Nontuberculous Mycobacterial Infections

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KEYWORDS

• Nontuberculous mycobacteria • *Mycobacterium avium* complex • Bronchiectasis

KEY POINTS

- Pulmonary manifestations of NTM are mostly seen in elderly population with or without underlying lung disease. MAC is the most common agent.
- The most common imaging pattern is bronchiectatic disease in elderly females without prior lung disease, with imaging findings of bronchiectasis and nodules most commonly involving the midlung zones.
- The second most commonly seen pattern is cavitary disease in elderly males with preexisting underlying lung disease, with similar radiological findings as pulmonary tuberculosis.
- Diagnostic criteria include both imaging and recurrent isolation of mycobacterium from the sputum or one isolation from bronchial wash in a symptomatic patient.

INTRODUCTION

Mycobacterial species other than *Mycobacterium tuberculosis* and *Mycobacterium leprae* constitute nontuberculous mycobacteria (NTM), also termed atypical mycobacteria. NTM infections are increasing worldwide likely due to increase in immunocompromised patients, improved diagnostic techniques, and increased life expectancy, particularly in elderly women.[1–3] NTM are ubiquitous organisms commonly found in a variety of environmental sources. Pulmonary manifestations account for 80% to 90% of disease caused by NTM.[4,5] These infections can happen in those with or without preexisting lung diseases such as chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis, pneumoconiosis, and prior tuberculosis.[6,7] Depending on the scenario, patients may present acutely or with chronic manifestations, such as chronic cough. Imaging plays a key role in the diagnosis and monitoring of NTM infection.

Epidemiology and Sources of Infection

NTM are ubiquitous free-living organisms and are found abundantly in the natural environment. They have been isolated from tap and surface water resources, soil, animals, and food and milk products.[8,9] Humans are therefore constantly exposed to these organisms, and infection occurs mostly from aerosolized droplets from these environmental sources. Human to human transmission is rare although postulated in some cystic fibrosis lung transplant centers.[2,10] In immunocompromised patients, like patients with HIV/AIDS, infections commonly occur through the gastrointestinal route.[8] These organisms then gain access through lymphovascular invasion of the gastrointestinal tract leading to disseminated infection.[6,11]

Runyon in 1959 classified mycobacteria according to their rate of growth, pigmentation in response to light, and colony morphology. They are classified as *Mycobacterium tuberculosis* complex (TB), rapidly growing NTM, and slowly growing NTM. Slowly growing mycobacteria are divided into 3 groups: photochromogens, scotochromogens, and nonchromogens based on pigmentation with light exposure.[6,9]

Mycobacterium avium complex (MAC), also sometimes called *Mycobacterium avium intracellulare*, is the most common species causing human infections in the United States. It is followed

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by *Mycobacterium fortuitum* and *Mycobacterium kansasii*, and all 3 of these are slowly growing NTM. Rapid growing *Mycobacterium abscessus* is increasing in prevalence particularly due to its involvement in cystic fibrosis patients.[2,5,12] The prevalence of NTM has been increasing worldwide and is 2 to 3 times more common than tuberculosis in the Western world.[13] MAC is commonly seen in the United States and East Asia, and *M kansasii*, *Mycobacterium xenopi*, and *Mycobacterium malmoense* are more prevalent in Europe.[13]

MAC most commonly causes pulmonary disease, both cavitary and noncavitary forms. Hypersensitivity pneumonitis and solitary pulmonary nodules are less commonly seen. Disseminated infections occur in severely immunocompromised patients such as those with AIDS. *M kansasii* is the second most common respiratory isolate after MAC in the United States.[14] It causes a cavitary pattern of pulmonary disease resembling tuberculosis in COPD patients and disseminated infection in immunocompromised patients such as those with AIDS. However, unlike other NTM, *M kansasii* is not found in soil or natural water supplies but has been frequently recovered from tap water in endemic areas. Rapidly growing *M abscessus* typically causes pulmonary disease in patients with bronchiectasis, similar to the bronchiectatic type typically caused by MAC. The rapid growing *M fortuitum* typically causes skin and soft tissue as well as catheter-related infections mostly by direct inoculation; and *Mycobacterium chelonae* causes disseminated infection in immunocompromised patients as well as rare infection in patients with esophageal dysmotility.[12,13]

Diagnostic Criteria

Making the diagnosis of NTM is sometimes difficult because these organisms frequently colonize the airways in patients with preexisting lung disease, such as those with COPD or bronchiectasis. Moreover, cultures can also be falsely negative in infected patients, particularly in those without cavities.[15] As a result, the American Thoracic Society requires clinical and radiologic criteria, in addition to microbiological results, for appropriate diagnosis (**Box 1**).

Clinical symptoms are nonspecific and include dry or productive cough, shortness of breath, fatigue, malaise, and hemoptysis. Fever and weight loss are less commonly seen. As infection can coexist with preexisting pulmonary disease, symptoms and physical examination may be masked by the underlying pulmonary condition. Thus, it may be difficult to attribute any symptoms to the mycobacterial infection; following patients over time may be necessary to correlate the course of the infection with clinical symptoms.

Microbiological evaluation and drug susceptibility testing are essential for the accurate diagnosis and identification of NTM species and their appropriate management.[5,16]

Sputum testing

Smear and culture of at least 3 separate expectorated morning sputum specimens are recommended. Sputum sent for culture must be decontaminated first for elimination of common bacteria and fungi. In addition, in patients with suspected tuberculosis, sputum nucleic acid amplification tests should be performed for exclusion of that diagnosis. At least 2 positive sputum cultures are needed for the diagnosis of NTM infection.

Bronchial lavage and biopsy

In case of negative sputum testing, additional testing such as bronchoscopy with bronchoalveolar lavage (BAL) or transbronchial biopsy can be performed. At least one positive BAL culture is adequate. Alternatively, lung or transbronchial biopsy with mycobacterial histopathological features and culture is diagnostic. For either sputum or BAL samples, nucleic acid probes are also commercially available that are highly accurate and can identify MAC and *M kansasii* within a day.[17,18]

Clinical Syndromes and Imaging Findings

Cavitary type (classical)

This form typically occurs in white, middle-aged to elderly males with preexisting lung diseases such as COPD or prior granulomatous disease (including tuberculosis and sarcoidosis). It is clinically and radiologically similar in appearance to postprimary, or reactivation, tuberculosis.[6,19,20] Patients commonly develop cough with sputum, fatigue, and weight loss, which can simulate relapse of prior tuberculosis. MAC is the frequent culprit; however, *M kansasii* and *M abscessus* can also cause similar patterns of disease.[20] Cough and dyspnea are common symptoms, which are difficult to distinguish from the underlying disease such as COPD. Fever and hemoptysis are less common compared with tuberculosis.[2]

In patients with pre-existing bronchiectasis, such as from treated tuberculosis, MAC can develop in prior areas of lung involvement. It is characterized by upper lobe cavitary lesions (**Fig. 1**A, B) as well as centrilobular and tree in bud nodules (**Fig. 1**B, C). Peribronchial consolidation, architectural distortion, and scarring can also occur, as seen in tuberculosis. Computed tomography (CT) will better characterize the cavities and

Box 1
Criteria for diagnosing NTM

Clinical and radiologic criteria

- Pulmonary symptoms AND
- Nodular or cavitary opacities on chest radiograph or bronchiectasis with multiple small nodules on CT AND
- Appropriate exclusion of other diagnoses

Microbiologic criteria

- Positive culture from at least two separate sputum samples. If results are nondiagnostic, consider repeat sputum AFB smears and cultures **OR**
- Positive culture result from at least one bronchial wash or lavage (regardless of AFB smear result) **OR**
- Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) **AND** positive culture for NTM; **OR**
- Biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) **AND** one or more sputum or bronchial washings that are culture positive for NTM

Additional considerations

Expert consultation should be obtained when NTM recovered that are infrequently encountered or that usually represent environmental contamination.

Patients who are suspected of NTM lung disease but not meeting diagnostic criteria should be followed until diagnosis is firmly established or excluded.

Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.

show associated volume loss and traction bronchiectasis. Spread of infection through bronchi is common and may involve the contralateral lung; it is characterized on CT by tree-in-bud nodules.[6,15,20] Reportedly, NTM infections are more indolent with smaller cavities compared with TB, but this distinction is not helpful clinically.[15] Lymphadenopathy and pleural effusions are relatively uncommon.[15,20,21]

Nodular-bronchiectatic type (non-classic)

This is the most frequently seen type in the United States and Canada. It commonly develops in nonsmoking middle-aged to elderly white women without underlying lung disease and is sometimes referred to as the Lady Windermere syndrome.[22] MAC and *M kansasii* are the most common culprits; however, *M chelonae* and *M abscessus* can also cause this type of infection. The clinical presentation is indolent, with many years of chronic progressive cough with or without sputum, and recurrent respiratory infections.[22] Fever, dyspnea, and other constitutional symptoms such as weight loss may also occur.[2] This syndrome is associated with bronchiectasis, although it is not clear if bronchiectasis is the predisposing factor leading to the infection or is the result of the infection, likely both may occur.[20] Notably, cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations are seen at increased prevalence in patients with this form of NTM, even in patients without clinically apparent cystic fibrosis, and this may be a predisposing factor to developing NTM infection.[23] Sputum cultures are less sensitive for the diagnosis as compared with the cavitary form, and thus more invasive approaches such as BAL may be required.

Chest x-ray may show atelectasis and scarring, most commonly affecting the right middle lobe and lingula (**Fig. 2**). CT shows bronchiolitis (centrilobular and tree in bud nodules) and bronchiectasis with predilection for the midlung zones, particularly

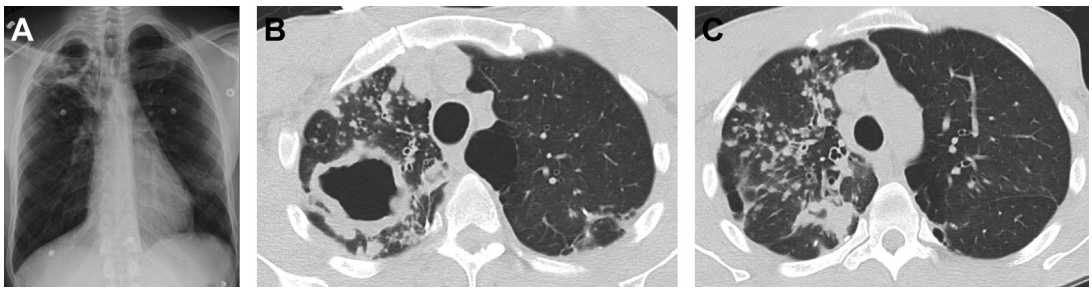

Fig. 1. 72-year-old man with *M kansasii*. (*A*) Chest radiograph shows cavitary consolidation in right upper lung with adjacent nodular opacities. (*B*) and (*C*), Axial chest CT shows cavity in right apical segment with adjacent centrilobular and tree in bud nodules. Note the underlying paraseptal emphysema.

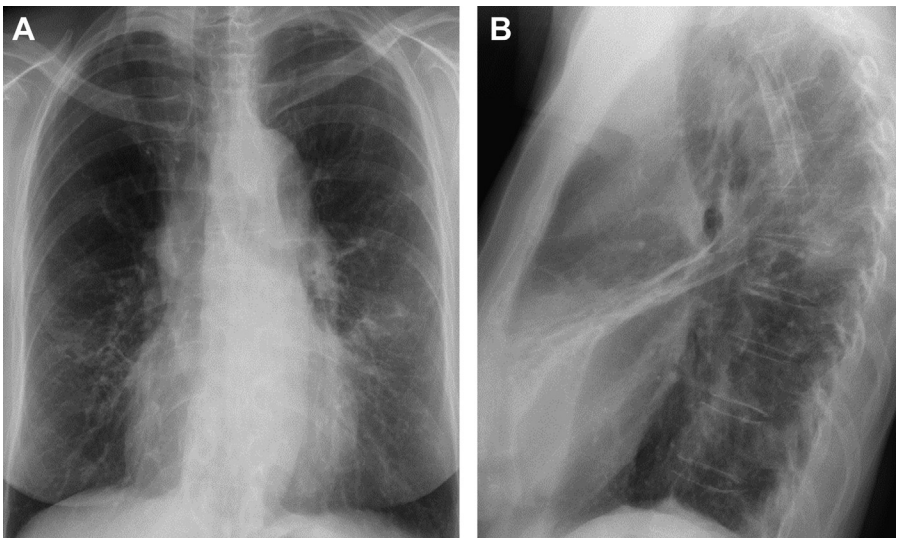

Fig. 2. 69-year-old woman with MAC. (*A*) Frontal and (*B*) lateral chest radiographs show areas of atelectasis and scarring in the right middle lobe and the lingula with bronchiectasis.

the right middle lobe and lingula (Fig. 3). Cavities and consolidation are uncommonly seen in this form as compared with the cavitary form of NTM[22,24] (Fig. 4). Bronchiectatic airways may also contain foci of mucous plugging and are associated with air trapping (mosaic attenuation). Lymphadenopathy is rare. Atelectasis and scarring are commonly seen in the regions of bronchiectasis, again particularly in the right middle lobe and lingula.[20,25,26] In addition, bronchiectatic NTM is associated with scoliosis and pectus excavatum.[27]

The imaging differential diagnosis for bronchiectatic NTM includes allergic bronchopulmonary aspergillosis (ABPA), which also presents with bronchiectasis. However, ABPA does not commonly demonstrate mid-lung predominance, and is more likely to manifest an upper lobe predilection. The presence of high-attenuation mucus in dilated airways is characteristic of ABPA, though not always present. Patients will have a history of asthma or cystic fibrosis; diagnostic testing will show elevated total and aspergillus-specific IgE levels.[28] Other causes of bronchiectasis (eg, cystic fibrosis, ciliary dyskinesia, or chronic aspiration) tend to involve the upper or lower lung zones predominantly, rather than the mid-lung zones as with NTM.

Hypersensitivity pneumonitis

This entity, also known as hot tub lung, represents an immune reaction to inhalation of MAC, typically related to repeated exposure from hot tubs by aerosolization.[29] It is subacute in presentation and characterized by fever, cough, and dyspnea. Hot tub lung is similar in appearance and presentation to other forms of hypersensitivity pneumonitis, best characterized on CT by centrilobular or confluent ground glass with areas of air trapping. Patients

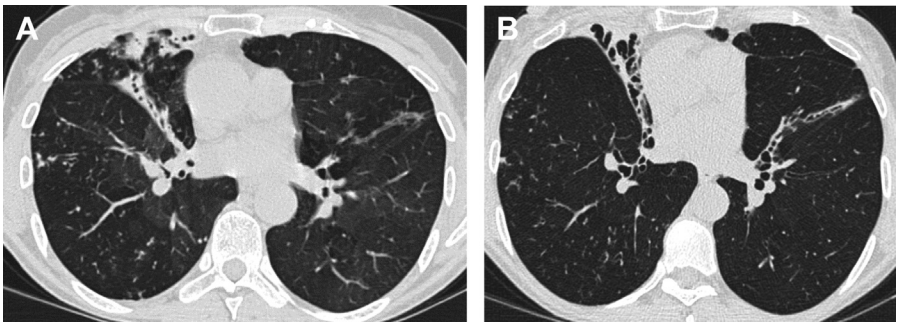

Fig. 3. 67-year-old woman with MAC. Axial CT images (*A*, *B*) show bronchiectasis in the right middle lobe and lingula with tree-in-bud nodules in the middle and lower lobes. Also, note mosaic attenuation indicative of air trapping.

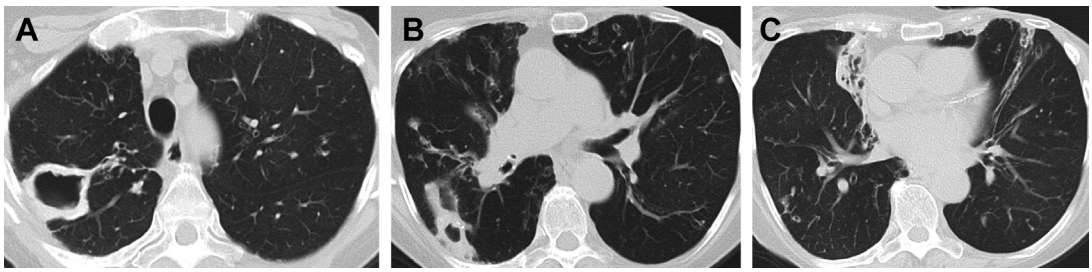

Fig. 4. 76-year-old woman with MAC, predominantly the nodular-bronchiectatic form. Axial chest CT images show midlung-predominant bronchiectasis (*B, C*) as well as several cavities in the right upper and lower lobes (*A, B*).

may develop fibrosis with long-term exposure.[13,30] Lung biopsies will show features of hypersensitivity pneumonitis such as cellular bronchiolitis and nonnecrotizing granulomas, and cultures are often positive for MAC. The treatment is avoiding the exposure, as well as use of steroids.[2,13,30,31]

Solitary pulmonary nodules

MAC pulmonary infection can present as solitary (or multiple) pulmonary nodules, occasionally resembling lung cancer.[32] The patients are typically asymptomatic.[20]

On CT, the nodules may display calcification and therefore be confidently diagnosed as benign. However, they are often noncalcified, causing a diagnostic dilemma (**Fig. 5**). Several clues may help make the correct diagnosis preoperatively. These include a tubular or branching morphology, indicating bronchiectasis with endobronchial mucus. The presence of multiple clustered nodules is also very helpful in suggesting this diagnosis. The nodules may also be cavitary (**Fig. 6**).[6,20]

Disseminated in Immunocompromised Patients

Patients with HIV

NTM may cause disseminated disease in patients with HIV/AIDS. MAC is the most common agent involved, and this entity is typically seen in patients with CD4 count less than 100 cells/mm^3.[21] Dissemination occurs by hematogenous spread from the gastrointestinal tract, which is often the initial site of infection.

Patients typically present with systemic symptoms like fever, weight loss, abdominal pain, and diarrhea. Hepatosplenomegaly and lymphadenopathy are commonly found on physical examination. Blood culture or lymph node biopsy is needed for diagnosis.

CT imaging typically shows disseminated lymphadenopathy, particularly in the mediastinum and abdomen[33] (**Fig. 7**). Disseminated infection can also involve other organs such as the liver and bone marrow leading to microabscesses and osteomyelitis.[34] Lung involvement may present as miliary nodules or, rarely, consolidation. Pleural effusions are uncommon.[20] In these severely immunocompromised patients, disseminated MAC may occur simultaneously with other opportunistic infections (eg, *Candida*, *Pneumocystis*, *Cytomegalovirus*) or Kaposi sarcoma[20] (**Fig. 8**).

In addition to MAC, *M xenopi* also causes disseminated disease in patients with HIV/AIDS, whereas *M kansasii* causes localized infection to the lungs, which can manifest as consolidation, often with lymphadenopathy and pleural effusions.

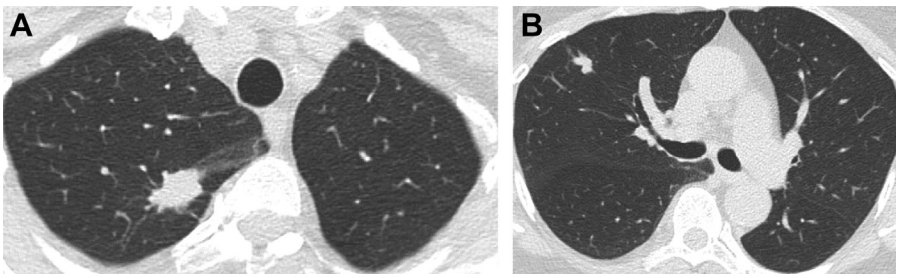

Fig. 5. 67-year-old woman with a history of breast cancer status postlumpectomy and radiotherapy presenting with chronic cough with sputum. Axial CT chest shows (*A*) right apical nodule (*B*) additional right upper lobe nodule. Subsequent FDG PET-CT showed FDG avidity in both nodules (not shown). She underwent VATS with 2 wedge resections. Pathology showed necrotizing granulomas with AFB stain suspicious for Mycobacteria. A culture of the tissue was negative and a BAL culture showed no growth. An induced sputum sample obtained was smear-positive and recovered *Mycobacterium mucogenicum*.

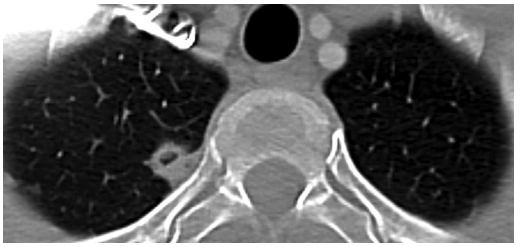

Fig. 6. 41-year-old woman with a history of colon cancer and Lynch syndrome. Axial chest CT shows a solitary cavitary nodule in the right upper lobe. Surgical resection revealed necrotizing granuloma and acid-fast bacilli, presumed NTM.

Other immunocompromised patients such as those with solid organ transplants, hematologic malignancies, or those on immunosuppressive drugs (particularly TNF-alpha inhibitors) can also develop disseminated NTM, usually with MAC and *M kansasii*, but this occurs much less commonly than in patients with HIV/AIDS.[20,33] As discussed earlier, NTM may be isolated from blood cultures in disseminated disease. Clinical and radiological manifestations are similar to those seen in patients with HIV. Localized abscess may also be seen throughout the body in disseminated infection[20] (**Fig. 9**).

The differential diagnosis of disseminated NTM in immunocompromised patients includes other disseminated infections (TB, bacterial, and fungal), although mycobacteria are more commonly associated with necrotic lymphadenopathy than other agents. Disseminated malignancy, including Kaposi sarcoma and lymphoma, may also lead to diffuse lymphadenopathy.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) may develop in patients with HIV and MAC infection after beginning antiretroviral therapy. IRIS represents a response of the now healthier immune system to a pre-existing infection. IRIS has been associated with a variety of preexisting pathogens, such as tuberculosis, MAC, cryptococcus, cytomegalovirus, and *Pneumocystis jirovecii*. Fever, shortness of breath, night sweats, and weight loss are common symptoms and mimic worsening of the infection itself.[35] Patients with AIDS with low pretreatment CD4 count (<100 cells/μL) are at particular risk.[36,37] The diagnosis is made on clinical grounds and based on positive virological and immunologic response to antiretroviral therapy,[38] although occasionally repeat biopsy may be pursued. The treatment for IRIS is to continue both antiretroviral and antimicrobial therapies. Steroids may be needed in those patients who develop severe symptoms.[39]

Radiological findings mimic worsening of the infection in the setting of improving immunologic function. The most common finding consists of intrathoracic lymphadenopathy, which may be necrotic. Consolidation and tree in bud nodules, as well as pleural and pericardial effusions, may also occur though less commonly.[20]

MonoMAC syndrome

Monocytopenia and mycobacterial infection (MonoMAC syndrome) is a clinical phenotype of germline GATA2 mutations, resulting in loss of function of a gene controlling many aspects of hematopoiesis and lymphatic formation.[40] Patients present with peripheral cytopenias and are at risk of transformation to acute leukemia. Bone marrow biopsy will show a hypocellular bone marrow; the diagnosis is then made via gene sequencing.[40] Severe and recurrent NTM infections, as well as opportunistic fungal (most commonly Histoplasma) and disseminated human papillomavirus infections, are commonly seen.[40,41] Imaging patterns are similar to other disseminated NTM infections including lymphadenopathy and nodular opacities in the lungs (**Fig. 10**).

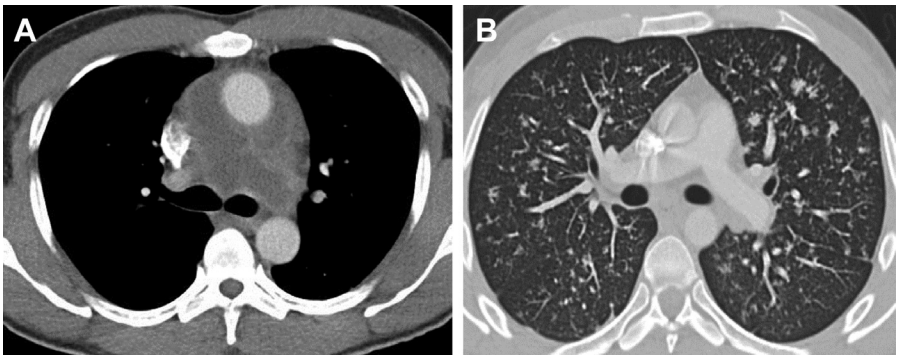

Fig. 7. 43-year-old man with HIV/AIDS. Axial CT images show (*A*) extensive necrotic mediastinal lymphadenopathy and (*B*) diffusely scattered nodules in both lungs.

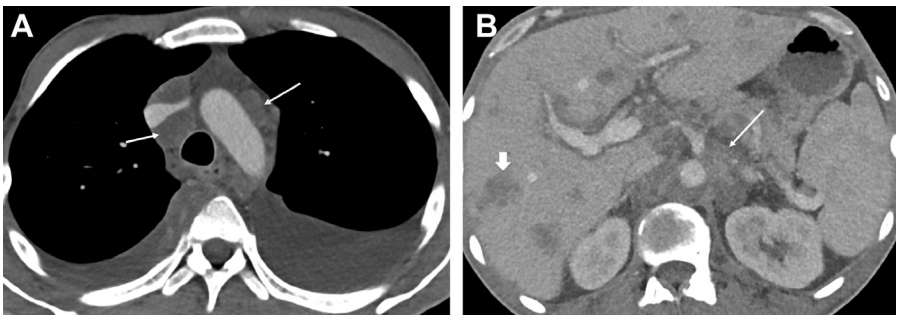

Fig. 8. 37-year-old man with AIDS and CD4 count of 14/μL, diagnosed with cutaneous and lymph node Kaposi sarcoma as well as disseminated MAC infection. CT images show (*A*) mediastinal and abdominal lymphadenopathy (*white arrows*), biopsy-proven MAC, as well as (*B*) multiple hepatic lesions, likely Kaposi sarcoma (*broad white arrow*).

Patients with Esophageal Dysmotility

Rapidly growing mycobacterial species such as *M fortuitum* and *M chelonae* have been isolated in infections in patients with esophageal dysfunction, such as from achalasia, hiatal hernia, stroke, and prior esophagectomy. Chronic aspiration is most likely the mechanism of infection and may be complicated by lipoid pneumonia.[20,42] Chest radiograph and CT show unilateral or bilateral patchy nodular or consolidative opacities resembling aspiration.[6] Lung abscesses due to recurrent aspiration have also been described.[43,44] Treatment of esophageal disorders is important for prevention and recovery in these patients.[42]

Management

The need for and goals of treatment for NTM depend on multiple factors, including the clinical syndrome and patient immune status. Here we will briefly review considerations for the most common agent, MAC. Note that patients must first meet the clinical, radiographic, and microbiologic criteria for NTM infection (see **Box 1**).

The mainstay of therapy for MAI is prolonged, multiagent therapy as detailed below. Because these agents are sometimes difficult to tolerate, a risk-benefit analysis must be considered for each patient. For patients with noncavitary nodular bronchiectatic disease, close observation with serial sputum cultures and CT imaging is an initial option. More than half of patients with nodular bronchiectatic disease eventually progress with time and require treatment; however, some untreated patients may clear MAC from their sputum spontaneously.[45]

For patients with cavitary disease or positive sputum culture, treatment should be considered.[46,47] The goal of therapy is achieving 12 months of negative culture[16] and imaging stability. In patients with macrolide-sensitive noncavitary MAC infection, at least 3-drug combination therapy is advised, usually a combination of a macrolide (azithromycin or clarithromycin), rifampin, and ethambutol.[16,48] For patients with severe (cavitary) and life-threatening infections, a parenteral aminoglycoside such as amikacin should be used for an initial 8 to 12 weeks of therapy or even longer. For those who have mild disease and cannot tolerate 3 drugs, a 2-drug regimen (azithromycin or clarithromycin and ethambutol) can be considered.[49]

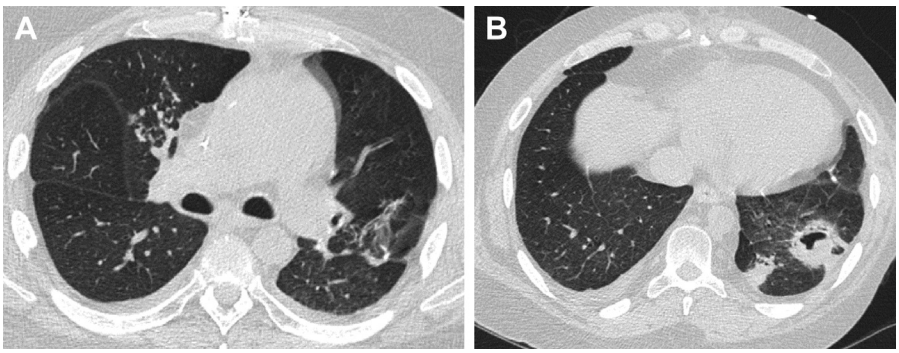

Fig. 9. 57-year-old man status postcardiac transplant, with *M kansasii* infection. Axial chest CT images show tree-in-bud nodules in the right upper lobe and a left lower lobe cavity, representing a lung abscess.

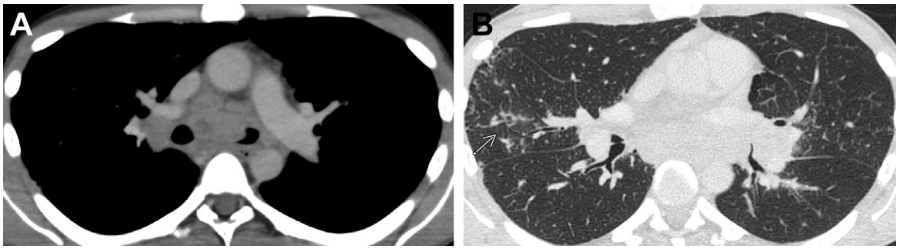

Fig. 10. 33-year-old man with MonoMAC syndrome (GATA2 mutation). (*A*) CT shows extensive mediastinal and hilar lymphadenopathy and (*B*) tree-in-bud nodules in the right middle lobe (*arrow*).

In patients with macrolide-resistant infection, ethambutol is still used as an immunomodulator, and a combination of rifamycin or rifabutin, ethambutol, clofazimine, and a parenteral aminoglycoside are used. For *M kansasii* infection, the preferred regiment is combination therapy with isoniazid, rifampin, and ethambutol.[5,50]

Surgical resection by lobectomy for localized disease or pneumonectomy for extensive cavitary disease is considered in some patients who fail medical therapy.[44,51,52] One study showed that only 16% of patients were culture-positive after surgery compared with 44% before surgery.[53]

SUMMARY

NTM infections are on the rise worldwide, particularly in the Western world. They cause a wide range of pulmonary and systemic manifestations described by various clinical and radiological types. The two most common types are as follows: classical cavitary type, seen with preexisting lung disease, and the nonclassical bronchiectatic type, seen in elderly women without preexisting lung disease. Disseminated infections by the hematogenous route are common in immunocompromised patients including those with HIV.

CLINICS CARE POINTS

- Bronchiectatic NTM presents with bronchiectasis and tree-in-bud nodules in the mid-lung zones.
- Cavitary NTM disease is most common in elderly males with pre-existing lung disease and simulates tuberculosis.
- Disseminated NTM infections occur in severely immunocompromised patients, particularly those with HIV/AIDS.

DISCLOSURE

The authors have nothing to disclose.

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