Disseminated Mycobacteriosis in Patients with Severe Hematologic Disorders

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Abstract

During a 20-year period disseminated mycobacteriosis occurred in 11 (1.1%) of a total of 1006 patients with severe hematologic disorders, with the frequency remaining almost unchanged. The diagnosis in three patients (27%) was made only at autopsy. Tuberculosis accounted for 64% of all cases. Female preponderance was seen with a male-to-female ratio of 3:8. The major factors associated with dissemination included immunosuppression, weight loss, old age, and diabetes mellitus. Fever was the most common clinical symptom. Chest X-ray abnormalities, hypoproteinemia, liver dysfunction, and hypoxemia were noted in most cases. The prognosis of tuberculosis depended mainly on early diagnosis and treatment, while that for the nontuberculous variety was largely influenced by the underlying disease. Thus, our findings indicated that clinicians must suspect disseminated mycobacteriosis especially in any febrile patient with recent pulmonary pathology on chest X-ray, so that an adequate trial of therapy can be provided.

Introduction

Disseminated mycobacteriosis, although uncommon, remains a significant and life-threatening complication during the treatment of patients with hematologic malignancy\(^3\).\(^{\text{2}}\). Mycobacterial infections in this patient group are most likely to occur in disseminated forms\(^3\). The clinical features, however, resemble those of other frequent infectious complications as well as those found in the underlying disease\(^4,5\). Indeed, the diagnosis was in some cases made only at autopsy\(^6\). This report reviews our experience with 11 cases of disseminated mycobacteriosis in patients with severe hematologic disorders at Kanazawa University Hospital during the past two decades.

Patients and Methods

Patients Studied

We reviewed the case records of all patients with severe hematologic disorders who developed active mycobacteriosis at Kanazawa University Hospital during the years 1971–1990. The underlying diseases included aplastic anemia, acute leukemia, chronic leukemia, malignant lymphoma, multiple myeloma,
myelofibrosis, and malignant reticulosis.

**Diagnosis of Disseminated Mycobacteriosis**

Disseminated mycobacteriosis was defined as isolation of mycobacteria from one site together with culture evidence and/or demonstration of granulomas with or without positive stains for acid-fast bacilli from a second anatomically distinct site; a miliary pattern on the chest roentgenogram together with culture evidence from at least one site; or positive blood cultures together with clinical manifestations that could be produced by the circulating mycobacteria. The term “miliary” was used to describe disseminated disease with numerous small lesions up to twice the size of a millet-seed. Tuberculosis was regarded as disease caused by *Mycobacterium tuberculosis*, identified with a positive niacin test, while nontuberculous mycobacteriosis referred to disease caused by niacin-negative mycobacteria, which were differentiated using Simplified Identification Tests for Mycobacteria (Kyokuto, Tokyo).

**Results**

**Incidence of Disseminated Mycobacteriosis**

During the 20-year period, active mycobacteriosis was documented in 20 (2.0%) of a total of 1006 patients with severe hematologic disorders (Table 1). Disseminated infection occurred in 11 patients (55%)
(seven of the 15 with tuberculosis and four of the five with nontuberculous mycobacteriosis), giving an overall incidence of 1.1%. Tuberculosis accounted for 64% of all cases with dissemination.

There was a significant increase in the incidence of active mycobacteriosis during the 5-year period, 1986-1990 (12 of 341, or 3.5%), compared with the 15-year period, 1971-1985 (eight of 665, or 1.2%) ($X^2=5.07$, $p<0.05$ by chi square test with Yates' correction) (Table 2). The incidence of disseminated mycobacteriosis, however, was slightly but not significantly higher in the second period than in the first period (seven patients, or 2.1% vs. four patients, or 0.6%; $X^2=3.15$, $p<0.10$).

Female preponderance in disseminated mycobacteriosis was seen with a significantly higher incidence among females (three of 610, 0.5% vs. eight of 396, 2.0%; $X^2=3.87$, $p<0.05$).

The median age in the group with tuberculosis was 69 years, as compared with 48 years in the group with the nontuberculous variety, which coincided with the median age in the total population.

**Approach to Diagnosis**

Disseminated mycobacteriosis was diagnosed during life in eight (73%) of the 11 patients (tuberculosis and the nontuberculous variety in four each). All of them had antemortem culture evidence with or without chest X-ray abnormalities. Because of thrombocytopenia, biopsy of the lung and liver was performed in two patients, confirming recent granuloma formation with epithelioid cells. Bone marrow aspiration and biopsy were obtained from four patients, of whom three had culture and histopathologic evidence. On the other hand, miliary tuberculosis was diagnosed only at autopsy in three patients, who had been suspected of having *Pneumocystis carinii* pneumonia. In one patient, however, retrospective study revealed miliary mottling on chest X-ray. At autopsy, the bone marrow contained granulomas with positive stains for acid-fast bacilli in these patients.

**Mycobacterial isolates**

The mycobacteria isolated were *M. tuberculosis* (seven patients), *Mycobacterium avium* complex (two patients), and *Mycobacterium chelonae* and *Mycobacterium aurum* (one patient each). In seven of the eight patients diagnosed antemortem, the specimens yielding mycobacteria on culture were the sputum and/or gastric juice (six patients), and bone marrow (three patients), urine and bronchoalveolar lavage fluid (two patients each), and stool and pericardial effusion (one patient each). In the other patient with acute myelofibrosis who had a long-term intravenous catheter in place, conventional blood cultures yielded a rapidly growing *Mycobacterium* species, subsequently identified as *M. aurum* by courtesy of Drs. Hiroshi Murata and Michio Tsukamura, National Chubu Hospital, Obu. On the other hand, the three patients diagnosed postmortem had *M. tuberculosis* isolated from autopsy specimens (lung in two and hilar node in one).

Drug sensitivity testing showed *M. tuberculosis* (five isolates) and *M. aurum* (one isolate) to be sensitive to at least three of the commonly used agents including streptomycin, isoniazid, rifampicin, ethambutol and $\rho$-aminosalicylic acid, whereas *M. avium* complex (two isolates) and *M. chelonae* (one isolate) were resistant to these agents. Incidentally, the *M. aurum* isolate proved sensitive by disk to gentamicin and cefoperazone.

**Host Factors**

Nine patients (82%) received immunosuppressive therapy with at least one antitumor agent for hematologic malignancy or high-dose methylprednisolone for severe aplastic anemia during the two months prior to diagnosis. The other two patients (chronic myelogenous leukemia and acute myelofibrosis in one each) remained untreated until death because of disseminated nontuberculous mycobacteriosis discovered at the time of admission.

Seven patients (64%) had diabetes mellitus prior to the diagnosis (five with tuberculosis and two with the nontuberculous variety).
There was no history of tuberculosis or chronic pulmonary disease in the 11 patients studied in this series. A history of tuberculous contact was obtained from one patient with Hodgkin’s disease and miliary tuberculosis, whose mother suffered from pulmonary tuberculosis about 20 years previously.

**Presenting Clinical Features at the Time of diagnosis**

**Symptoms:** The complaints consisted mainly of systemic symptoms, such as malaise (eight patients), and anorexia (five patients), and respiratory symptoms such as cough (eight patients), sputum and dyspnea (six patients each), and hemoptysis and pleuritic chest pain (two patients each).

**Physical Findings:** Fever above 38.0°C was present in all the patients. Rales (seven patients), maculopapular rash (three patients), and jaundice and chorioretinitis (one patient each) were noted. On the other hand, hepatosplenomegaly (two patients), and lymphadenopathy (one patient) were explained largely by the underlying disease. The seven patients whose body weight was recorded once weekly showed a median

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**Table 3** Chest roentgenogram abnormalities in patients with disseminated mycobacteriosis

<table>
<thead>
<tr>
<th>Roentgenogram appearance</th>
<th>Mycobacteriosis, no. of patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tuberculous</td>
<td>Nontuberculous</td>
</tr>
<tr>
<td>Miliary motting</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Miliary + pulmonary</td>
<td>2†</td>
<td></td>
</tr>
<tr>
<td>Interstitial pneumonia</td>
<td>2‡</td>
<td>2</td>
</tr>
<tr>
<td>Simple pneumonia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1†</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

†Concurrent disease of the pleura was found in one patient.
‡The roentgenogram showed diffuse, bilateral reticulonodular infiltrates.
§Miliary tuberculosis was diagnosed at autopsy in both patients.
¶The patient had *M. aurum* bacteremia.

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**Fig. 1** Plain chest roentgenogram and computed tomographic scan of thorax showing miliary motting.

A 50-year-old man with acute promyelocytic leukemia in complete remission developed miliary *M. chelonae* infection with associated chorioretinitis. Culture of a bronchoalveolar lavage fluid grew the organism. Miliary motting in the chest roentgenogram (A) could be more clearly visualized by computed tomography (B).
weight loss of 5 kg (range, 1—9 kg) during the three months prior to diagnosis. None of the patients presented with signs of meningeal or peritoneal irritation.

Radiology: The chest roentgenogram showed miliary mottling in six patients (five with tuberculosis and one with the nontuberculous variety) (Table 3). Miliary M. chelonae disease occurred with chorioretinitis (Fig. 1).

Laboratory Tests: Both leukocyte and platelet counts were mostly governed by the underlying disease and/or its treatment. The median neutrophil count was 970/mm³ (range, 30—8550/mm³), while the median lymphocyte count was 330/mm³ (range, 30—1550/mm³). Monocytosis above 950/mm³ was noted in one patient. None of the patients showed coagulation abnormalities.

Hypoproteinemia below 6.0 g/dl was observed in seven patients (64%). Serum alkaline phosphatase and glutamic oxaloacetic transaminase determinations were elevated in eight patients (73%) each, but in most cases the elevations remained less than twofold above the normal range.

Blood-gas analysis performed in nine patients revealed a decrease in arterial oxygen tension (median, 69 mmHg; range, 51—81 mmHg) with an increased alveolar-arterial oxygen gradient (median, 33 mmHg; range, 22—50 mmHg). Pulmonary function tests done in four patients disclosed a decrease in the diffusing capacity for carbon monoxide to less than 50% of normal.

Tuberculin Test: The tuberculin test was performed in five patients (two with tuberculosis and three with the nontuberculous variety), all of whom had a history of positive results. Only one patient with severe aplastic anemia who developed M. avium complex infection was positive at the time of diagnosis. In one patient with non-Hodgkin’s lymphoma who recovered from miliary tuberculosis, however, the skin test converted to positive six months post-treatment, although antitumor therapy proved ineffective.

Treatment and Outcome

In the seven patients with disseminated tuberculosis the median survival after the diagnosis was made was 12 days (range, 0—233 days). Two of the three patients who received standard antituberculous therapy for more than two weeks survived more than two months. On the other hand, in the four patients with the nontuberculous variety the median survival after the diagnosis was made was 117 days (range, 72—232 days). Three patients with nonbacteremic infection received triple antituberculous therapy despite the in vitro multiple drug resistance of the isolates. The other patient with M. aurum bacteremia was treated with gentamicin and cefoperazone, resulting in defervescence prior to removal of the intravenous catheter.

Discussion

The present study revealed the current status of disseminated mycobacteriosis in patients with severe hematologic disorders in Japan. During the 20-year period the disease occurred in 1.1% of this patient population, with the frequency remaining almost unchanged.

As many as 55% of our patients with active mycobacteriosis developed disseminated disease, reflecting host defenses impaired mainly by the underlying disease and/or its treatment, weight loss, old age and diabetes mellitus. Depressed cellular immunity may play a major role in the Infectious process with dissemination. Indeed, a decreased tuberculin skin reaction was observed in this series.

Seventy-three percent of our patients with disseminated mycobacteriosis were over 50 years of age. Miliary tuberculosis tended to occur mostly in the aged in contrast with the nontuberculous variety in younger adults. M. tuberculosis is generally considered more pathogenic than nontuberculous mycobacteria. This paradox therefore remains to be elucidated.

Miliary M. chelonae disease with ocular lesions was noted in this series. Miliary dissemination has been considered pathognomonic of M. tuberculosis infection. Recent reports indicated, however, that
nontuberculous mycobacteriosis with miliary dissemination may be more frequent than originally believed. Tuberculosis is virtually impossible to differentiate histopathologically from nontuberculous mycobacteriosis\textsuperscript{10}. The isolation of mycobacteria is therefore essential to diagnose miliary disease.

Rapidly growing mycobacteria have recently been described as a cause of intravenous catheter-related bacteremia especially in patients with cancer\textsuperscript{13,14}. Such bacteremic infections have been in most cases successfully treated with antimicrobial agents including amikacin, gentamicin, cefoxitin, doxycycline, vancomycin, and sulfonamides\textsuperscript{13,14}. In our case of \textit{M. aurum} bacteremia the intravenous catheter was considered the most probable portal of entry. Furthermore, therapy with gentamicin and cefoperazone proved effective in producing defervescence prior to catheter removal. In this regard, Davison et al.\textsuperscript{14} reported that catheter removal is not necessarily required as long as appropriate therapy is given.

Disseminated mycobacteriosis may be easily overlooked in patients with severe hematologic disorders, not only because of the infrequency of the infection but also because of the similarity of its clinical features to those of the underlying disease or other frequent infectious complications\textsuperscript{2,4}. Furthermore, as indicated in the present study, the prognosis of miliary tuberculosis depends largely on early diagnosis and therapy, while that for the nontuberculous variety is, if anything, influenced by the underlying disease. In order to diagnose disseminated mycobacteriosis positively during life, therefore, clinicians must maintain a high index of suspicion especially for any febrile patient with recent abnormalities on chest X-ray. In this regard, bone marrow aspiration and biopsy may well be considered the most useful diagnostic methods\textsuperscript{4,12} that can be performed irrespective of thrombocytopenia.

References


重症血液疾患患者の播種性抗酸菌症

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要 旨

過去20年間に、重症血液疾患1,006例の11例（1.1％）に播種性抗酸菌症がみられた。この間の合併頻度にはほとんど変化がなかった。3例（27％）は剖検で诊断された。結核症が全体の64％を占めた。男女比は3：8で女性発症例が多かった。発症例の背景要因には、免疫抑制療法、体重減少、高齢、糖尿病が高頻度であった。発熱が最も頻度の高い症状であった。胸部写真の異常、低蛋白血症、肝機能障害、低酸素血症が多数例でみられた。播種性結核症の予後は概ね早期診断や治療と相関したが、非結核性抗酸菌症の予後は基礎疾患の経過に影響された。それで、重症血液疾患の発熱患者に胸部写真の異常をみたら播種性抗酸菌症を疑ってみることが適切な治療への鍵になる。