

DRUG RESISTANT TUBERCULOSIS

Radiologic Imaging Manifestations

Bernard F. Laya, Ma. Carmela L. Sto. Domingo, Xanthe Marie Javier and Marion Sanchez

St. Luke's Medical Center, Philippines

Abstract

Tuberculosis (TB) remains a global health problem despite the fact that the burden is slowly declining each year and millions of lives are saved through effective diagnosis and treatment. Still, the death toll from this preventable disease is still unacceptably high. Development of drug resistant TB strains is now adding to the complexity in managing this disease. The aim of this review article is to highlight the importance and impact of drug resistant TB and present the typical imaging manifestations which can be helpful in its early diagnosis.

Key Facts

MDR-TB

- Resistant to at least isoniazid and rifampicin
- 5% of all TB cases
- In 2013, there were 480,000 MDR-TB cases worldwide, and 210,000 died
- 3.5 % of new TB cases and 20.5% of previously treated cases have MDR-TB

XDR-TB

- MDR-TB + resistance to a fluoroquinolone and at least 1 of 3 injectable 2nd-line drugs (amikacin, kanamycin or capreomycin)
- 9.0% of MDR-TB cases are XDR-TB

The Burden of Drug Resistant Tuberculosis

Tuberculosis (TB) is considered a global health crisis with a wide epidemiological variability between the different geographical areas. About two billion people around the world have come into contact with mycobacterium TB and acquired the infection, approximately 85% of cases is in Asian and African continents (1). Drug resistant TB (DR-TB) has emerged as a new face of the disease, causing an impact in the epidemiology, and posing a major threat in TB control. It results from inappropriate drug treatment or patient non-adherence to treatment. Resistance may be defined as either primary or secondary. "Primary" or "initial" resistance is identified in an individual who has never been treated with anti-TB therapy or who had undergone such therapy for less than a month. DR-TB is referred to as "secondary" or "acquired" when resistance follows the failure of previous treatment of TB (2-3). Previously treated TB patients have a significantly higher risk of DR-TB compared with new cases (2, 4).

Multidrug-resistant TB (MDR-TB) are TB strains which are resistant to at least isoniazid and rifampicin. Globally, 5% of TB cases are estimated to have MDR-TB. In 2013, there are about 480,000 cases of MDR-TB among the world's estimated 9 million incident TB cases. An estimated 210,000 people died from MDR-TB, which is relatively high compared to the total number of incident cases. About 3.5 % of new TB cases and 20.5% of previously treated cases have MDR-TB. Of all the diagnosed cases of MDR-TB, an estimated 9.0% of these patients had XDR-TB. Extensively drug resistant TB (XDR-TB), defined as MDR-TB plus resistance to a fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin or capreomycin) has been identified in at least 100 countries. (1-2).

DR-TB also occurs in children but there is limited published information about this. The diagnosis of pediatric DR-TB is often delayed due to reliance on the diagnosis of the adult contact case of DR-TB. Resistance patterns in children have generally been found to be similar to those of adults from same areas and similar background, and the proportion of DR-TB in children and adults with bacteriologically confirmed TB is broadly similar (5). The clinical presentation of DR-TB is similar in children of all ages (6). DR-TB is no more infective than normal TB and clinical presentation is the same. However, it is a more serious infection, requiring prolonged administration of anti-TB drugs, has higher morbidity and mortality, and patients remain infectious for a longer period once treatment is started (7).

Laboratory Diagnosis

- Bacteriological confirmation and determination of drug resistance are critical
- Sputum smear microscopy is not highly sensitive, particularly in children and HIV patients
 - No information on viability and drug susceptibility
 - Cannot distinguish between TB and NTM
- Culture is gold standard but results take weeks, and needs a well-equipped laboratory with highly trained staff
- Xpert MTB/RIF is endorsed by WHO for rapid simultaneous detection of TB and rifampicin resistance

Radiologic Clues

- **Radiograph**
 - Multiple, bilateral cavities
 - Multiple lung nodules
 - Bronchiectasis
 - Infiltrates
- **CT Scan**
 - Multiple, bilateral cavities
 - Multiple lung nodules
 - Bronchiectasis
 - Infiltrates
 - Tree-in-bud pattern
 - Pleural involvement
 - Fibrosis
- DR-TB is highly suspected in patients with the combination of above findings, without response to anti-TB drugs or with history of previous TB therapy
- These findings can also be seen in DS-TB
- It is difficult to differentiate MDR-TB from XDR-TB from imaging alone

Laboratory Diagnosis

Bacteriological confirmation of TB and the determination of drug resistance are critical to ensuring that a patient is correctly diagnosed with TB. Sputum smear microscopy has been the primary method used to detect resistance to first and second line TB drugs. However, microscopy is not a sensitive test, particularly in people living with HIV and in children: it provides no information on the viability and drug susceptibility of the bacilli, and it cannot distinguish between *Mycobacterium tuberculosis* complex and non-tuberculosis mycobacteria (NTM). Culture is considered the reference standard but results take weeks to obtain and testing requires a well-equipped laboratory, highly trained staff, and an efficient transport system to ensure viable specimens. Detection of TB without investigating for drug resistance can lead to ineffective treatment, further development and spread of drug-resistant strains, and additional suffering and costs for patients. The inclusion of drug susceptibility testing is now targeted as a universal standard in patient care, for both new and previously treated patients. Rapid and more sensitive tests are now available to replace or complement existing conventional tests. The utilization of Xpert MTB/RIF, a rapid molecular test that simultaneously detects TB infection and rifampicin resistance, has been endorsed by the WHO as the initial diagnostic test in adults and children suspected of having TB, especially those suspected of having MDR-TB and HIV-associated TB (1-2). Laboratory confirmation of TB and drug resistance is key to ensuring that symptomatic individuals with TB are correctly diagnosed (1). However, pulmonary TB may be asymptomatic or pauci-symptomatic with symptoms that are nonspecific.

Radiologic Imaging Findings

Screening with radiologic imaging plays an important role in early detection and prompt management (8). Imaging modalities are helpful in the confirmation and defining the extent of lung involvement. It could also act as a guiding tool whenever surgical resection of the involved lung area is the treatment option.

One of the earliest studies comparing the radiographic findings of MDR-TB and drug-sensitive TB (DS-TB), published in 1998, concluded that radiographic findings and patterns among the two groups are similar (9). In this study, there is difference in imaging patterns depending on how MDR-TB was acquired. In patients who developed MDR-TB during an outbreak, the predominant radiographic pattern were non-cavitary consolidations, pleural effusions, and lymphadenopathy, similar to a primary form of TB. In those patients who acquired MDR-TB due to low adherence to treatment protocol, most findings were consistent with that of secondary TB, with cavitary lesions in 50% of patients. However, about one-third of the patients did not show the expected radiographic pattern (9). Soon after, several studies showed different results. Zahirifard and colleagues reviewed chest radiographs of non-HIV-infected patients with MDR-TB which showed cavitary lesions in 80% of patients, pulmonary infiltration in 89%, pulmonary nodules in 83%, lymphadenopathy in 77% and calcification in 46% (10) [Fig. 1]. In the same study, Chest CT scans were also evaluated and revealed bilateral, multiple pulmonary cavitation in all patients. Other signs noted

are "tree in bud" sign (80%), lymphadenopathy in 73%, lung fibrosis in 67%, and collapse in 47%. Ninety three percent had pleural involvement, in contrast to only 31% seen on radiographs (10). Several other studies reported that multiple cavities are more frequently observed in MDR-TB patients as compared to DS-TB patients (3, 11-13). Cavities are formed when an area of caseous necrosis liquefies and communicates with the bronchial tree. Cavitory lesions are a key means of disease transmission because of its high bacillary load, which likely increases the probability of establishing drug-resistant mycobacterial organisms. The cavitory lining tends to reduce the amount of drug that can penetrate the source of infection (3, 14). Although most of these studies involve adult patients, studies in children also report a high percentage of cavitory disease on chest radiographs. This could be due to disease progression because of the delay in diagnosis, but it also implies that children can contribute to the spread of MDR-TB (15). Large nodules and bronchial dilation (bronchiectasis) were also noted to be more frequently observed in DR-TB patients as compared to DS-TB patients (14) [Fig. 2 and 3]. These imaging manifestations may be useful indicators of possible DR-TB patients, to facilitate early detection and eventual prompt management for such infected patients (3).

In addition to comparing DS-TB and DR-TB imaging patterns, some studies also compared MDR-TB and XDR-TB features on imaging. However, no significant differences were determined in the frequency and extent of parenchymal abnormalities between MDR-TB patients and XDR-TB patients in CT scan (14, 16). Therefore, it does not seem to be possible to differentiate between MDR-TB and XDR-TB based on imaging findings alone (14).

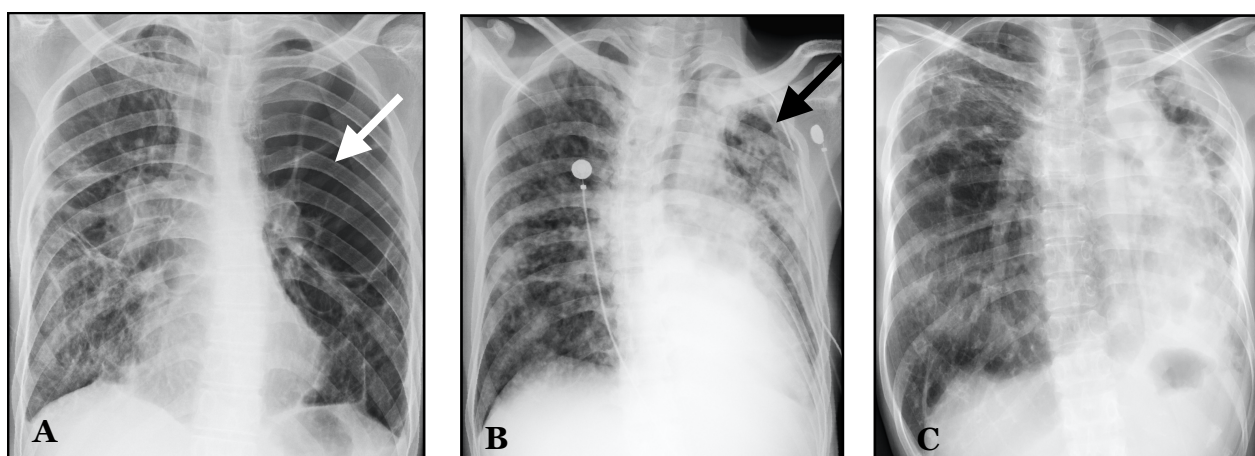


Figure 1. Spectrum of Chest Radiographic appearance in patients with MDR-TB. Patient A demonstrates significant lung disease with extensive fibrosis, nodules, and multiple cavities, largest in the left upper lung (white arrow). B shows nodules throughout both lung fields. A chest tube was placed in the left lung following rupture of a lung cavity (black arrow). Patient C demonstrate extensive fibrosis with cavities and bronchiectasis. The left lung is nearly destroyed.

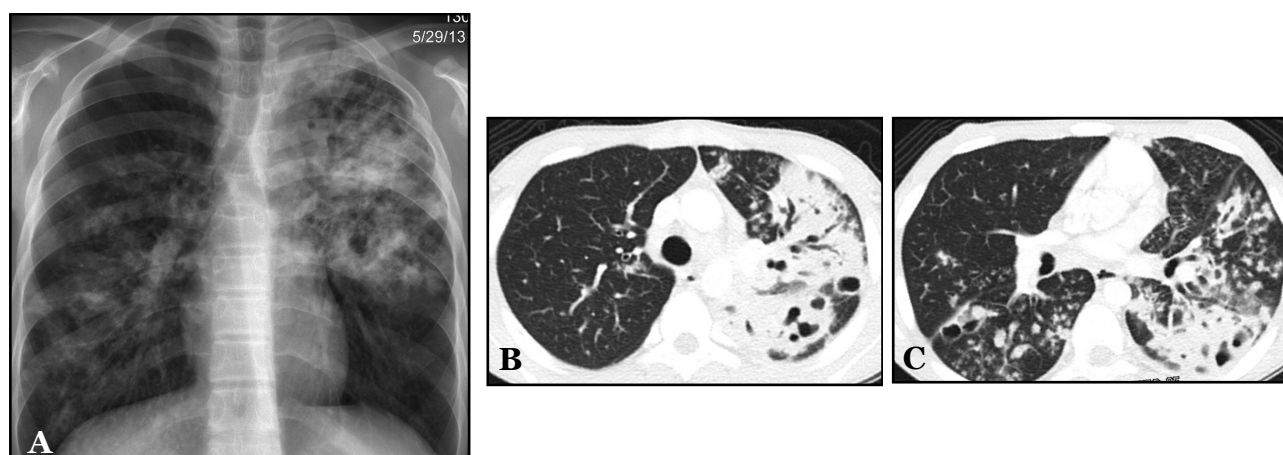


Figure 2. MDR-TB in a 15-year-old boy. Frontal chest radiograph (A) demonstrates patchy infiltrates on both lung fields. There is suggestion of bronchiectasis and cavities in the left upper lobe. Contiguous axial CT images confirms the multiple cavities and bronchiectasis on the left upper lobe (B), with multiple nodules, tree-in-bud pattern, and multiple cavities in both lower lobes (C).



Figure 3. MDR-TB in a 8-year-old boy with history of non-compliance to TB treatment. Axial CT scan image in bone window reveals destruction of a mid-thoracic vertebral body with soft tissue mass (white arrow) compatible with TB spondylitis (A). Corresponding lung window shows fibro-nodular densities in the right upper lobe (B). Consolidation with cavities (black arrow) are noted in the left lower lobe (C).

Prevention Strategies

The management of MDR-TB not only comprises the use of complex second and third-line anti-TB drug regimens, but patients with the disease are required to spend prolonged periods in hospital negative pressure rooms with specialist nursing care, multidisciplinary medical input, and extensive use of laboratory services(10). The WHO devised five priority actions, from prevention to cure, to address the MDR-TB epidemic. These are: 1) high-quality treatment of drug-susceptible TB to prevent MDR-TB; 2) expansion of rapid testing and detection of MDR-TB cases; 3) immediate access to quality care; 4) infection control; and 5) increased political commitment, including adequate funding for current interventions as well as research to develop new diagnostics, drugs and treatment regimens (1-2).

Conclusion

DR-TB, either MDR-TB or XDR-TB are already present worldwide and has worse prognosis compared with DS-TB. The most characteristic imaging findings are the presence of multiple pulmonary cavities, significant number of nodules, and bronchiectasis. Although these findings can also be seen in DS-TB, the combination of these imaging manifestations could strongly suggest DR-TB in a patient not responding to first line anti-TB medication or with previous history of TB treatment. The limited drug penetration into the cavities that harbors a large mycobacterial load is believed to contribute to the drug resistance. Other findings include infiltrates, fibrosis and pleural involvement. XDR-TB shares a lot of common imaging findings with MDR-TB and maybe difficult to differentiate from each other. Laboratory tests remain the cornerstone for TB diagnosis but knowledge of typical radiological findings suggestive of DR-TB may enable early detection and prompt management for infected patients.

References

1. World Health Organization. Global Tuberculosis Report 2014. WHO
2. WHO Supplement: Drug-resistant TB surveillance & response. Global Tuberculosis Report 2014
3. Kim SH, Min JH, Lee JY. Radiological findings of primary multidrug-resistant pulmonary tuberculosis in HIV- seronegative Patients. Hong Kong J Radiol 2014;17:4-8
4. Van Rie A, Warren R, Richardson M, et al. Classification of drug-resistant tuberculosis in an epidemic area. Lancet 2000; 356:22-5
5. Signal M, Sismanidis C, Falzon D, et al. Multidrug-resistant tuberculosis in children: evidence from global surveillance. Eur Respir J 2013;42(3):701-7. doi: 10.1183/09031936.00175812. Epub2012 Dec 6

6. Shah I, Chilkar S. Clinical profile of drug resistant tuberculosis in children. *Indian Pediatr* 2012;49(9):741-4. Epub 2012 Jun 10
7. Burrill J, Williams CJ, Bain G et al. Tuberculosis: a radiologic review. *Radiographics* 2007;27:1255-73
8. Pirina P, Spada V, Arcadu A, et al. Emerging clinical-radiological pattern of pulmonary tuberculosis in immunocompetent patients. *EMJ European Medical Journal* December 2014;1-6
9. Fishman JE, Sais GJ, Schwartz DS, Otten J. Radiographic findings and patterns in multidrug-resistant tuberculosis. *J Thorac Imaging* 1998;13(1):65-71
10. Zahirifard S, Amiri MV, Bakhshayesh Karam M, et al. The radiological spectrum of pulmonary multidrug-resistant tuberculosis in HIV-negative patients. *Iran J. Radiology* 2003;162-166.
11. Kim HC, Goo JM, Lee HJ, et al. Multidrug-resistant tuberculosis versus drug-sensitive tuberculosis in human immunodeficiency virus-negative patients: computed tomography features. *J Comput Assist Tomogr* 2004;28(3):366-71
12. Chung MJ, Lee KS, Koh WJ, et al. Drug-sensitive tuberculosis, multidrug-resistant tuberculosis, and nontuberculous mycobacterial pulmonary disease in nonAIDS adults: comparisons of thin-section CT findings. *Eur Radiol* 2006;16(9):1934-41. Pub 2006 March 1
13. Blanchard JS. Molecular mechanisms of drug resistance in *Mycobacterium tuberculosis*. *Annu Rev Biochem* 1996;65:215-39
14. Cha J, Lee Hy, Lee KS, et al. Radiological findings of extensively drug-resistant pulmonary tuberculosis in non-AIDS adults: comparisons with findings of multidrug-resistant and drug-sensitive tuberculosis. *Korean J Radiol* 2009;10(3):207-16
15. Schaaf HS, Shean K, Donald PR. Culture confirmed multidrug resistant tuberculosis: diagnostic delay, clinical features, and outcome. *Arch Dis Child* 2003;88:1106–1111
16. Lee ES, Park CM, Goo JM, et al. Computed tomography features of extensively drug-resistant pulmonary tuberculosis in non-HIV-infected patients. *J Comput Assist Tomogr* 2010;34(4):559-63

Corresponding Author:
Bernard F. Laya, MD, DO
St. Luke's Medical Canter, Philippines
Email: bernielaya@gmail.com