and a lack of tuberculous lesions. Coexistence of NTM with MTB in sputum, cross-contamination, and specimen mislabeling could be the cause (8, 9). Misdiagnosis of MDR-TB may cause serious harm to the patient because it will result in the unnecessary abandonment of an effective treatment. It is thus important to carefully observe the solid media to distinguish between colonies of NTM (smooth type) and MTB (rough type), and share information about the
patient’s background and clinical course between laboratory staff and the physicians to avoid misdiagnosis.

False positives for NTM in MTB nucleic acid amplification tests (NAATs)

An important part of the initial assessment of suspected pulmonary mycobacterial disease is the determination of whether it is PTB exhibiting human-to-human transmission. Currently, MTB NAATs are mainly used for rapid diagnosis (7 kits are currently available in Japan), and their sensitivities in patients with sputum smear-positive or negative PTB are 94-100% and 62-80%, respectively (10, 11). They also have excellent specificity (99-100%) (10, 11), but yield false positives for several NTM due to the homology of the gene sequence of the amplification site.

For example, TRCRapid M. TB (Tosoh Bioscience, Tokyo, Japan) utilizing a transcription-reverse transcription concerted (TRC) method that allows rapid detection of the target RNA yields false positives for several NTM, including Mycobacterium shinjukuense (12-21). If NAAT is positive in a suspected TB patient but the subsequent clinical course is inconsistent with TB, the isolate should be identified by the newly developed matrix-assisted laser desorption ionization-time of flight mass spectrometry or sequence analysis (22). False-positive reactions in MTB NAATs may occur or have already occurred for unidentified NTM species without being noticed.

Microbial substitution

Most of the MAC or Mycobacterium abcessus complex (MACB) isolates re-identified after negative sputum culture conversion obtained by anti-NTM chemotherapy are the result of reinfections with mycobacteria of different genotypes (23, 24). Furthermore, in the Japanese 2014 survey, the incidence rate of MACB disease increased five-fold in 7 years and microbial substitution of MAC to MABC is regarded as one of the reasons (1). MACB is classified into M. abscessus spp. abscessus, M. abscessus spp. bolletii and M. abscessus spp. massiliense. The ribosomal methyl transferase gene erm (41) confers inducible macrolide resistance (susceptible on day 3 but resistant on day 14 of DST) in M. abscessus spp. abscessus and bolletii. However M. abscessus spp. massiliense is susceptible to clarithromycin even after prolonged incubation because its erm (41) does not work (24-27). In Japan, the rapidly growing mycobacteria identification kit using nucleic acid chromatography (KANEKA Corporation, Osaka, Japan) has made it possible to evaluate MABC subspecies and the erm (41) genotype in clinical practice. Management of NTM disease requires regular assessment of microbial substitution and reconsideration of treatment plans.

Abnormal radiological manifestations caused by NTM: Not what it seems

PNTMD generally presents as bronchiectasis with clustered centrilobular nodules (nodular bronchiectatic disease) or upper-lobe cavitary lesions (fibrocavitary disease). However, it occasionally develops as unexpected lesions.

1. Pneumonia-like shadows

The clinical manifestations of pulmonary mycobacterial diseases are affected by the immunological background of the host. For example, significant differences have been reported in chest radiographic and computed tomography (CT) findings of TB depending on the status of human immunodeficiency virus (HIV) infection and CD4 T cells (28, 29). TB can develop in the early stage of HIV infection, but NTM disease usually develops in the late stage (30, 31). Therefore, in HIV-positive patients with NTM disease, granulomas are not sufficiently formed and exudative lesions become predominant (32). On the other hand, rapidly progressive pulmonary consolidation due to granulomatous inflammation in a patient with PNTMD without immunodeficiency was reported and similar shadows have been found in patients with rheumatoid arthritis (33-34). In such cases, an excessive immune response is assumed to be the principal pathological condition and steroid therapy is usually effective (33-34).

2. Miliary pulmonary opacities

A miliary pattern, randomly distributed nodular opacities, on chest radiographs is generally caused by a systemic disorder such as hematogenous spread of infection or cancer, and sarcoidosis. TB is a well-known infectious disease that can present with a miliary pattern (35), but NTM disease may also exhibit the same pattern. In an autopsy-based study, a miliary pattern was found in cases of disseminated NTM disease with pulmonary involvement, but not in cases of PNTMD alone (36).

However, miliary opacities are known to be observed in patients with hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, and inhalation of aerosols containing NTM (mainly MAC) can induce a similar clinical presentation. Hot tub lung (HTL) is a typical disease of this condition and pathologically a granulomatous lung disease (37-39). Like HP, HTL shows apparent improvement either spontaneously or in response to glucocorticoid therapy after avoiding exposure to the pathogen without anti-NTM chemotherapy (39). The fact that bacillus Calmette-Guerin (BCG) immunotherapy for bladder cancer sometimes induces systemic granulomatous inflammation supports the hypothesis that HTL is an allergic reaction rather than an infection (40, 41). In addition, the possibility of endobronchial spread of NTM (M. xenopi) was reported in an immunocompromised patient (42).

3. Large pulmonary solitary mass

NTM, especially MAC, infections sometimes cause solitary pulmonary nodules (SPN) (43). In Japan, the proportion of M. intracellulare cases is high in the southwestern region (44), but SPN are mainly due to M. avium infections. SPN in patients with NTM infection are less likely to cause satellite lesions and calcification than those in patients with MTB infection. Therefore, this type of disease may not be diagnosed until surgical resection is performed for suspected lung cancer (43). In addition, granulomas and expanded bronchi with purulent exudate can aggregate together to form a large mass. We previously reported a lobulated mass with marked 18-fluorodeoxyglucose (FDG) uptake, mimicking pulmonary mucinous cystadenocarcinoma due to Mycobacterium kansasi infection (45). As the presentations of PNTMD are protean, NTM infection should not be excluded from the differential diagnosis of pulmonary disease simply based on radiological manifestations alone.

FEATURES OF EXTRAPULMONARY NTM DISEASES THAT ARE DIFFERENT FROM THE CORRESPONDING TUBERCULOUS DISEASES

As MTB survives only in humans and exhibits aerial transmission, it is not directly transmitted into the extrapulmonary organs from outside of the body. During primary infection, hematogenous and lymphatic spread of MTB to extrapulmonary organs occurs before adaptive T-cell immunity is firmly established. There are two presentations: early-onset following primary infection and endogenous recurrence from long-surviving MTB in microgranulomatous lesions (46). However, NTM residues in natural environments (soil and water) and can transmit through the skin, gastrointestinal tract, and sharps injuries to form extrapulmonary lesions.
Pleurisy

Tuberculous pleurisy that follows primary infection (primary TB pleurisy) is the most common extrapulmonary TB in Japan, and its pathogenesis is considered to be a delayed-type allergic reaction to TB antigens in the pleural cavity (47). Multiple cytokines released mainly from immune cells increase the permeability of the pleural capillaries and cause pleural effusion (48, 49). This condition can resolve spontaneously, but recurrence was observed in approximately half of untreated cases resulting in serious presentation (50, 51). However, in asymptomatic patients with pleural thickening suspected to be caused by primary TB pleurisy, antituberculous chemotherapy is usually not administered. We previously reported the usefulness of FDG positron emission tomography/CT evaluation in such a case (52).

On the other hand, primary TB pleurisy (i.e., without distinct pulmonary involvement) is rare, probably because NTM are environmental mycobacteria inducing desensitization in hosts before its infection (53). NTM pleurisy may be caused by a direct extension of infection from pulmonary lesions into the pleural cavity and is often intractable (54-56). Endoscopic examination to diagnose PNTMD was reported to cause NTM pleuritis with pneumothorax probably due to the rupture of a subpleural lesion during the procedure (20, 57). Recently, Furuchi et al. reported a case of PNTMD with pleural effusion, suggesting that evaluation of pleural fluid anti-GPL-core IgA antibody can be a supplementary diagnostic method for the pleural involvement of MAC (58).

Vertebral osteomyelitis

Vertebral osteomyelitis (VO) is now an uncommon clinical presentation of TB, but tuberculous VO was reported to be increasing in the elderly. Patients with bone and joint TB usually have few typical symptoms and inflammatory markers in patients are often not elevated. In addition, age-related changes in the vertebra, such as spinal joint deformities and osteoporosis, can affect radiological findings, leading to oversights or delays in the diagnosis of tuberculous VO (59).

NTM also cause VO, with about half of the cases occurring in otherwise healthy patients (60-64). Blunt-force trauma was reported to be a risk factor for VO due to mycobacterial infection, and it is hypothesized that macrophages which have phagocytosed NTM migrate to the injury site for tissue restoration but release the pathogen resulting in the development of VO (62). An interesting case of M. abscessus spp. abscessus disease was recently reported, which was initially diagnosed as primary pleurisy, but later turned out to be disease progression from VO (65). The major pathogen of VO, including cases with exudative pleural effusion, is Staphylococcus aureus (66, 67), but NTM infection should be considered, especially in patients with a history of pre-disposing trauma.

Disseminated mycobacterial disease

Disseminated TB is defined as the hematogenous spread of tuberculous infection involving multiple noncontiguous sites (35). Miliary TB is a term that refers to miliniary granulomas under the same conditions generally with innumerable tiny spots on a chest radiograph (68).

Disseminated NTM disease has been observed in adults with advanced HIV infection and in cases of severe cellular immune dysfunction caused by immunosuppressive therapy such as after hematopoietic stem cell and organ transplantation (30, 31, 69). In recent years, neutralizing anti-interferon-γ autoantibody has received a great deal of attention as a new etiology of this condition (70-72). It should be noted that the main primary site of transmission of disseminated MAC (mainly M. avium) disease is the intestinal mucosa and this condition does not necessarily have a preceding lung lesion (73). Blood cultures play an important role in the diagnosis (74) and rapidly growing mycobacteria may be detected in commonly used aerobic culture bottles. However, BACTEC Myco/F Lytic culture vials are more suitable for the detection of mycobacterium, especially for slowly growing species, including MAC (75). NTM can also be the causative pathogens of catheter-related bloodstream infections (76).

Mycobacterial Diseases Associated With Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is a condition noted in some cases of rapid reconstruction or activation of immune function, which increases the immunoinflammatory response to antigens mainly derived from microorganisms. It typically causes the development of a new opportunistic infection (unmasking IRIS) or paradoxical clinical exacerbation of a pre-existing infection (paradoxical IRIS) (77). Mycobacterial diseases in representative clinical settings of IRIS are described below.

Introduction of antiretroviral therapy (ART)

Paradoxical exacerbation of existing TB during antituberculous chemotherapy was observed in 36% of HIV-positive patients who were additionally treated using ART. The median duration of antituberculous chemotherapy before the onset of paradoxical TB-IRIS was 8 weeks (interquartile range 5.5-11.5 weeks), whereas the median duration of ART was only 4 weeks (interquartile range 2-10 weeks). In addition to the exacerbation of the preceding lesions, new lesions may develop in extrapulmonary organs, including the central nervous system (78, 79). In this setting, NTM disease is often recognized as unmasking IRIS and superficial lymphadenitis is common. Unlike disseminated NTM disease, lesions may be localized and the positive rate on blood culture is low (79).

Discontinuation of TNF inhibitors and immunosuppressive drugs

Tumor necrosis factor (TNF)-α is required for the formation and maintenance of granuloma, which confine microbial pathogens difficult to eradicate. Therefore, administration of TNF inhibitors to patients with autoimmune diseases, such as rheumatoid arthritis, can induce granulomatous infections, including activation of latent TB (80, 81). Discontinuation of anti-TNF therapy at the onset of TB can cause paradoxical exacerbation (82). According to the Japanese guidelines, if the susceptibility of MTB to anti-TB drugs is known and TNF inhibitors can be safely administered, continuation of the treatment using a biological product during antituberculous chemotherapy should be considered (83).

Regarding NTM diseases associated with anti-TNF therapy, the majority of patients were administrated either corticosteroids or methotrexate at the same time, and extrapulmonary lesions were frequently observed (84). The paradoxical exacerbation of NTM diseases in patients with autoimmune diseases while undergoing dose reduction, or after the discontinuation of TNF inhibitors or immunosuppressive drugs has also been reported (85-87). In general, NTM disease is refractory to treatment, making it difficult to notice the paradoxical exacerbation. However, in the above cases, persistent infection with NTM was excluded by AFB tests. Moreover, the introduction of steroid therapy or increase in the dose of glucocorticoid and immunosuppressive drug was effective.
Introduction of immune checkpoint inhibitors (ICIs)

The development of a new opportunistic infection during ICI therapy has become a concern and many TB cases were considered to be unmasking IRIS. Therefore, confirmation of a negative IGRA result prior to ICI administration may be beneficial, similar to before the administration of TNF inhibitors (88). Approximately half of the cases of unmasking TB during ICI therapy were detected before the onset of subjective symptoms by CT performed for the purpose of evaluation of ICI therapy against malignancy (89). The paradoxical exacerbation of existing TB during nivolumab therapy was also reported in a lung cancer patient (90). Regarding NTM disease during ICI therapy, there are only a few reported cases from Japan. Nodular bronchiectatic disease developed in advanced lung cancer patients previously treated using cytotoxic chemotherapy and thoracic radiotherapy (91). Conversely, there was a case in which the existing pulmonary M. abscessus sp. massilience disease was improved by ICI therapy for advanced lung cancer (92). The accumulation of cases of NTM disease in this setting is necessary in order to improve the management of ICI-induced immune-mediated events.

Recovery from immunosuppression by treatment for the underlying disease

Paradoxical clinical exacerbation of TB has been recognized, usually after initial improvement, in otherwise healthy patients receiving antituberculous chemotherapy, and is referred to as a paradoxical response or paradoxical reaction (PR) (93). This phenomenon may be attributed to an excessive immune response to massive antigen release from dying MTB coincided with recovery from TB-induced immunosuppression. In general, the duration of antituberculous chemotherapy before paradoxical exacerbation is longer in HIV-negative patients than in HIV-positive patients on ART (94).

Several cases of PR in otherwise healthy patients treated for NTM have also been reported, among which exacerbation of existing lesions and the development of new lesions were noted after negative conversion of the sputum AFB smear results without redetection of NTM (95, 96). These lesions gradually improved without changing the chemotherapy regimen.

Recovery from an immunosuppressive condition during pregnancy

Pregnancy is regarded as an immunosuppressive condition to maintain fetal tolerance and the Th1 response recovers rapidly from the suppressed state during the postpartum period resulting in the development of new infections including TB (unmasking IRIS) (97, 98). In postpartum TB cases, the frequencies of extrapulmonary and central nervous system involvement were reported to be approximately 90 and 70%, respectively. The mortality rate and frequency of sequelae were 38 and 14%, respectively (99). Postpartum tuberculosis may progress to PR without initial improvement on the same IRIS spectrum (100).

To the best of our knowledge, there are no reports of postpartum PNTMD. However, many cases of postcesarean section wound infection caused by MABC have been reported, although the involvement of immune reconstitution has not been discussed (101, 102).

CONCLUSIONS

In the diagnosis and treatment of pulmonary mycobacterial disease, it is important to confirm that there is no discrepancy between the clinical course and the results of AFB tests. If necessary, new and/or existing samples must be examined to confirm the mycobacterial species. As the presentations of PNTMD are protean, NTM infection should not be excluded from the differential diagnosis of pulmonary disease simply based on radiological manifestations alone. The development of extrapulmonary NTM diseases is different from that of corresponding tuberculous diseases because NTM are environmental mycobacteria that can transmit through the skin, gastrointestinal tract and sharps injuries to form extrapulmonary lesions. In addition, noninvasive trauma may be a risk factor for VO due to NTM infection. Moreover, it is necessary to pay sufficient attention to the immune function and its modifiers. As an opportunistic infection, NTM disease usually develops with more advanced immunosuppression than TB and is more likely to be disseminated. On the other hand, NTM disease associated with IRIS is less common and unmasking disease is often localized compared with TB. The paradoxical exacerbation of NTM disease as IRIS is usually responsive to the increase in immunosuppression.

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