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Clinical relevance of ground glass opacity in 105 patients with miliary tuberculosis

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Summary

Background: After the application of chest computed tomography (CT), ground glass opacity (GGO) was introduced as one of major accompanying findings of miliary tuberculosis (MT) in addition to miliary nodules. However, little is known about whether GGO is associated with the clinical manifestations and outcomes of MT. Therefore, the present study examined the clinical relevance of GGO in patients with MT.

Methods: Chest radiographs and CT scans of MT patients were retrospectively reviewed. Clinical manifestations and outcomes were compared in terms of the extent of GGO revealed by chest CT. **Results:** Confirmed 105 MT patients were included. GGO was observed in 70 (67%) patients. MT patients with an extent of GGO >50% ($n = 21$) had symptoms of shorter duration, more frequent dyspnea, and more pronounced changes in the levels of acute phase reactants. Miliary nodules were less discernible on CT in those with an extent of GGO >50%. MT patients with an extent of GGO >50% were significantly associated with a longer hospital stay ($p = 0.02$) and with acute respiratory failure ($p < 0.001$) than those with an extent of GGO ≤50%. However, mortality among MT patients was not associated with the extent of GGO.

Conclusion: MT patients with an extent of GGO >50% had more rapidly progressive manifestations and a greater potential for delayed diagnosis and poorer prognosis. Nevertheless, mortality was not higher in confirmed MT patients with an extent of GGO >50% than in those with an extent of GGO ≤50%.

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Introduction

Miliary tuberculosis (MT) results from massive lymphohematogenous dissemination of *Mycobacterium tuberculosis* (MTB) during both primary and post-primary tuberculosis (TB) [1,2]. Despite the availability of effective treatments, mortality remains high. The clinical manifestations range from a rapidly progressive course to a slow and prolonged course with subtle clinical findings [2–4].

Findings of a classic miliary pattern on chest radiography provide an important clue when making a diagnosis of MT; however, initial chest radiographs often show a non-classic pattern or they can even be normal [5]. Thus, some patients with MT represent a diagnostic challenge. Chest computed tomography (CT) is more helpful and enables the early recognition of MT, even in patients with atypical or normal findings on chest radiography. Therefore, patients with suspected miliary nodules often undergo a chest CT. After the application of chest CT, several studies reported that ground glass opacity (GGO) was one of major accompanying findings of MT in addition to miliary nodules [6–9]. However, little is known about whether the extent of GGO is associated with the clinical manifestations and outcomes of these patients.

Therefore, the aim of the present study was to examine the clinical relevance of GGO in patients with MT. In addition, because a previous study noted that some MT patients had larger nodules in the lung apices than in the lung bases [6], we also identified these patients and described their clinical characteristics.

Materials and methods

Patients

The study was conducted at Kyungpook National University Hospital, a tertiary referral hospital in South Korea set in an area with an intermediate prevalence of active TB (149 cases per 100,000 population in 2011) [10]. All MT patients (aged ≥ 15 years) attending the hospital from April, 2001 to December, 2012 were retrospectively selected using ICD-10 code A190-A199. Those with available chest radiographs and CT scans were enrolled. Details regarding patient demographics, clinical manifestations, risk factors (e.g., human immunodeficiency virus (HIV) infection, malignancy, diabetes mellitus, immunosuppressive drug therapy, solid organ transplantation, end-stage renal disease, chronic liver disease, gastrectomy, alcoholism, or pregnancy), laboratory and microbiological data, histological data (if available), hospital course (initial admitting department, time from admission to the start of anti-tuberculous treatment, length of hospital stay, occurrence of respiratory failure, and the use of mechanical ventilation), and in-hospital mortality were obtained from the medical records. A final diagnosis was made in those patients suspected of having MT on the basis of clinical and radiographic examinations when a respiratory specimen or non-respiratory specimen (tissue other than lung or urine) was found to be culture-positive for MTB, or when there was histological evidence of chronic granulomatous inflammation and the

tissue was positive for the acid fast bacilli (AFB) test or TB-polymerase chain reaction (PCR).

The study was approved by the Institutional Review Board of the Kyungpook National University Hospital.

Chest radiography and CT findings

Chest radiography and CT scans performed on admission were retrospectively reviewed by one board-certified radiologist and two board-certified pulmonologists who were blinded to the patient's clinical data. The initial chest radiographs and CT scans were obtained within 3 days of each other (median 0 day [interquartile range (IQR), 0-1]). Chest CT scans were performed with two multidetector CT scanners (LightSpeed, General Electric Medical Systems, Milwaukee, WI, USA; Aquilion 64, Toshiba Medical Systems, Otawara, Japan). Continuous axial images were obtained with 2.5 mm or 3 mm collimation from the lung apices to the bases at full inspiration. Images were reconstructed using a high spatial frequency (bone) algorithm and photographed in the mediastinal (window width, 350–240 H; level, 15–25 H) and lung windows (window width, 1500 H; level, –600 to –800 H).

The investigators independently assessed the pattern of the miliary lesions (classic miliary vs. non-classic miliary) on chest radiographs and the presence of miliary nodules (recognizable vs. non-recognizable) suggestive of MT on CT scans. A “classic” miliary pattern was defined as a collection of tiny discrete pulmonary opacities that were generally uniform in size and widespread in distribution, each of which measured ≤ 3 mm in diameter [2]. A “non-classic” miliary pattern was defined as the obscuring of background miliary nodules by diffuse GGO or the major findings characterized by an asymmetric nodular pattern, coalesced nodules, a mottled appearance, a snowstorm appearance, or air-space consolidation [2]. On chest CT, recognizable miliary nodules were defined when randomly distributed micro-nodules were well discernible on chest CT. By contrast, non-recognizable miliary nodules were defined when micro-nodules could not be clearly discernible on chest CT as the micro-nodules were superimposed on a background of other radiologic findings, such as GGO. However, patients in the latter group showed miliary nodules on short-term follow-up chest radiographs and/or CT scans taken after the other radiologic findings have resolved. The extent of GGO observed on chest CT was categorized as follows: 1) none; 2) less than one-quarter of the whole lung field; 3) less than one-half of the whole lung field but greater than one-quarter of the field; 4) greater than one-half of the whole lung field [7]. The zonal prominence (upper vs. even) of the nodules in size (when viewed along the cephalocaudal axis) was estimated by comparing the size of the miliary nodules at two levels of the chest CT scan: the upper end of the aortic arch and the lower end of the left atrium. Pre-existing active TB lesions, cavities, pleural effusion, nodules ≥ 4 mm in diameter, and mediastinal lymphadenopathy were comprehensively examined. A final decision on the findings was reached when the consensus of two observers was obtained (JL and JKL). A third observer (CHK) gave the final assessment if consensus could not be reached.

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