Imaging features of thoracic atypical mycobacterial infection

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Learning objectives

- To review and illustrate Chest Radiography (CR) and Computed Tomography (CT) findings of pulmonary atypical mycobacterial (ATB) infection.

- To recognize clinical-radiographic patterns of ATB infection and related risk factors, including host immune status.

- To identify imaging and epidemiological features that can help to distinguish ATB infection from *Mycobacterium tuberculosis* (MTB) infection.
Background

Epidemiology

Mycobacteria that cause human disease can be divided into two broad groups. ATB, also known as nontuberculous mycobacteria (NTMB) or mycobacteria other than tuberculosis, are environmental organisms widely distributed in nature and have been isolated from natural and treated water, soil, domestic and wild animals, milk, and food. The other group of mycobacteria includes \textit{M. tuberculosis} complex, \textit{M. bovis} and \textit{M. leprae} [1-3].

ATB are responsible for both asymptomatic infection and symptomatic disease in humans, with incidence rates varying from 1.0 to 1.8 cases per 100,000 persons [2].

The spectrum of disease includes predominately thoracic infections, such as pneumonia, lung abscess, and pleural infection. Lung ATB infection usually affects immunocompetent patients; moreover, recent reports have found a female preponderance in patients with pulmonary disease. The most common ATB that cause bronchopulmonary disease are \textit{M. avium-intracellulare complex} (MAC) and \textit{M. kansasii}.

NTMB may involve many other organ systems and cause infections such as lymphadenitis, especially in children, skin and soft tissues infections, gastrointestinal infections, meningitis, osteomyelitis or even intravenous catheter-related infection. Disseminated disease occurs in severely immunocompromised hosts, namely AIDS patients.

Infection may occur by various routes, mainly inhalation of the organisms from environmental exposures, but also by ingestion, direct inoculation, or iatrogenic infection.

In contrast to MTB, no human-to-human transmission occurs and there is no evidence of reactivation following latent infection. However, the specific source of infection generally is not identified [1-3].

In patients with AIDS, the portal of entry appears to be the gastrointestinal tract rather than the respiratory system, as in the majority of patients. There is subsequent access to the lymphatic and vascular systems, resulting in bacteremia and disseminated infection.
Even though the rate of exposure to ATB is high, the rate of clinical infection is low. Therefore, these organisms are low-grade pathogens that commonly cause low-grade, chronic infections, often with minimal symptoms [4].

**ATB classification**

Since their first identification in the late 19th century, more than 150 ATB species have been cataloged. Recently, there has been a dramatic increase in the total and clinically significant number of ATB species, mostly due to advances in microbiologic and molecular techniques. Among them, at least 20 organisms potentially cause human disease and only a fraction is responsible for thoracic infection [3,5].

ATB are traditionally divided into four groups according to Runyon criteria based on their growth rates, colony morphology, and pigmentation in the presence and absence of light:

- Slowly growing mycobacteria
  - Photochromogens (Runyon group I) - *M. kansasii, M. marinum*;
  - Scotochromogens (Runyon group II) - *M. szulgai, M. gordonae*;
  - Nonphotochromogens (Runyon group III) - MAC, *M. ulcerans, M. malmoense*

- Rapidly growing mycobacteria (Runyon group IV) - *M. fortuitum, M. abscessus, M. chelonae*.

Rapidly and slowly growing organisms form visible colonies on agar plates within or longer than 7 days, respectively. Photochromogens are mycobacteria that produce a yellow pigment after being exposed to light; scotochromogens produce a yellow pigment without exposure to light, and nonphotochromogens produce no pigment. This classification has clinical utility as rapidly growing mycobacteria are habitually resistant to first-line antituberculosis drugs [2,5,6].
The increasing importance of ATB infection

There has been an improved awareness of the importance of these organisms as human pathogens over the past several decades. In fact, ATB became more commonly recognized only after the 1950s, with the emergence of pulmonary infection in relatively immunocompetent individuals with chronic lung disease.

Later, HIV/AIDS epidemic revealed its association to ATB infection, with great increases of disseminated MAC disease.

In addition, NTMB lung disease is increasing in frequency in the non-AIDS population and may occur in otherwise healthy subjects, particularly elderly women. Although the actual mechanisms are not known, more frequent environmental exposures and increased host susceptibility have been suggested [2,3].

Host factors that may predispose to ATB infection

Most patients with pulmonary ATB infection have an underlying structural lung disease, most commonly chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, asbestosis, silicosis, or previous pulmonary tuberculosis.

Patients with chronic disability, namely cirrhosis, heart disease, diabetes mellitus and malignancy, also appear to be predisposed to developing NTMB infection.

Immunosuppression is a risk factor of developing severe mycobacterial infections, which affects patients with renal or cardiac transplantation, chronic corticosteroid use, and leukemia or with deficiencies in cell-mediated immunity such as AIDS and interleukin-12 and interferon-gamma pathway genetic defects. However disseminated NTM disease is very rare with any form of immunosuppression other than advanced HIV disease.

Achalasia is associated with *M. fortuitum-chelonei complex* infection in patients with recurrent aspiration resulting from stasis of food.
In particular among older women with ATB lung disease, there is often a group of physical findings: bronchiectasis, thin body habitus, scoliosis, pectus excavatum, mitral valve prolapse and joint hypermobility. To date, neither significant immunological abnormality nor cause for these associations has been discovered; one possibility is that these skeletal features predispose patients to infection due to reduced secretion drainage. The ability of mycobacteria to live in biofilm may, to some extent, explain their survival in the mucus of the airways of patients with bronchiectasis, even in the presence of antibiotics [1-3,7].

**Treatment**

Treatment of ATB pulmonary disease is difficult. Response to drug therapy is often incomplete because these organisms are uniformly resistant to standard anti-tuberculous drugs, in addition to exhibiting variable *in vitro* susceptibilities to other anti-mycobacterial agents. This is particularly true for MAC infections and in some cases mycobacterial eradication may not be possible.

Besides that, these therapies involve multiple antibiotics with frequent side effects, which are expensive, typically difficult to tolerate, and often require intravenous administration.

Many patients need physically demanding and time-consuming bronchial hygiene. Limited experience suggests that resectional lung surgery may help in some cases [2,3,8].
Findings and procedure details

This pictorial review of CR and CT features of thoracic ATB infection is based on a casuistic of about eighty patients of our centre with the diagnosis ATB infection in the last five years.

There are several clinical-radiographic patterns depending on the immune status of the host and the presence of risk factors.

- "Classic" form of infection

The "classic" form of ATB infection is most often encountered in older men who are heavy smokers with underlying chronic lung disease, such as COPD (Fig. 1 on page 18.)

![CR showing the "classic" form of ATB infection in a 66-year-old patient with history of smoking and COPD. Consolidation in right upper lobe and heterogeneous](image)

**Fig. 1**: CR showing the "classic" form of ATB infection in a 66-year-old patient with history of smoking and COPD. Consolidation in right upper lobe and heterogeneous
opacities and cavitation at left upper lobe, radiographically mimicking tuberculosis. M. kansasii was isolated from sputum samples.

**References:** Department of Radiology, Centro Hospitalar de Lisboa Ocidental, Lisbon/Portugal 2015

This pattern also affects patients with silicosis or bronchiectasis.

Imaging findings are similar to reactivation tuberculosis, with consolidation, cavitation, scar formation and small nodules suggesting bronchogenic spread of infection involving upper lobes (mostly the apical and posterior segments) and the superior segment of lower lobes. Cavitation is frequent, and multiple cavities may be present. Apical pleural thickening is commonly associated.

Pleural effusion, lymphadenopathy and miliary spread are distinctly unusual.

The disease tends to be slowly progressive [4-6,9-10].

- "**Nonclassic**" form of infection

The "nonclassic" form of MAC lung disease affects mostly elderly women (more than 60 years of age) who are usually nonsmokers, considered immunologically competent and that share similar clinical characteristics and body morphotype, as described before.

CT features comprise cylindrical bronchiectasis and multiple focal centrilobular nodules ("tree-in-bud") measuring about 5 mm; large nodules (> 1 cm) may exist in some cases. These findings are predominantly seen in the middle lobe and lingula, but any lobe may be involved (Fig. 2 on page 18 Fig. 3 on page 19 Fig. 4 on page 20) [4-6,9-10].
**Fig. 2:** "Nonclassic" form of ATB infection in a 79-year-old woman. CT findings of infection caused by MAC: cylindrical bronchiectasis in lingula and middle lobe (A) as well as large nodules (B).

**References:** Department of Radiology, Centro Hospitalar de Lisboa Ocidental, Lisbon/Portugal 2015
**Fig. 3**: CR findings of "nonclassic" form of MAC infection in the same patient as Fig. 2. Scattered reticular and nodular opacities predominantly seen in mid and lower zones.  
*References*: Department of Radiology, Centro Hospitalar de Lisboa Ocidental, Lisbon/Portugal 2015
Fig. 4: Nonclassic" form of ATB infection in a 65-year-old woman (M. kansasii infection). CT demonstrates multiple small centrilobular nodules (A-D) and cylindrical bronchiectasis in middle lobe (C, D) and lingula (D).

References: Department of Radiology, Centro Hospitalar de Lisboa Ocidental, Lisbon/Portugal 2015

Occasionally, patchy air-space consolidations representing foci of organizing pneumonia may also be found [4].
Fig. 5: CT images of M. avium infection in a 74-year-old male patient with multiple, bilateral ground-glass opacities with a peribronchovascular distribution.

References: Department of Radiology, Centro Hospitalar de Lisboa Ocidental, Lisbon/Portugal 2015

Evidence indicates that it is the MAC infection that causes the bronchiectasis rather than colonizing preexisting disease [10].

- **Hypersensitivity-like disease**

This pattern, previously termed "hot-tub lung", resembles hypersensitivity pneumonitis and is a unique and potentially serious clinical condition acquired via exposure to environmental mycobacteria in contaminated water. Patients are usually nonsmokers and younger than individuals with MAC- or other ATB-associated pulmonary disease.

There appear to be components of both lung inflammation and infection causing diffuse radiological manifestations: patchy ground-glass opacities and poorly defined ground-
glass centrilobular nodules throughout all lung fields. Air trapping and mosaic pattern are frequent associated findings.

**Fig. 8:** CT features of MAC infection in a woman with "hot-tub lung": diffuse ground-glass opacities and centrilobular nodules accompanied by mosaic pattern.

**References:** Department of Radiology, Centro Hospitalar de Lisboa Ocidental, Lisbon/Portugal 2015

The clinical presentation is usually subacute, with shortness of breath, cough, and fever, but chronic forms of NTMB hypersensitivity-like lung disease can also occur.

NTMB predisposition for growth in indoor hot tubs is due to their relative resistance to agents used for disinfection and capability of growing in a wide range of temperatures, particularly high temperatures. Ceasing the exposure to contaminated water can result in resolution of the condition [2,3,5].

**ATB infection in AIDS patients**
Patients with AIDS are particularly susceptible to ATB infection. The incidence increases as the CD4 cell count declines and clinically overt MAC infection occurs when levels falls below 50 cells/µL.

The most common presentation is mediastinal and hilar adenopathy, which may show low attenuation on CT (although this feature is more characteristic of MTB). Small nodules, usually centrilobular, with air-space consolidation are occasionally demonstrated and solitary pulmonary nodules may also constitute the radiological presentation in this setting.

![CT appearance of M. xenopi infection in a 36-year-old woman with AIDS.](image)

**Fig. 9**: CT appearance of M. xenopi infection in a 36-year-old woman with AIDS. Diffuse air-space disease, with bilateral small centrilobular nodules, peripheral ground-glass opacities and cavitations (arrows) in middle and lower lobes.

**References**: Department of Radiology, Centro Hospitalar de Lisboa Ocidental, Lisbon/Portugal 2015

Hepatosplenomegaly is another common finding.
M. kansasii is the second most common cause of opportunistic mycobacterial infections associated with AIDS. Consolidation and nodules are habitually located in the mid and lower lung zones, a distinct pattern from that observed in non-HIV patients, in which upper lobe cavities predominate. Cavitations are associated to a worse outcome in these patients. Other concomitant infections are frequent [2,4,5].

**Diagnosis of ATB lung infection**

Symptoms and physical findings of NTMB pulmonary disease are variable, nonspecific and indistinguishable from those of MTB. One of the most common symptoms is chronic cough; others include sputum production, fatigue, malaise, dyspnea, fever, hemoptysis, chest pain, and weight loss. Constitutional symptoms are gradually more prevalent with advancing disease [1,2,4].

The pathologic patterns of most ATB infections are also analogous to that of MTB infection: tissue destruction, necrosis, cavitation, and, sporadically, endobronchial spread of infection or miliary disease [5].

In patients with underlying chronic pulmonary abnormalities (eg. emphysema, bronchiectasis) superimposed features often complicate their clinical and pathologic assessment. Besides, ATB are ubiquitous in environment and colonization of the respiratory tract may be seen in these patients with underlying structural disease of the lung. This happens most commonly with MAC.

For these reasons, certain clinical, radiological, and microbiologic criteria must be met to make the diagnosis of invasive ATB lung disease. Accordingly to the American Thoracic Society and Infectious Disease Society of America guidelines, the evaluation of a patient suspected of ATB lung disease should comprise:

- a CR or, in the absence of cavitation, chest high-resolution CT scan (HRCT);
- three or more sputum specimens for acid-fast bacilli analysis;
- exclusion of other disorders, namely TB.

Clinical criteria imply the presence of pulmonary symptoms and radiologic criteria as well as appropriate exclusion of other diagnoses. Radiologic criteria are nodular or cavitary opacities on the CR or a HRCT scan that shows multifocal bronchiectasis with multiple small nodules.

The main microbiologic criteria include positive culture results from at least two separate expectorated sputum samples or positive culture results from at least one bronchial wash or lavage [2,7].
**Fig. 10:** CT findings of a 53-year-old patient with symptoms of fatigue and left thoracic pain. There are two irregular and ill-defined peripheral opacities in the left upper lobe, contacting the pleura. Bronchoalveolar lavage revealed M. gordonae infection.

**References:** Department of Radiology, Centro Hospitalar de Lisboa Ocidental, Lisbon/Portugal 2015

A diagnosis of ATB pulmonary disease does not necessarily imply the implementation of therapy; it is an individual-based decision, according to the potential risks and benefits to each patient [10].

Patients with suspected ATB lung disease who do not meet the diagnostic criteria should be followed until the diagnosis is established or excluded [2].

**ATB vs MTB infection**

There are some differences between ATB and MTB infection, not only epidemiological but also radiological and therapy-related, as shown in Table 1 on page 27 [2-5,8].
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<tr>
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<td>decline</td>
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**Fig. 6:** CR of a "nonclassic" form of M. kansasii infection before (A) and several months after (B) treatment. There is regression of some of the peripheral ill-defined nodular opacities in the right upper and mid lung zones.

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**Fig. 7:** CR of a patient with M. avium infection, showing ill-defined opacites in the left upper, middle and lower zones, more evident in the upper zone.

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- **Imaging findings/Patterns of disease**
  - **“Classic” form:** pleural effusion, lymph node enlargement and miliary spread are unusual;
  - **“Nonclassic” form:** bronchiectasis and centrilobular nodules in middle lobe and lingula in elderly women;
  - **Hypersensitivity-like disease**

- **Duration of the disease**
  - ATB: 4 - 10 years (indolent)
  - MTB: 8 months

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  - ATB: 18-24 months
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  - ATB: ++
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  - ATB: Expected to steadily increase
  - MTB: Expected to steadily decline

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Conclusion

The importance of ATB infection is increasing and presents diagnostic and therapeutic challenges, as it is slowly progressive and frequently difficult to treat effectively.

Recognition of epidemiologic and risk factors associated to ATB infection led to a clearer understanding of the disease, for which diagnosis clinical, radiological, and microbiologic criteria are required.

Knowledge of the clinical-radiographic patterns of pulmonary ATB infection is essential to ensure an accurate diagnosis and facilitate the treatment of this indolent disease.
Personal information

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