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ORIGINAL ARTICLE

Radiological Findings of Primary Multidrug-resistant Pulmonary Tuberculosis in HIV-seronegative Patients

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ABSTRACT

Objective: *To compare the computed tomography findings of patients with primary multidrug-resistant tuberculosis (MDR TB) and those with drug-sensitive tuberculosis (DS TB) who were human immunodeficiency virus (HIV) seronegative.*

Methods: *The computed tomography findings of 40 patients with MDR TB and 40 with DS TB were retrospectively reviewed. The presence of centrilobular nodules, consolidation, cavity, bronchiectasis, calcification, pleural effusion, lymphadenopathy, laterality and number of involved lobes were looked for. Statistical comparison entailed the use of Student's T test, the Chi-square test, and the Mann-Whitney* U *test.*

Results: *Cavities were more frequently observed in patients with primary MDR TB than those with DS TB ($p = 0.007$), and when present, these were more numerous in the former patients than in the latter ($p = 0.001$). There was no statistically significant difference between primary MDR TB and DS TB in terms of centrilobular nodules, consolidation, bronchiectasis, calcification, pleural effusions, lymphadenopathy, laterality, and number of involved lobes.*

Conclusions: *In HIV-seronegative patients, the presence of multiple cavities was a significantly more common computed tomography finding in the MDR TB patients than in the DS TB patients. This computed tomography finding may enable early detection and appropriate therapy for such infected patients, as it can be obtained rapidly.*

Key Words: *Lung; Tomography, X-ray computed; Tuberculosis, multidrug-resistant*

中文摘要

HIV血清反應陰性患者中原發性多重耐藥性肺結核的的影像學表現

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目的：比較人類免疫缺陷病毒（HIV）血清反應陰性的原發性多重耐藥性肺結核（MDR TB）患者和藥物敏感性肺結核（DS TB）患者電腦斷層掃描的結果。

方法：將40例MDR TB和40例DS TB的電腦斷層掃描結果進行回顧分析。從掃描結果中尋找出小葉中心型結節、實變、空洞、支氣管擴張、鈣化、胸腔積液、淋巴結腫大、偏側性和受累肺葉數目。使

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用Student's T檢驗、卡方檢驗和Mann-Whitney *U*檢驗進行統計比較。

結果：原發性MDR TB患者空洞發生率高於DS TB患者（p = 0.007）；且一經發生，前者空洞數目多於後者（p = 0.001）。在小葉中心型結節、實變、支氣管擴張、鈣化、胸腔積液、淋巴結腫大、偏側性和受累肺葉數目方面，兩組患者並無統計學顯著差異。

結論：在HIV血清反應陰性的患者中，MDR TB患者電腦斷層掃描結果中多發性空洞發生率顯著高於DS TB患者。由於電腦斷層掃描結果可以快速獲取，使該方法能讓這類感染患者得到早期檢測及適當治療。

INTRODUCTION

Global emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* in recent years has greatly complicated the management and control of transmission of these infections. MDR tuberculosis (MDR TB) has surged as a public health problem worldwide.[1] In South Korea, although the overall prevalence of TB has decreased to below 1.0%, the rate of drug resistance, particularly multidrug resistance, in previously treated groups is still high.[2] A national survey disclosed 35,269 new cases of all TB in South Korea (73 per 100,000 population) in 2005,[3] and MDR TB occurred in 3% of new cases and in 14% of previously treated cases.[4] The major concerns of drug resistance relate to the spread of drug-resistant organisms and the ineffectiveness of chemotherapy for such patients, particularly those who are human immunodeficiency virus (HIV) seropositive. Thus, prompt diagnosis and treatment of MDR TB is also essential for community public health.

Although much faster today, determining drug resistance still takes several weeks. Moreover, sputum culture is of limited diagnostic value (20%-55% being positive) in active pulmonary TB.[5] Therefore, radiological findings suggestive of MDR TB may enable early detection and appropriate therapy for infected patients because they can be sought rapidly. The purpose of this study was to describe the computed tomography (CT) findings of MDR TB and to compare them with those with drug-sensitive (DS) TB in HIV-seronegative patients.

METHODS

Patients and Diagnoses

From September 2007 to January 2012, a computer search was performed to identify all patients with MDR TB and who underwent a chest CT. Informed consent was waived for this retrospective study. MDR TB was defined as TB resistant to at least isoniazid and rifampin. The mode of acquisition of drug resistance was defined as 'primary', when it was identified in an individual who had never received any antituberculous therapy or who had had such therapy for less than 1 month. Acquired drug resistance referred to resistance that developed in a patient who had received antituberculous therapy for more than 1 month in the past.[6] Radiological findings might show advanced features with an ongoing infection (chronic TB infection) during the development of acquired resistance. Thus, we included only patients who had a primary resistant form of MDR TB. Forty patients (27 males and 13 females; mean age, 43 years; age range, 20-82 years) were finally enrolled in this study. A control group of 40 patients with DS TB (defined as no resistance to any drug) was formed by random selection from all patients who had cultures positive for *M. tuberculosis* and who had undergone chest CT during the same period. They consisted of 30 males and 10 females (mean age, 50 years; age range, 21-81 years).

All 80 of these patients were HIV-seronegative as documented by negative results of a Western blot or an enzyme-linked immunosorbent assay test.

Image Acquisition and Analysis

All CT was performed using a multidetector row spiral CT scanner (Asteion; Toshiba Medical, Tokyo, Japan). None of the patients were administered any intravenous contrast medium. Data were reconstructed using a bone algorithm and 2.5-mm thickness for transaxial images. Scanning was performed at 120 kV with a 512 x 512 matrix. Chest CT scans were reviewed by two radiologists who had no knowledge of the patients' clinical information, and conclusions were reached by consensus.

The assessed patterns of parenchymal abnormalities included centrilobular nodules (including a tree-in-bud pattern), consolidation, cavity (presence and number),

bronchiectasis, and calcification. The cavities in areas of lung destruction were not included in the count of cavities. In addition, the presence of mediastinal or hilar lymph node enlargement and pleural effusions or thickening was recorded. Enlarged lymph nodes were defined as having a short-axis CT diameter of more than 1 cm. The laterality (unilateral or bilateral) and the number of involved lobes of lung lesions were also analysed. In each patient, six locations (right upper lobe, right middle lobe, right lower lobe, left upper lobe, lingular segment, and left lower lobe) were evaluated.

Statistical Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (Windows version 19.0; SPSS Inc, Chicago [IL], US). Statistical comparisons were performed using the Chi-square and the Mann-Whitney *U* tests for univariate analyses and demographic data (sex and age) of patients with primary MDR TB and DS TB. Student's T test was used to compare the number of lobes affected by parenchymal lesions and the number of cavities. A p value of <0.05 was considered statistically significant.

Table. Computed tomography (CT) findings in patients with primary multidrug-resistant tuberculosis (MDR TB) and drug-sensitive tuberculosis (DS TB).

CT findings	No. (%) of patients*		p Value
	Primary MDR TB (n = 40)	DS TB (n = 40)	
Centrilobular nodules	38 (95)	39 (98)	1.000
Consolidation	36 (90)	35 (88)	1.000
Cavity			
Presence	34 (85)	22 (55)	0.007
Mean No.	3.1	1.2	0.001
Bronchiectasis	9 (23)	5 (13)	0.378
Calcification	9 (23)	6 (15)	0.568
Pleural effusion	7 (18)	12 (30)	0.293
Lymphadenopathy	4 (10)	2 (5)	0.675
Laterality			
Unilateral	17 (43)	21 (53)	
Bilateral	23 (58)	19 (48)	0.502
No. of involved lobes	3.2	2.8	0.438

* Except otherwise indicated.

RESULTS

The mean age (p = 0.052, Student's T test) and sex ratios (p = 0.622, Chi-square test) were not significantly different in the MDR TB and DS TB patient groups.

The CT findings of both groups are summarised in the Table. Cavities were more frequently observed in patients with primary MDR TB than the control patients (p = 0.007; Chi-square test; Figures 1 and 2). Cavities ranged in number from 0 to 23 in patients with MDR TB (mean, 3.1) and from 0 to 5 in patients with DS TB (mean, 1.2). When present, there were more cavities in the MDR TB patients than in the DS TB patients (p = 0.001; Mann-Whitney *U* test).

There was no statistically significant difference between primary MDR TB and DS TB patients with respect to centrilobular nodules, consolidation, bronchiectasis, calcification, pleural effusions, lymphadenopathy, laterality, and number of involved lobes.

DISCUSSION

Whilst relatively few drug resistance surveys have been conducted outside industrialised nations, in Korea the MDR TB rate has been reported to be 14.5%.[7] Treatment of MDR TB warrants prolonged and expensive chemotherapy with second-line drugs that have heightened toxicity. The national goal of TB control is closely related to the control of drug resistance.

The CT findings of DS TB include centrilobular nodules, consolidation, cavity, and bronchial wall thickening involving mainly the upper lobes or the superior segments of the lower lobes.[8-10] Multiple

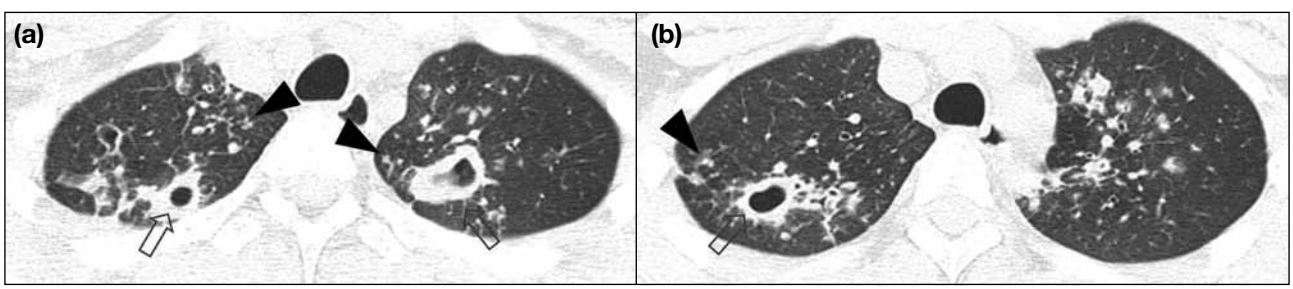

Figure 1. Primary multidrug-resistant tuberculosis in a 46-year-old man: transverse thin-section computed tomography scans show multiple cavities in both upper lobes (open arrows). Also note centrilobular nodules in both upper lobes (arrowheads).

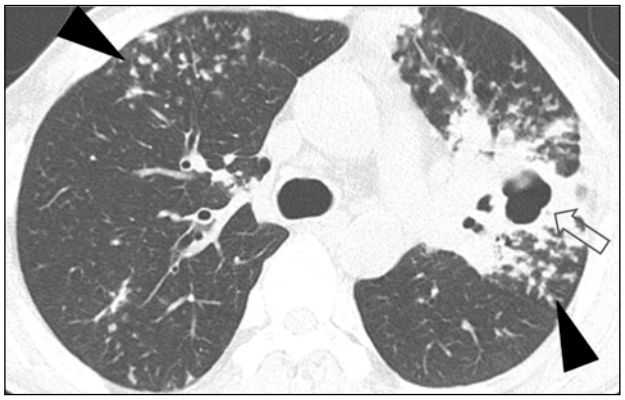

Figure 2. Drug-sensitive tuberculosis in a 40-year-old man: a transverse thin-section computed tomography scan shows one cavity in left lingular segment (open arrow) and multiple centrilobular nodules in both upper lobes and superior segment of left lower lobe (arrowheads).

cavities are more frequently observed in MDR TB patients than those with DS TB infections.[11,12] Cavities are formed when an area of caseous necrosis liquefies and communicates with the bronchial tree. Cavitary pulmonary lesions are a key means of disease transmission. The lining of the cavity tends to reduce the amount of drug that can penetrate the source of infection from the bloodstream. Moreover, high bacillary titres in cavities increase the probability of establishing drug-resistant bacterial populations.[13,14] It is therefore believed that lung cavities are the biological foundation for MDR and extensively drug-resistant TB. Our results are similar to previous results.[15,16] In our study, cavitation was more common in MDR TB patients as compared to DS TB patients. In addition, in patients with cavities, the mean number was larger in those with primary MDR TB than in those with DS TB. Fishman et al[17] reported that most patients with primary drug resistance showed a primary pattern such as noncavitary consolidation, pleural effusion and lymphadenopathy, whereas cavitary disease is common in patients who acquire MDR TB secondary to non-compliance with therapy. However, all of the patients with primary MDR TB in the study reported by Fishman et al[17] were HIV positive. Geng et al[18] reported that the most important radiological pattern determinant of parenchymal abnormalities was patient immunity rather than the drug resistance of the organisms. Therefore, radiological findings in the patient cohort described by Fishman et al[17] may have resulted from their immune status and diminished ability to mount a defense. In our study, all patients were HIV-seronegative and had primary drug resistance. Thus, multiple cavities could be suggestive of MDR TB in a TB-endemic country that is not associated with the HIV epidemic.

One limitation of this study was selection bias. Not all patients with MDR TB and DS TB underwent CT. Patients with more grave symptoms and signs or atypical clinical manifestations tend to undergo CT. Moreover, chest CT scan is more often performed in patients with cavitary TB, as they may warrant surgical treatment. Therefore, our study may have a selection bias for patients who were surgical candidates or had atypical clinical manifestations of TB. A second limitation was that the exact time between symptom onset and the CT was not always available owing to the long period over which relevant data were retrospectively collected. Thus, the duration of infection may well have affected the likelihood of cavity formation. A third limitation was that diabetes mellitus (an important risk factor of drug resistance),[6] was not systematically looked for in our patients.

CONCLUSION

The presence of multiple cavities was a significant CT finding in primary MDR TB patients who were seronegative to HIV, which was in contrast to the finding in those with DS TB. Such CT findings may be useful indicators of possible MDR TB patients, and facilitate early detection and appropriate therapy for such infected patients.

REFERENCES

1. Espinal MA. The global situation of MDR-TB. Tuberculosis (Edinb). 2003;83:44-51. crossref
2. Hong YP, Kim SJ, Lew WJ, Lee EK, Han YC. The seventh nationwide tuberculosis prevalence survey in Korea, 1995. Int J Tuberc Lung Dis. 1998;2:27-36.
3. Korean Center for Disease Control and Prevention. Annual report on the notified tuberculosis patients in Korea, 2005. Seoul: Korean Center for Disease Control and Prevention; 2006.
4. Bai GH, Park YK, Choi YW, Bai JI, Kim HJ, Chang CL, et al. Trend of anti-tuberculosis drug resistance in Korea, 1994-2004. Int J Tuberc Lung Dis. 2007;11:571-6.
5. Goo JM, Im JG. CT of tuberculosis and nontuberculous mycobacterial infections. Radiol Clin North Am. 2002;40:73-87, viii. crossref
6. Lee JH, Chang JH. Drug-resistant tuberculosis in a tertiary referral teaching hospital of Korea. Korean J Intern Med. 2001;16:173-9.
7. Cohn DL, Bustreo F, Raviglione MC. Drug-resistant tuberculosis: review of the worldwide situation and the WHO/IUATLD global surveillance project. Clin Infect Dis. 1997;24:S121-30. crossref
8. Im JG, Itoh H, Shim YS, Lee JH, Ahn J, Han MC, et al. Pulmonary tuberculosis: CT findings — early active disease and sequential change with antituberculous therapy. Radiology. 1993;186:653-60.
9. Lee KS, Im JG. CT in adults with tuberculosis of the chest:

characteristic findings and role in management. AJR Am J Roentgenol. 1995;164:1361-7. cross ref
10. Lee KS, Hwang JW, Chung MP, Kim H, Kwon OJ. Utility of CT in the evaluation of pulmonary tuberculosis in patients without AIDS. Chest. 1996;110:977-84. cross ref
11. Kim HC, Goo JM, Lee HJ, Park SH, Park CM, Kim TJ, et al. Multidrug-resistant tuberculosis versus drug-sensitive tuberculosis in human immunodeficiency virus-negative patients: computed tomography features. J Comput Assist Tomogr. 2004;28:366-71. cross ref
12. Chung MJ, Lee KS, Koh WJ, Kim TS, Kang EY, Kim SM, 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;16:1934-41. cross ref
13. Blanchard JS. Molecular mechanisms of drug resistance in *Mycobacterium tuberculosis*. Annu Rev Biochem. 1996;65:215-39. cross ref
14. David HL. Probability of distribution of drug-resistant mutants in unselected populations of *Mycobacterium tuberculosis*. Appl Microbiol. 1970;20:810-4.
15. Zahirifard S, Amiri MV, Karam MB, Mirsaeidi SM, Ehsanpour A, Masjedi MR. The radiological spectrum of pulmonary multidrug-resistant tuberculosis in HIV-negative patients. Iran J Radiol. 2003;1:161-6.
16. Cha JH, Lee HY, Lee KS, Koh WJ, Kwon OJ, Yi CA, 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;10:207-16. cross ref
17. Fishman JE, Sais GJ, Schwartz DS, Otten J. Radiographic findings and patterns in multidrug-resistant tuberculosis. J Thorac Imaging. 1995;13:65-71. cross ref
18. Geng E, Kreiswirth B, Burzynski J, Schluger NW. Clinical and radiographic correlates of primary and reactivation tuberculosis: a molecular epidemiology study. JAMA. 2005;293:2740-5. cross ref