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Prognostic factors in patients with miliary tuberculosis

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ABSTRACT

Background and purpose: Acute respiratory distress syndrome (ARDS) complication has long been considered a factor associated with poor prognosis in patients with miliary tuberculosis. However, few reports exist on the prognostic factors of miliary tuberculosis including those complicating ARDS.

Subjects and methods: We retrospectively examined prognoses and other clinical information obtained from medical records of a total of 68 patients diagnosed with miliary tuberculosis. Clinical findings were compared between patients who died within three months (non-survivor group) and those who survived beyond three months (survivor group), and risk factors for death within three months of diagnosis were examined using logistic regression analysis.

Results: Fifteen of 68 patients diagnosed with miliary tuberculosis died within three months. Most patients were aged 60 years or older (63 patients; 91.2%), with a peak in the 80 s (32 patients; 47.1%). Of the 68 patients with miliary tuberculosis, 13 (19%) had ARDS. The risk of death within three months increased with increasing age and ARDS onset during the disease course. The results of multivariate analysis revealed that, in addition to age (odd ratio (OR): 15.5) and the presence/absence of ARDS (OR: 12.0), consciousness disturbance (OR: 81.53) and high BUN levels (OR: 5.71) were independent factors for death within three months.

Conclusion: In patients with miliary tuberculosis, old age, ARDS, consciousness disturbance, and high BUN levels were factors associated with poor prognosis.

1. Background

Miliary tuberculosis is a fatal disease caused by hematogenous dissemination of *Mycobacterium tuberculosis* infection. It is also a rare cause of acute respiratory distress syndrome (ARDS). In many cases, the prognosis of miliary tuberculosis can be improved by introducing effective anti-tuberculosis agents; however, elderly patients and patients with ARDS are likely to suffer a poor prognosis. Only a few reports have described ARDS associated with miliary tuberculosis, with mortality reported to be 33–100% [1–9]. Moreover, due to poor prognoses, few cases have been reported in which treatment was found to be effective in improving serious conditions [2–6, 10, 11]. Furthermore, in elderly patients with tuberculosis, older age is considered a risk of mortality, as it relates to decreased function of pulmonary epithelial cells, increased comorbidities, delay in diagnosis due to decreased cognitive ability of patients themselves as well as increased atypical symptoms, and progression of disease state [12]. Many reported studies to date are from high-prevalence countries, targeting relatively young subjects, and few studies have been conducted in elderly patients with tuberculosis. In recent years, a considerably high proportion of patients with tuberculosis in Japan have characteristically been older patients. In this study, we examined prognostic factors in a population of miliary tuberculosis patients including those with ARDS, which predominantly comprised elderly patients.

2. Methods

2.1. Patients

Over a period of 22 years (January 1, 1994–October 1, 2016), 2293 patients were hospitalized at the National Hospital Organization Omuta Hospital with the diagnosis of tuberculosis. Of these, 70 patients were

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diagnosed with miliary tuberculosis. Two patients who did not undergo chest CT were excluded from analysis. All patients who died due to tuberculosis did not survive beyond three months. Therefore, the remaining 68 patients were divided into those who survived longer than three months (survivor group: $n = 53$) and those who died within three months of diagnosis (non-survivor group: $n = 15$).

The following clinical information at hospitalization was collected from medical charts: age, sex, history of smoking, alcohol intake, underlying diseases, symptoms, performance status (PS), microbiological data (including the drug sensitivity pattern of *M. tuberculosis* isolates), PaO2/FiO2 ratio, laboratory findings, time from onset to admission, time from admission to anti-tuberculosis therapy, time from onset to anti-tuberculosis therapy, length of hospital stay, presence or absence of ARDS, and mechanical ventilation. Consciousness disturbance was defined as that with the Glasgow Coma Scale (GCS) of 12 or less.

2.2. Diagnosis of miliary tuberculosis

Miliary tuberculosis was diagnosed by one radiologist and two respiratory physicians, based on the observation of randomly distributed, uniformly sized diffuse bilateral nodules on chest CT. A definitive diagnosis of tuberculosis was made when at least one of the following three criteria was met: (1) positive acid-fast bacilli (AFB) smear and/or culture for *M. tuberculosis* from clinical specimens such as sputum, bronchial lavage fluid, pleural fluid, urine, and bone marrow aspirate; (2) histopathological identification of a tuberculosis granuloma in biopsied tissues of lung, pleura and/or bone marrow; or (3) clinical and radiological improvement after anti-tuberculosis treatment.

2.3. Diagnosis of ARDS

ARDS was diagnosed according to the Berlin definition of ARDS, based on chest x-ray and chest CT findings and the PaO2/FiO2 ratio after having excluded all differential diagnoses, such as heart failure, pneumonia, pulmonary haemorrhage, acute interstitial lung disease, and drug reactions [13].

2.4. Statistical analysis

Age, PS, platelets, CRP, ALP, total bilirubin, and number of days from hospitalization to the initiation of anti-tuberculosis treatment were comparatively examined between the case group (i.e., patients who died within three months of diagnosis) and the control group (i.e., survivors). Statistical tests were performed using the Wilcoxon rank sum (Mann–Whitney) test. With respect to white blood cell count, neutrophils, AST, ALT, LDH, BUN, creatinine, number of days from onset to hospitalization, and number of days from onset to the initiation of anti-tuberculosis treatment, geometric mean values were comparatively examined between the two groups. In the case of 0 days, logarithmic conversion was performed as 0.1 days.

Next, using the case-control study method, risk factors for death within three months of diagnosis were examined. Based on results from previous studies, old age and ARDS onset were suspected to be strongly associated with the risk of death within three months. Since the present study also yielded similar results (described in the following section), analyses of other associated factors were constantly adjusted for age and presence/absence of ARDS, and odds ratios for each factor were obtained using logistic regression analysis.

Furthermore, in order to assess which of the examined factors were strongly associated, clinically relevant factors with a p value < 0.1 in the analysis adjusted for presence/absence of ARDS were incorporated as the first explanatory variables, and thereafter, variables were selected using the stepwise method.

3. Results

3.1. Demographic data and clinical characteristics (Table 1)

The median age of the 68 patients with miliary tuberculosis (18 men and 50 women) was 83.0 years (range, 27–93 years). Most patients were aged 60 years or older (63/68; 91.2%), with a peak in the 80 s (32/68; 47.1%). Ten patients (15%) had a history of smoking, and 8 patients (12%) consumed alcohol. There were 102 underlying diseases in 57 patients: dementia (16), liver disease (8), diabetes (18), connective tissue disease with steroid treatment (9), renal disease (7), heart disease (15), cerebrovascular disease (12), aortic aneurysm (3), neuromuscular disease (3), and malignancy (11). Eight patients (11.8%) had a history of tuberculosis. Symptoms were fever (51/68, 75%), dyspnea (20/68, 29%), cough (19/68, 28%), sputum (14/68, 21%), loss of appetite (44/68, 65%), general malaise (45/68, 66%), consciousness disturbance (8/68, 12%) and lumbar pain (7/68, 10%). The median (range) PS was 3 (1–4). Of the 68 patients with miliary tuberculosis, 13 patients (19%) had ARDS; 11 patients had already developed ARDS at the time of first visit, and the other two developed ARDS during hospitalization.

3.2. Diagnostic findings

Among 26 patients showing only bilateral diffuse nodules on chest CT, 8 had pleural effusion (Fig. 1A). Among 29 patients showing partially fused nodules as well as infiltrations, in addition to bilateral diffuse nodules, 11 had pleural effusion (Fig. 1B). Among 13 patients who fell under the criteria for ARDS imaging diagnosis and showed ground-glass opacities / infiltrations in the entire lungs in addition to bilateral diffuse nodules, 3 had pleural effusion (Fig. 1C).

A definitive diagnosis of tuberculosis was made according to the above-mentioned criteria; 63 patients (93%) were ultimately verified to have *M. tuberculosis*. Of these, 49 had AFB smear-positive clinical specimens during hospitalization, 2 had positive sputum samples by PCR only, and 1 had PCR-positive sputum and bone marrow biopsy tissue showing epithelioid granulomas. Of the AFB smear positive patients, 42 had a positive–PCR for *M. tuberculosis* (MTb) initially. Another 7 patients had a negative–PCR for MTb in the initial investigation, but culture was subsequently positive. The remaining 11 patients had positive cultures during follow-up. In all cases, the presence of *M. tuberculosis* was verified using specimens form the respiratory system or respiratory samples (sputum, fluid from endotracheal tube suction, and bronchial lavage fluid). Moreover, 24 patients also had *M. tuberculosis* culture-positive extrapulmonary specimens (urine, 8; pleural effusion, 6; gastric effusion, 5; blood, 2; and scrotal pus, 12). Subsequently, three patients were confirmed to have tuberculosis by histopathological examination of biopsy tissue (transbronchial biopsy, 1; bone marrow biopsy, 2). As for the remaining two patients, clinical diagnosis was ultimately obtained; these patients had a fever of $\geq 38\,^{\circ}C$, and as antibiotics administered for ≥ 1 week were ineffective, they were referred to our hospital. At the initial visit, one showed only nodules on chest CT, and another showed infiltrations in addition to nodules. Both patients showed improvements in clinical course and imaging findings after treatment with anti-tuberculosis agents was initiated. Based on these courses, the two patients were diagnosed with miliary tuberculosis.

The drug susceptibility test was performed with 57 isolates of *M. tuberculosis*. Of these, 49 isolates (86%) were found to be susceptible to all anti-tuberculosis agents (isoniazid [H], rifampicin [R], ethambutol [E], pyrazinamide [Z], cycloserine, para-aminosalicylic acid [PAS], ethionamide, ofloxacin, streptomycin [S], kanamycin, and enviomycin). On the other hand, the remaining 8 strains (14%) were resistant to at least one agent (3 to H, 1 to S, 3 to E, and 1 to H and S).

The numbers of days from onset to hospitalization, from hospitalization to treatment, and from onset to treatment were 37 days (range,