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Comparison of High-resolution CT Findings between Miliary Metastases and Miliary Tuberculosis[1]

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Purpose: To compare the findings of high-resolution computed tomography (HRCT) between patients with miliary metastases and miliary tuberculosis.

Materials and Methods: Between May 1998 and April 2002, 11 patients with miliary metastases and 18 with miliary tuberculosis underwent HRCT, and we reviewed the findings. In miliary metastases, the primary lesions were adenocarcinoma of the lung ($n=2$), stomach ($n=1$), or pancreas ($n=1$), or of unknown origin ($n=5$), and papillary carcinoma of the thyroid ($n=2$). Two radiologists blinded to the clinical and pathologic data reached a consensus regarding nodule size and margin, their distribution and coalescence, interstitial involvement, and other ancillary HRCT findings. Data were analyzed using the chi-square test.

Results: CT scans showed numerous 1 to 5-mm nodules randomly distributed throughout both lungs of all patients. Nodules larger than 1.5 mm in diameter were more often seen in miliary metastases (81.9%). In six (54.5%) patients with miliary metastases and in three (16.7%) with miliary tuberculosis, nodule size varied ($p<0.05$). Pleural effusion occurred in three (27.3%) patients with miliary metastases and three (16.7%) with miliary tuberculosis. Interlobular septal thickening (100%) and peribronchovascular thickening (63.6%) were more common in miliary metastases than in miliary tuberculosis ($p<0.01$). Lymph node enlargement was seen in 11 (100%) patients with miliary metastases and five (27.8%) with miliary tuberculosis ($p<0.001$).

Conclusion: At HRCT, lymph node enlargement and both interlobular and peribronchovascular thickening are more commonly observed in miliary metastases than in miliary tuberculosis.

Index words : Lung neoplasms, CT
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Miliary lung disease is characterized by the development of numerous small "millet seed" nodular lesions throughout the lungs, a pattern which indicates hematogenous or lymphatic spread. In such cases, accurate localization of pathologic change occurring within the lobule could be helpful in the differential diagnosis of certain pulmonary parenchymal diseases investigated by means of HRCT (1, 2). Nodules distributed both along the course of visible arteries and along lobular borders (septal, pleural, or fissural surfaces) have been classified as "panlobular" or "random" (hematogenous) (3). Random distribution of miliary nodules occurs during the hematogenous spread of tuberculosis, fungal infection, or metastases from a variety of primary sources (2, 4), the most common causes of these nodules are miliary tuberculosis and metastases. In some patients, miliary metastases resembling miliary tuberculosis occur in the absence of a known primary tumor and differentiation between miliary tuberculosis and metastases at HRCT, of great importance for treatment, is troublesome. To our knowledge, prior studies have simply stated that compared with the nodules occuring in miliary tuberculosis, those occurring in miliary metastases were slightly larger though more variable in size, and had relatively well-defined margins (5, 8).

In this study, we reviewed and compared the HRCT findings of miliary metastases and miliary tuberculosis, focusing on the differential points and demonstrating the value of HRCT in the diagnosis of miliary metastases.

Materials and Methods

We reviewed the HRCT findings in 11 patients [M:F = 2:9 ; age, 28 - 65 (mean, 47.4) years] with miliary metastases and 18 patients [M:F = 13:5; age, 22 - 82 (mean, 44.4) years] with miliary tuberculosis who were examined between May 1998 to April 2002.

In metastasis, the primary lesions were adenocarcinoma of unknown origin ($n=5$), adenocarcinoma of the lung ($n=2$), papillary carcinoma of the thyroid ($n=2$), adenocarcinoma of the stomach ($n=1$), and adenocarcinoma of the pancreas ($n=1$). Metastatic disease was diagnosed in all patients by transbronchial biopsy ($n=4$), needle biopsy ($n=2$), or microscopic examination of sputum ($n=5$). A diagnosis of miliary tuberculosis was based on demonstration of Mycobacterium tuberculosis either by culture ($n=11$), microscopic examination of sputum ($n=1$), or in a specimen obtained at transbronchial lung biopsy ($n=1$). In the remaining five patients, the diagnosis was established by combining all the following criteria: (a) characteristic chest radiographic findings; (b) positive results of skin testing using purified protein derivative; and (c) a good response to antituberculous chemotherapy.

HRCT scanning was performed in the absence of intravenous contrast material, using a Highlight (General Electric Medical Systems, Milwaukee, Wis., U.S.A.) or Somatom-Plus scanner (Siemens Medical Systems, Erlangen, Germany). Scans of 1 mm thickness were obtained at 10-mm intervals, from the lung apices to the bases, using a 35-cm field of view, a 512×512 reconstruction matrix, 137 kV, 220 - 270 mA, and 1-second scanning time. Images were reconstructed using a high spacial frequency algorithm. For lung windows, level/width was -600 HU/1,500 HU, and for mediastinal windows the corresponding setting was 0/300 HU.

Two radiologists analyzed all the images, and final decisions regarding the findings were determined by consensus. The assessment criteria used were as follows: size, margin, distribution and coalescence of nodules; ground-glass opacity, and interlobular septal and peribronchovascular thickening. Nodules were classified as <1.5, 1.5 - 3 or >3.0 mm in diameter; where their size was not uniform, a concensus was reached. Margins were classified as well or poorly defined: well defined if the nodule was sharply and distinctly separated from surrounding normal lung; or poorly defined if it was hazy or indistinct, with its edge merging imperceptibly into surrounding lung. Distribution was classified as predominantly in the upper, middle, or lower zone of the lung, and as mainly central or peripheral. A location superior to the aortic arch was deemed 'upper zone'; one inferior to the inferior pulmonary vein was 'lower zone'; and a location between the aortic arch and the inferior pulmonary vein was 'middle zone'. Lung cortex was defined as one or two rows of well-organized and well-defined secondary pulmonary lobules, which together formed a layer about 3 - 4 cm in thickness. An area of slightly increased attenuation in which the bronchial walls and vessels remained visible was considered as ground-glass opacity, and apparent thickening of the bronchial wall and an apparent increase in size or change in the nodular appearance of the pulmonary arteries was identified as peribronchovascular interstitial thickening. In addition the presence of pleural effusion or a lymph node was recorded. A lymph node was considered enlarged when the short-axis di-

ameter was more than 1 cm at the hilum and mediastinum.

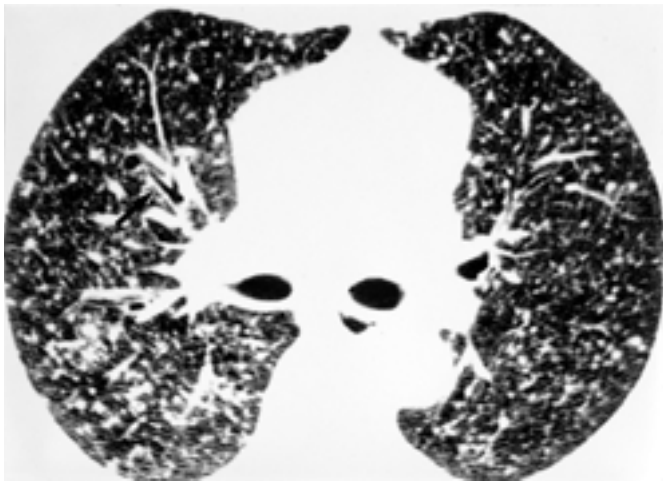
To determine whether differences in HRCT findings between the miliary metastasis and miliary tuberculosis groups were statistically significant, the Chi-square test was used. Differences in the frequency of each abnormality in each subgroup were evaluated using Fisher's exact test when the former test was inappropriate. Probability values of less than 0.05 were considered significant. For statistical analysis, a software package (SAS for windows, version 6.12) was used.

Results

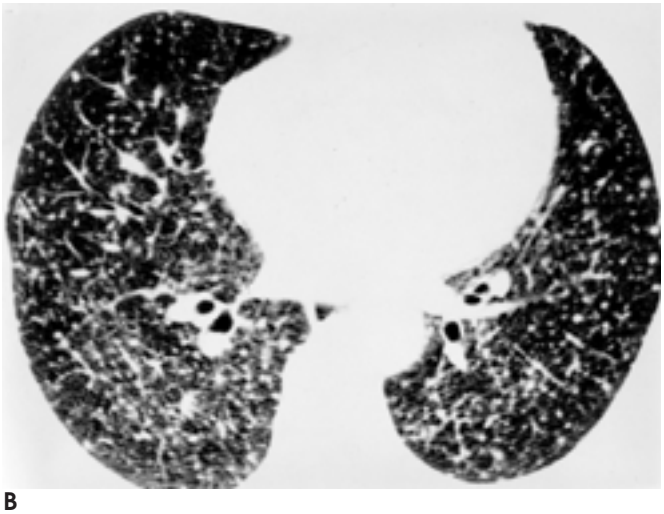
CT scans depicted numerous tiny 1 to 5-mm nodules distributed throughout both lungs. Nodules of more than 1.5 mm in diameter were seen in 81.9% (9/11) patients with miliary metastases and in 50.0% (9/18) with miliary tuberculosis. There was no significant difference in the size of nodules between the two groups (Table 1). Nodules varied in size in 54.5% (6/11) patients with miliary metastases and in 16.7% (3/18) of those with miliary tuberculosis ($p < 0.05$). In 72.7% (8/11) of patients with metastases and 72.2% (13/18) of tuberculosis patients, a well-defined margin was observed. Lower zone predominance was seen in 54.5% (6/11) with metastases and in 16.7% (3/18) of tuberculosis patients. In the miliary metastasis group, interlobular septal thickening (100%; 11/11) and peribronchovascular thickening (63.6%; 7/11) were more common than in the miliary tuberculosis group ($p < 0.01$). Lymph node enlargement was visible in 100% (11/11) patients with miliary metastases and 27.8% (5/18) with miliary tuberculosis. Lymph node enlargement was more common in the miliary metastasis group ($p < 0.001$); the right lower paratracheal area was

Table 1. Comparison of Size of Nodules

	< 1.5 mm	1.5 - 3 mm	> 3 mm
Miliary metastases (n = 11)	2 (18.2%)	6 (54.5%)	3 (27.3%)
Miliary tuberculosis (n = 18)	9 (50.0%)	7 (38.9%)	2 (11.1%)



A



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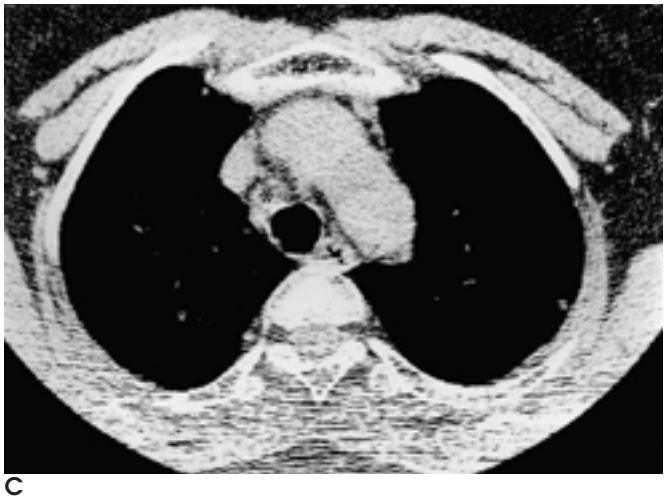


C

Fig. 1. A 61-year-old man with miliary metastases and unknown primary adenocarcinoma.
A. CT scan obtained at the level of the bronchus intermedius shows nodules in random distribution in the lungs. Also note that peribronchovascular thickening (arrow).
B. CT scan obtained at the level of the inferior pulmonary vein shows interlobular septal thickening (arrow) are seen in the right lung.
C. Transverse thin-section CT scan obtained at the level of the top of the aortic arch shows a lymph node enlargement (*) in right lower paratracheal area.

the most common site, identified in 64% of patients (Table 2).

Discussion

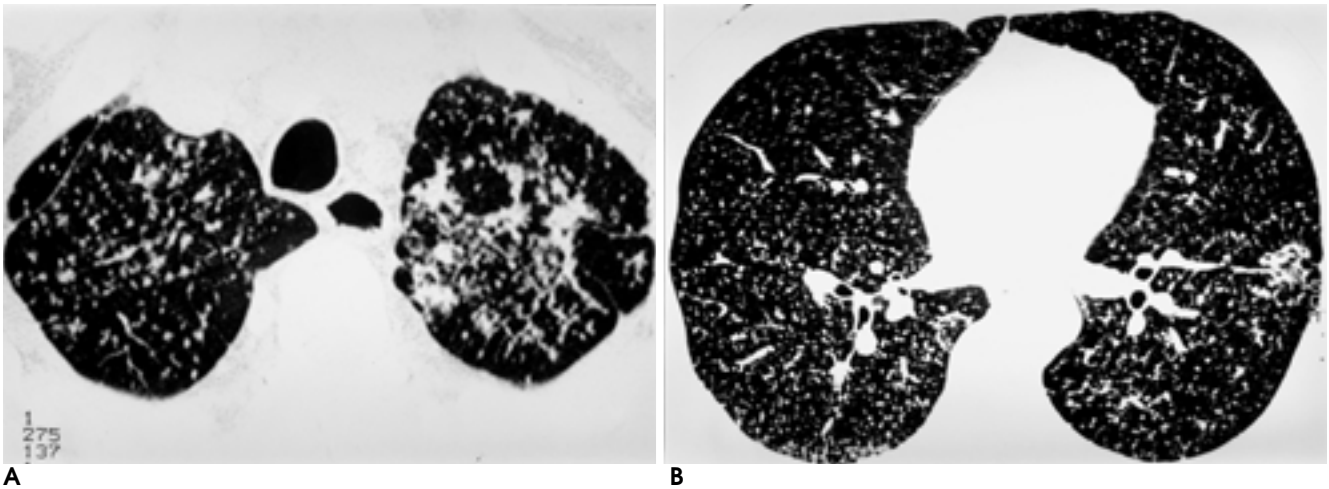
It has been shown at HRCT that in patients with miliary metastases (9, 10) or tuberculosis (6), the micronodules in the secondary pulmonary lobule were randomly distributed. In most miliary metastases (81.8%), the diameter of the nodule was more than 1.5mm. The nodules involved in miliary metastases were larger than those in miliary tuberculosis (6). In addition, variations in size were more frequently observed in patients with miliary metastases ($p < 0.05$). These HRCT appearances were in agreement with those of Lee et al. (5) and Oh et al. (6). A well-defined nodular margin was not, however, helpful for differential diagnosis between miliary metastasis and tuberculosis. In terms of distribution patterns, there was no statistically significant difference between miliary metastases and tuberculosis.

Our study showed that most patients with miliary metastases had abnormalities of the interlobular septa and peribronchovascular bundles, and this may indicate lymphangitic spread of the tumor. Lung lesions were mainly multiple well-defined nodules, and lymphangitic spread was observed in some areas surrounding the nodules. It therefore seemed reasonable to assume that hematogenous metastatic nodules could cause local lymphangitic spread of the tumor along pulmonary vessels in contact with the nodule. At HRCT, this spread appeared as thickening of bronchovascular bundles or perilobular structures connected to the nodule. It was believed that malignant cells were carried hematogenously and dispersed into the interstitium. Thereafter, they entered the lymphatics, giving rise to lymphatic spread. To explain the radiologic abnormalities seen in bronchovascular bundles and interlobular septa, four mechanisms have been proposed (11 - 13): (a) obstruc-

Table 2. Comparison of Miliary Metastases and Tuberculosis

	Nodules					Interstitial involvement			Ground-glass opacity	Pleural effusion	Lymph node enlargement
	Size (>1.5 mm)	Diversity in size	well defined margin	Distribution LZP	Distribution Even	Coalescence	ILST	PVBT			
Metastases ($n=11$)	9 (81.9%)	6 (54.5%)	8 (72.7%)	6 (54.5%)	4 (36.4%)	10 (90.9%)	11 (100%)	7 (63.6%)	8 (72.7%)	3 (27.3%)	11 (100%)
Tuberculosis ($n=18$)	9 (50.0%)	3 (17%)	13 (72.2%)	3 (16.7%)	13 (72.2%)	11 (61.1%)	9 (50%)	0	9 (50%)	3 (16.7%)	5 (27.8%)
p-value	$p > 0.05$	$p < 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.01$	$p < 0.01$	$p > 0.05$	$p > 0.05$	$p < 0.001$

LZP; lower zone predominance, ILST; interlobular septal thickening, PVBT; peribronchovascular thickening



A **B**

Fig. 2. A 37-year-old man with miliary tuberculosis.
A. Transverse thin-section CT scan obtained at the level of the lung apex shows miliary nodules in both lungs and areas of airspace consolidation in left lung.
B. Transverse thin-section CT scan obtained at the level of the inferior pulmonary vein shows typical tiny numerous miliary nodules in both lungs. Note that coalescence of nodules are seen at lateral basal area.

tion by malignant cells within lymphatics may cause their distension; (b) growth of a tumor within the interstitium may be a direct cause of interstitial thickening; (c) interstitial pulmonary edema may be related to lymphatic involvement; and (d) desmoplastic reaction may be related to malignant spread. According to Hirakata et al. (14), lymphangitic spread was histopathologically confirmed in 11 (79%) of 14 pulmonary metastatic patients. However, the pulmonary arteries leading to the metastatic nodules were often thrombosed by the tumor, and a tumor thrombus might also cause the thickened bronchovascular bundle seen at HRCT (12). Similarly, miliary infection, particularly tuberculosis, can cause interstitial abnormalities, typically septal lines (6). McGuinness et al. (15) assumed that innumerable tiny granulomas scattered throughout the pulmonary interstitium could account for diffuse intra- and interlobular thickening. In this study, interlobular septal thickening was present in 9 of 18 patients with tuberculosis. Bronchovascular bundle thickening and interlobular septal thickening were considered to be characteristic points of differentiation between miliary metastases and miliary tuberculosis.

The ancillary findings of miliary metastases have included lymph node enlargement and pleural effusion. In our study, the former was more common in patients with miliary metastases than in those with tuberculosis ($p < 0.05$), a difference which could help distinguish the two conditions. Hong et al. (7) reported that pleural effusion occurred in 16% of miliary tuberculosis cases, and in our study pleural effusion occurred in three (27%) patients with miliary metastasis and three (17%) with miliary tuberculosis. There were no significant difference between the two groups in terms of coalescence or groud-glass appearance.

A limitation of this study was its retrospective design, and because of the limited number of cases, further investigation is required. There is, in addition, a need for correlative pathologic study.

In conclusion, the major points of difference between miliary metastases and miliary tuberculosis were that in the former, involvement of the interlobular septa, peribronchovascular bundle thickening, and lymph node enlargement were more freguent. These findings can help differentiate the two diseases.

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속립성 폐전이암과 속립성 결핵의 고해상 CT소견 비교[1]

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목적: 속립성 폐전이암과 속립성 결핵의 고해상 CT소견을 비교하고자 하였다.

대상과 방법: 1998년 5월부터 2002년 4월까지 고해상 CT에서 직경 5 mm 이하의 소결절이 전 폐야에서 보이는 속립성 폐전이암 환자 11명 및 속립성 결핵환자 18명의 고해상 CT소견을 분석하였다. 속립성 폐전이암에서 원발성 병변은 원발미상의 선암 (n=5), 폐암 (n=2), 위암 (n=1), 췌장암 (n=1), 갑상선암 (n=2)이었다. 소결절의 크기, 변연, 분포 그리고 융합 등과 간질침범, 다른 보조적인 고해상 CT 소견 등을 임상적 병리적 정보를 알지 못한 상태의 두 명의 방사선과 의사가 합의 하에 분석하였다. 통계분석은 Chi-square법을 사용하였다.

결과: 모든 환자에서 CT 스캔상 1 mm 에서 5 mm 크기의 수많은 소결절들이 양폐야에 임의적 분포를 보였다. 1.5 mm 이상의 결절은 속립성 폐전이암 (81.9%)에서 더욱 자주 보였다. 결절 크기의 다양성은 속립성 전이암 환자 중 6명 (54.5%), 속립성결핵 환자중 3명 (17.0%)에서 보였다 (p < 0.001). 흉막삼출은 속립성 전이암 환자중 3명 (27.3%), 속립성 결핵환자 중 3명 (16.7%)에서 보였다. 엽간중격비후 (100%)와 기관지혈관주위비후 (63.6%)는 속립성 전이암 환자에서 더욱 빈번히 보였다 (p < 0.001). 림프절 증대는 속립성 전이암 환자중 11명 (100%), 속립성 결핵 환자중 5명 (27.8%)에서 보였다. 림프절 증대는 속립성 전이암에서 더욱 자주 보였다 (p < 0.001).

결론: 속립성 전이암의 특징적 소견으로 기관지혈관주위 및 엽간중격비후와 림프절 증대 등은 속립성 결핵보다 속립성 폐전이암에서 더 흔히 보였다.