S. Zahirifard MD,
M. V. Amiri MD,
M. Bakhshayesh Karam MD,
S. M. Mirsaeidi MD,
A. Ehsanpour MD,
M.R. Masjedi MD

The Radiological Spectrum of Pulmonary Multidrug-Resistant Tuberculosis

In HIV-Negative Patients

Background: Multidrug-resistant tuberculosis (MDR-TB) is a major worldwide health problem. In countries where TB is of moderate to high prevalence, the issue of MDR-TB carries significant importance. MDR-TB, similar to drug-sensitive TB, is contagious. Meanwhile its treatment is not only more difficult but also more expensive with lower success rates. Regarding clinical findings, there is no significant difference between MDR-TB and drug-sensitive TB. Therefore determination of characteristic radiological findings in cases of MDR-TB might be of help in early detection, and hence appropriate management of this disease condition.

Objective: To explain the radiological spectrum of pulmonary MDR-TB.

Patients and Methods: We retrospectively evaluated the radiographic images of 35 patients with clinically- and microbiologically-proven MDR-TB admitted to our tertiary-care TB unit over a period of 13 months. The latest chest X-ray of all patients and the conventional chest CT scan without contrast of 15 patients were reviewed by three expert radiologists who rendered consensus opinion.

Results: Of the 35 patients with imaging studies, 23 (66%) were male and 12 (34%) were female. The mean±SD age of participants was 38.2±17.3 (range: 16-80) years. 33 patients were known as secondary and only 2 had primary MDR-TB. Chest radiography revealed cavitary lesion in 80%, pulmonary infiltration in 89% and nodules in 80% of the cases. Pleurisy was the rarest finding observed in only 5 (14%) patients. All of 15 chest CT scans revealed cavitation, 93% of which were bilateral and multiple. Pleural involvement was seen in 93% of patients.

Conclusion: Presence of multiple cavities, especially in both lungs, nodular and infiltrative lesions, and pleural effusion are main features of MDR-TB as compared to drug-sensitive TB.

Keywords: Tuberculosis, Multidrug-Resistant, Computed Tomography, X-Ray, Tuberculosis, Pulmonary, Iran

Introduction

Tuberculosis (TB) is a disease that has been known since antiquity. It remains one of the leading causes of morbidity and mortality worldwide. Its management has become more complex because of increased resistance to commonly-used anti-TB agents. Although drug-resistant TB was first recognized subsequent to the first trials of streptomycin for treatment of the disease in 1948,[1] multi-drug resistant TB (MDR-TB) has surged as an important global problem since the last decade. Reliable information about the global incidence of drug-resistant TB is hard to obtain. Large surveys of worldwide drug-resistance have indicated that drug-resistant TB is a large and increasing problem, especially in certain countries such as Iran.[2-4]

In a survey of resistance in 58 sites in six continents conducted by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease from 1996 through 1999, primary resistance to at least one drug ranged from a rate as low as 1.7% in Uruguay to a value as high as 36.9% in Estonia (mean: 10.7%).

From
National Research Institute of Tuberculosis and Lung Diseases
Masseh Daneshvary Hospital,
Shaheed Beheshti University of Medical Sciences.
Corresponding author:
Dr Bakhshayesh Karam
Shaheed Bahonar ave, Darabad,
Tehran 19556, PO Box:19575/154
IRAN.
Tel: +9821 2282111
Fax:+9821 2285777

Most experts believe that MDR-TB will continue to be a problem in selected areas round the globe for many years to come. In Iran, MDR-TB was reported to present with a mean of 1.0%; though, it was reported as high as 5.0% in certain regions. Nowadays, Iran is identified as a region with high-prevalence of MDR-TB.

Resistance is defined as "primary" or "initial," when it was identified in an individual who has never been treated before, and referred to as "acquired" or "secondary," when the presence of resistance follows the failure of previous treatment of TB.[18]

Rates of primary MDR-TB were generally low, with a mean of 1.4%. However, secondary MDR-TB had a reported mean rate of 13.0%. A mathematical model estimated that 3.2% of all cases of TB in the world in the year 2000 were caused by multidrug-resistant strains.[5] MDR-TB is defined as resistance to rifampicin and isoniazid, with or without resistance to other anti-TB drugs.[6-7] The management of MDR-TB comprises far more than the use of complex second- and third-line anti-TB drug regimens. Patients with the disease often need to spend prolonged periods in hospital negative pressure rooms with specialist nursing care, multidisciplinary medical input, and extensive use of laboratory services.[8-11]

MDR-TB thus raises the specter of a return to the 18th and 19th centuries, when as many as 20% of all adult deaths in Europe and the United States have been attributed to TB.[12]

There are some controversies regarding the radiological findings in patients with primary and acquired pulmonary MDR-TB, especially about the effects of these lesions on patients' outcome. Also, we believe that the prevalence of certain radiological patterns vary over different areas due to specific characteristics of host defense mechanisms. Therefore, we hope the current study could help us in better identification of MDR-TB behaviors and explain different results in this setting.

Patients and Methods

Study Population

In a retrospective study, we reviewed the chest radiographs, computed tomography (CT) images and clinical charts of 79 non-HIV-infected patients suspected of having pulmonary MDR-TB. We defined pulmonary MDR-TB as a consistently positive sputum smear despite regular and directly observed treatment with conventional chemotherapy in addition to existence of progressive radiographic abnormalities consistent with pulmonary TB, and resistance at least to both rifampicin and isoniazide. Among these subjects, 35 patients fulfilled the inclusion criteria.

Abbreviations:
TB = Tuberculosis,
MDR-TB = Multidrug-resistant Tuberculosis;
CT = computed tomography,
DOTS = directly observed treatment with short course

Age, gender, duration of treatment, type of MDR-TB and the drug to which the microorganism had shown resistance were gathered from clinical charts of all patients.

Imaging Examinations

The last posteroanterior and lateral standard chest radiographs of all the patients were evaluated. All radiographic images had been obtained at 80 KVp using CGR 1000 mA. In 15 patients, conventional 10-mm collimation CT images had also been obtained from the apex to the base of the lung (Siemens somatom plus).

Image Analyses

The images were reviewed retrospectively, by three independent, experienced radiologists. CT images were reviewed after the chest radiographs to reduce the bias in interpretation. Differences in imaging interpretation were resolved by consensus. The chest radiographs and CT results were assessed for the presence and distribution of the following findings: 1) parenchymal consolidation, 2) cavitation, 3) interstitial infiltrates, including miliary and reticular changes, 4) adenopathy, and 5) pleural effusion. Lymph nodes were considered enlarged if they were ≥1 cm in short-axis diameter. Lymphadenopathy was characterized as containing low attenuation on contrast-enhanced CT if its attenuation was lower than muscle on visual assessment.

Laboratory Analyses

The results of microscopic examination of the sputum smear, sputum cultures (on Lowenstein Johnson culture media), antibiogram and ELIZA test for detecting anti-HIV antibody were determined for all the initial 72 patients with presumptive pulmonary MDR-TB.

Data Analyses

Statistical analyses were performed with SPSS® for Windows™ (ver. 11.5) software.

Results

Of 72 patients with presumptive pulmonary MDR-TB admitted to our referral tertiary care TB unit

between January 2001 and December 2002, 35 patients fulfilled our inclusion criteria mentioned earlier. Of 35 patients, 23 (66%) were male and 12 (34%) were female. The mean±SD age of patients was 38.2±17.3 (Range: 16 to 80) years. Twenty-three patients (66%) were Afghani immigrants and 12 patients (34%) were native Iranians. Two patients (6%) had primary and the rest (94%) had secondary MDR-TB. Of the 33 patients with secondary MDR-TB, 21 (60%) had previously received one course of conventional anti-TB regimen; nine (26%) had received two; two (6%) patients had three and one (3%) had four anti-TB regimen.

All the serologic samples taken from patients were negative for anti-HIV antibody.

Radiological findings

All patients had manifestations of lung involvement; 28 had bilateral and 7 had unilateral lung involvement.

Cavitary lesions were found in the chest X-rays of 28 patients (80%). Other most frequently observed findings on plain chest roentgenograms were pulmonary infiltration, noted in 31 patients (89%); followed by pulmonary nodules, lymphadenopathy and calcification that were presented in 29 (83%), 27 (77%) and 16 (46%) patients, respectively.

Pleural involvement manifested in various types. The most common form of pleural involvement was pleural thickening seen in 11 (31%) of the patients. Finally, pleurisy was noted in only 5 (14%) patients (Table 1).

Thoracic CT scan was done for 15 patients. All of them revealed cavitation, 12 patients had thick-walled cavitary lesions whereas 3 had thin-walled cavities. There were both thick- and thin-walled cavitations in one patient. Usually, cavitary lesions involved multiple areas in both lungs. Single lobe involvement was seen in only one patient. Other signs noted in the chest CT scan included "tree in bud" sign in 80% of cases, lymphadenopathy in 73%, lung fibrosis in 67%, and collapse in 47% of films. The pleural involvement was more prominent on CT scan and was observed in 14 (93%) patients; 12 with pleural thickening and 2 with pleural effusion.

Table 1: Distribution of plain radiography findings in the chests of 35 patients with MDR-TB

Plain Radiolography findings	Number of cases / %
cavitary lesions	28 / (80%)
Infiltration	31 / (89%)
Calcification	16 / (46%)
Pleurisies	5 / (14%)
pleural thickening	11 / (31%)
Lymphadenopathy	27 / (77%)
Nodules	29 / (83%)

Discussion

Nearly one-third of the world population, *i.e.*, two billion people, are infected with *Mycobacterium tuberculosis* and are at risk of developing the disease. Following HIV/AIDS, TB is the world's second commonest cause of death from infectious diseases. Annually, more than eight million people develop active TB, of whom about two million die.[13-14] The WHO estimates that 50 million people worldwide are infected with MDR-TB, and that 273,000 (3.1%) of the 8.7 million new TB cases in the year 2000 were caused by MDR-TB.

Tubercle bacilli are continually undergoing spontaneous mutations that create resistance to individual anti-TB drugs. However, the frequency of these single mutations is sufficiently low that if the appropriate combination chemotherapy is administered and reliably ingested, no clinically significant resistance will occur.[15] Most commonly, the development of acquired drug resistance occurs when there is a large multiplying bacillary population, such as what occurred in pulmonary cavities—when an inadequate drug regimen (inappropriate drugs, insufficient dosages, etc) is prescribed, or when there is a combined failure of both the patient and the provider to ensure that an adequate therapeutic regimen is taken.[16] Rarely, malabsorption of one or more anti-TB drugs may account for acquired resistance.[17]

Drug-resistant TB represents a threat to TB control programmers. Erratic and inappropriate use of currently available medications, HIV-TB co-infection, and concerns about transmission of drug-resistant strains in the general population, all contribute to a worrying picture. Unfortunately, the practitioner's error and poor patient adherence to the treatment may result in resistance and hence, treatment failure.

Obviously a critical element for the future control of MDR-TB is prevention. For already existing strains of drug-resistant *M. tuberculosis*, it is vital to halt their transmission in community or hospital, in particular, in our country where an outbreak of MDR-TB is highly probable (Figure 1). Health workers are in contact with a large number of patients with MDR-TB in referral hospitals. Early identification of cases with MDR-TB plays a crucial role in its prevention. We learned valuable lessons from the MDR-TB outbreak in New York City,[19] Therefore, we must be watchful of any signs that could help us to predict and prevent another catastrophic event.

One of those signs would be obtained from imaging modalities.

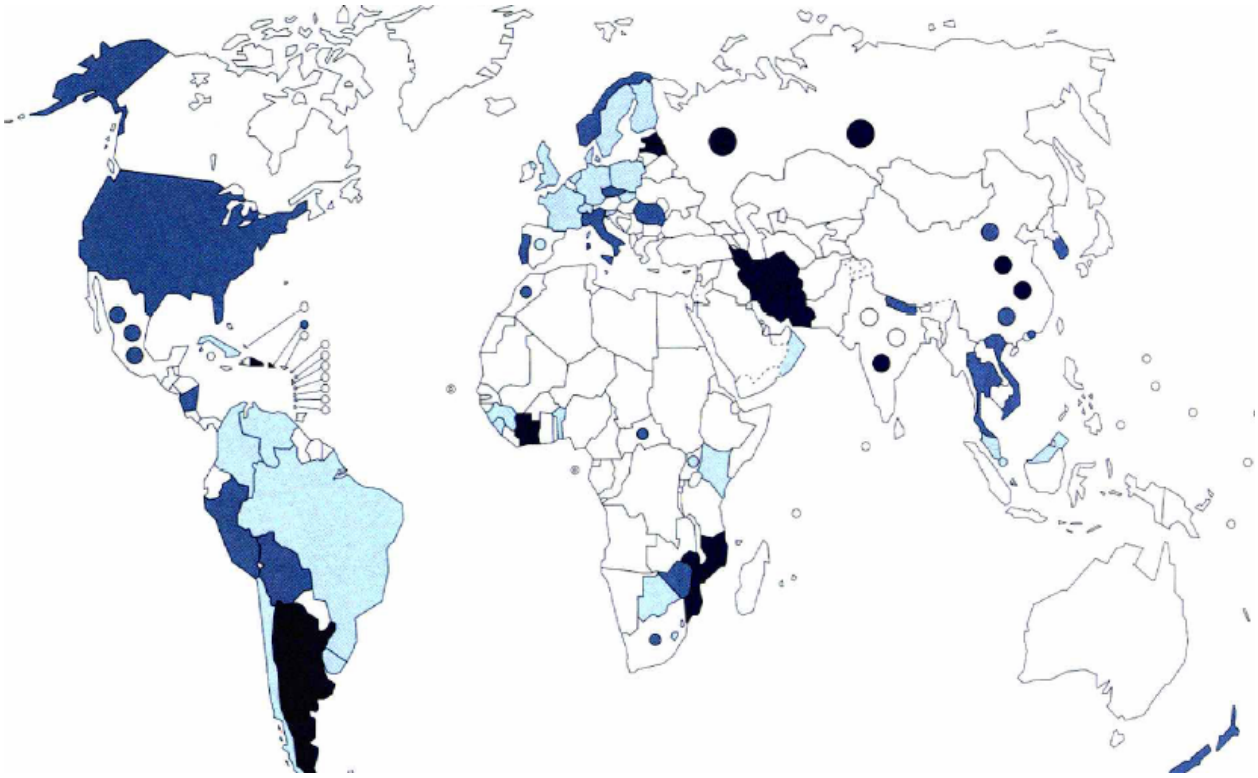

Figure 1: Prevalence of multidrug-rsistant tuberculosis among new tuberculosis cases in countries and regions surveyed, 1994-99 (▫: <1%; ■: 1-3%; ■: >3%; □: no data),

Pulmonary MDR-TB exhibits a wide range of radiological signs most of them having severe patterns. We do not know whether these harsh lesions correlate with more contagious behavior of strains involved in the pulmonary MDR-TB. Also, the role of these lesions in transmitting the microorganisms to other persons in contact with MDR-TB patients is questionable and the likelihood that a healthy host develops the disease following an exposure to a patient with MDR-TB has not been well declared. However, the molecular epidemiology of TB in the Netherlands indicated an under-representation of the drug-resistant strains in transmission clusters, suggesting limited transmissibility, infectiousness, or pathogenicity of the organisms.[20]

Another question regarding the role of radiological findings is about their effectiveness on determining the morbidity and mortality of patients suffering from MDR-TB. We know MDR-TB is associated with higher rates of failure and death than is drug-susceptible TB. However, the association between the extension of lesions on radiography and the mortality rate among patients with MDR-TB is still unclear.[21]

To the best of our knowledge, only one study has evaluated imaging findings in MDR-TB.[22] They compared chest X-rays of patients with MDR-TB and drug-susceptible TB and speculated that the overall radiographic findings and patterns among the two groups are similar. They found that once a patient developed MDR-TB during an outbreak, the predominant radiographic pattern was similar to that of a primary TB. In those patients who acquired MDR-TB due to low adherence to treatment protocol, most findings were consistent with that of secondary TB. In the latter condition, they found cavitary lesions in 50% of patients. However, about one-third of the patients did not show the expected radiographic pattern.

Kritski *et al*, in 1997 performed a study among patients requiring re-treatment and found that the presence of cavitary lesions was significantly associated with an unfavorable outcome. However, this finding was not associated with MDR-TB. In that study, presence of cavitary lesions had a positive predictive value of 54% for an unfavorable outcome.[23] Those findings were reproduced by Yew *et al*, in China. They performed a study to evaluate the outcome in patients with MDR-TB. Cavitary lesions were found in 50.8% of patients and significantly correlated with a poor outcome.[24] Two other studies, previously showed the relation between cavitary disease and MDR-TB.[25,26] In one study performed in Argentina, the authors reported radiological findings as minimal, moderate and advanced and noted sig-

nificant differences between the primary and acquired MDR-TB: The patients with acquired MDR-TB presented with a higher prevalence of advanced lung lesions (as high as 75% of subjects).[27] Based on these data, Long in 2000 suggested that one of the criteria for presuming MDR-TB was the presence of cavitary disease. He concluded that these lesions harbor greater numbers of bacilli so that the likelihood of MDR-TB rise in the presence of them.[28]

In comparison with the above studies, a recently published article which was on community-based therapy in MDR-TB done in Peru, found that 66.6% of patients have bilateral pulmonary disease and cavitary lesions, and that only 6% of patients have neither bilateral disease nor cavitary lesions. Cavitary lesions were absent in residual subjects. Surprisingly, the presence of cavitary lesions was not associated with adverse disease outcome.[29]

Finally, in management of pulmonary MDR-TB, imaging modalities could be as a guiding tool whenever surgical resection of involved lung area is the treatment option.[30]

Conclusion

Our study shows that the chest imaging of pulmonary MDR-TB reflects more frequently the extensive and destructive pattern. Physicians always ask themselves whether their patients are at risk for MDR-TB or not. Some authors suggest certain criteria for this concern.[31] We consider that radiological features in certain patients could raise suspicion of MDR-TB. Our study revealed some radiological findings that could be used as markers of MDR-TB; the presence of multiple cavities, especially in both lungs, nodular and infiltrative lesions with pleural effusion are main features of MDR-TB as compared to those of drug-sensitive TB. Radiologists should be familiar with different patterns in pulmonary MDR-TB and related complications in each finding so that they can inform clinicians of the future hazards.

References

1. Crofton J, Mitchison DA: Streptomycin resistance in pulmonary tuberculosis. *BMJ.* 1948; 2:1009-1015.
2. Espinal MA, Laszlo A, Simonsen L, et al: Global Trends in Resistance to Antituberculosis Drugs. *N Engl J Med* 2001 Apr 26; 344(17):1294-1303.
3. Cohn DL, Bustreo F, Raviglione: MCDrug-resistant tuberculosis: review of the worldwide situation and the WHO/IUATLD Global Surveillance Project. International Union Against Tuberculosis and Lung Disease. *Clin Infect Dis* 1997 Jan;24 Suppl 1:S121-30.
4. Pablos-Mendez A, Raviglione MC, Laszlo A, et al: Global surveillance for antituberculosis-drug resistance, 1994-1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 1998 Jun 4; 338(23):1641-9.
5. Espinal MA: *The global situation of MDR-TB. Tuberculosis* (Edinb) 2003; 83 (1-3):44-51.
6. Iseman MD: Treatment of multidrug resistant tuberculosis. *N Engl J Med* 1993; 329:784-791.
7. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53:536-548.
8. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53:536-548.
9. Public Health Laboratory Service. Mycobnet: *UK Mycobacterial Resistance Network Database.*, February 2000 (www.phls.co.uk)
10. Interdepartmental Working Group on Tuberculosis: The prevention and control of tuberculosis in the United Kingdom. *UK guidance on the prevention and control of transmission of HIV related tuberculosis; 2. Drug-resistant, including multiple drug resistant tuberculosis.* Department of Health, Scottish Office, Welsh Office: September, 1998.
11. Tuberculosis Committee of the British Thoracic Society: Chemotherapy and management of tuberculosis in the United Kingdom: *recommendations* 1998. *Thorax* 1998; 53: 536-548.
12. Horsburgh C. Jr: The Global Problem of Multidrug-Resistant Tuberculosis The Genie Is out of the Bottle. *JAMA* 2000; 283 (19): 2575-2576.
13. Dye C et al: Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. *Journal of the American Medical Association*, 1999, 282(7):677-686
14. Frieden TR, Sterling TR, Munsiff SS, et al: Tuberculosis. *The Lancet* 2003; 362: 887-899
15. David HL, Newman CM: Some observations on the genetics of isoniazid resistance in the tubercle bacilli. *Am Rev Respir Dis* 1971;104: 508–515.
16. Mahmoudi A, Iseman MD: Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. *JAMA* 1993; 270:65–68.
17. Canetti G: The J. Burns Amberson Lecture: present aspects of bacterial resistance in tuberculosis. *Am Rev Respir Dis* 1965; 92:687–703.
18. Van Rie A, Warren R, Richardson M, Gie RP, et al: Classification of drug-resistant tuberculosis in an epidemic area. *Lancet* 2000; 356:22-5.
19. Frieden TR, Sherman DR, Maw K, et al: A multi-institutional outbreak of highly resistant tuberculosis: epidemiology and clinical outcomes. *JAMA* 1996; 276: 1229-35.
20. Van Embden JDA: Molecular epidemiology of tuberculosis [lecture]. *American Society of Microbiology (ASM)* Conference on Tuberculosis: past, present and future; State of the Art: 1997 July; Coppermountain (CO)
21. Espinal MA, Kim SJ, Suarez PG, et al: Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA* 2000; 283:2537-45.
22. Fishman JE, Sais GJ, Schwartz DS, Otten J: Radiographic findings and patterns in multidrug-resistant tuberculosis. *J Thorac Imaging.* 1998 Jan;13(1):65-71.
23. Kritski AL, Rodrigues de Jesus LS, Andrade MK, et al: Retreatment tuberculosis cases: factors associated with drug resistance and adverse outcomes. *Chest* 1997; 111:1162–1167.
24. Wing Wai Yew,Chi Kuen Chan, Chi Hung Chau et al: Outcomes of Patients With Multidrug-Resistant Pulmonary Tuberculosis Treated With Ofloxacin/Levofloxacin-Containing Regimens. *Chest* 2000; 117:744–751.
25. Riley LW, Arathoon E, Loverde VD: The epidemiologic patterns of drug-resistant Mycobacterium-tuberculosis infections: a community-based study. *Am Rev Respir Dis* 1989; 139:1282-85.
26. Ben-Dov I, Mason GR: Drug-resistant tuberculosis in a southern California hospital: trends from 1969 to 1984. *Am Rev Respir Dis* 1987; 135:1307-10.

27. Palmero D, Ritacco V, Ambroggi M, et al: Multidrug-Resistant Tuberculosis in HIV-Negative Patients, Buenos Aires, Argentina. *Emerging Infectious Diseases* 2003; 9(8): 965-969
28. Long R: Drug-resistant tuberculosis. *CMAJ* 2000; 163(4):425-8
29. Mitnick C, Bayona J, Palacios E, et al: Community-Based Therapy for Multidrug-Resistant Tuberculosis in Lima, Peru. *N Engl J Med* 2003; 348:119-28.
30. Pomerantz BJ, Cleveland JC Jr, Olson HK, Pomerantz M: Pulmonary resection for multi-drug resistant tuberculosis. *J Thorac Cardiovasc Surg* 2001; 121:448–453.
31. Telenti A, Iseman M: Drug-Resistant Tuberculosis. What Do We Do Now? *Drugs* 2000; 59 (2): 171-179