—Report on Experiments and Clinical Cases—

Autopsy Cases of Miliary Tuberculosis: Clinicopathologic Features Including Background Factors

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Abstract

To assist physicians, especially young physicians, in identifying tuberculosis (TB) infection before the terminal stage, we analyzed 7 cases of numerous tuberculous granulomas in multiple organs and compared clinical and autopsy findings between cases. Patients ranged in age from 41 to 86 years at the time of death. The main chief complaint was fever of unknown origin (3 of 7 cases [43%]). The main underlying conditions were liver cirrhosis (2 of 7 cases [29%]) and chronic renal failure (2 of 7 cases [29%]). Two patients (29%) had been given methylprednisolone pulse therapy for various lung disorders. Active TB was not diagnosed before autopsy in 4 of 7 (57%) patients. Calcified lesions indicative of old TB were present in 4 of 7 (57%) patients. Thus, miliary tuberculosis may represent a re-emergence of latent TB infection in these cases. Various histologic features of nonreactive exudative inflammation were seen, along with granulomas containing Langhans giant cells with or without caseous necrosis in hypervascular organs, such as the lung, liver, and bone marrow. Physicians should be mindful of the possibility of miliary TB when older patients with hepatorenal disease and a history of TB infection have undergone immunosuppressive treatment. Active tuberculous infection can depend on the presence of an underlying disease and immunocompromise.
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Key words: miliary tuberculosis, latent tuberculosis, autopsy, immunosuppressive therapy

Introduction

After World War II, mortality due to infection by the human tubercle bacillus *Mycobacterium tuberculosis* decreased rapidly in Japan, as in other industrialized nations[1]. However, aging of the population and the concomitant increase in intensive medical treatments, such as immunosuppressive therapies and chemotherapies, have increased the number of medically compromised patients, which in turn has affected the incidence of tuberculosis (TB)

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in Japan[1]. In addition, various disease states can lead to immunocompromise and increase the risk of TB infection[1]. Owing to a resurgence of TB, the Japanese Ministry of Health, Labour and Welfare declared a "state of emergency" in 1998 and issued an alert for TB so that further increases could be prevented[1–3].

Miliary TB, characterized by the appearance of minute tubercles on one or more organs, is an acute form of TB that results from widespread hematogenous dissemination of tubercle bacilli[2–4]. It is often fatal if not promptly treated. Miliary TB accounts for 1% to 2% of cases of tubercle bacillus infection, but the purified protein derivative tuberculin skin test is positive in only 36% of patients with miliary TB[5]. In addition, the miliary pattern is not always evident radiographically upon presentation of symptoms, and another underlying pulmonary disease may be present[6–8].

The QuantiFERON-TB Gold test (QFT-G, Cellestis Limited, Carnegie, Victoria, Australia) was introduced in Japan in 2005 as a new method for diagnosing latent or active *M. tuberculosis* infection[5,9]. The QFT-G test is based on the assay of interferon-γ released from lymphocytes in response to the TB-specific antigens CFP-10 and ESAT-6 and is unaffected by Bacillus Calmette-Guérin vaccination[5,9–11]. However, there is a question whether QFT-G is effective for older patients (>50 years), patients with human immunodeficiency virus infection, or patients who have undergone immunosuppressive therapy with such agents as methylprednisolone[5,10–12]. Thus, a definitive diagnosis is not always possible, except with autopsy[8]. Autopsy findings include multiple miliary nodules without pulmonary cavitation[4,13]. Histologic examination shows granulomas containing multinucleated giant cells (Langhans giant cells) with or without caseous necrosis and nonreactive exudative inflammations in hypervascular organs[13,14].

The early diagnosis or prevention of miliary TB as a secondary infection is critical to saving lives. To assist physicians in identifying TB infection before the terminal stage, we analyzed 7 autopsy cases of numerous tuberculous granulomas in multiple organs, i.e., miliary TB, and compared clinical and autopsy findings.

Patients and Methods

Our study involved 7 cases of numerous tuberculous granulomas in multiple organs which were diagnosed at autopsy from January 1997 through June 2010 at 3 hospitals affiliated with Showa University. The 7 cases represent 0.2% of all autopsies (n=2,985) performed at these hospitals during this time (Showa University Hospital, 1,666 autopsies; Fujigaoka Hospital, 1,009 autopsies; and Yokohama Northern Hospital, 310 autopsies). The patients (1 man and 6 women) ranged in age at the time of death from 41 to 86 years, with 5 older than 70 years (**Table 1**). The 2 youngest patients (both aged 41 years) and patient 4 (aged 86 years) were the only patients in whom TB had been diagnosed before death. One of 2 patients with meningitis was an immigrant.

All organs removed at autopsy were preserved in fixative and examined grossly. Microscopic sections were made from tissues obtained at autopsy and were reviewed histologically. The presence of numerous tuberculous granulomas corresponding to miliary TB was defined as macroscopic dissemination of millet seed-sized lesions in pulmonary areas and pathologic evidence of lesions with an active granulomatous reaction in at least 2 organs[2–4]. The 7 cases were examined clinicopathologically. Data were obtained from the patients' hospital records and from the autopsy reports[15,16]. Clinical data obtained comprised the following: initial chief complaint; laboratory values upon admission (white blood cell [WBC] count; C-reactive protein [CRP], serum albumin, and alkaline phosphatase levels); underlying disease; history of TB; and therapy[3]. Autopsy data comprised the following: organs with granulomas containing Langhans giant cells, presence of calcified lesions indicative of old TB, positivity for acid-fast bacilli by Ziehl-Neelsen staining, pathologic confirmation of disease, and cause of death.

The study was performed in accordance with a protocol approved by the Institutional Review Board of Showa University (No. 946) and the ethics

Table 1 Clinical characteristic of patients with miliary tuberculosis

Patient	Age (yrs)/ sex	Chief complaint	Underlying disease	Clinical diagnosis	Treatment	Laboratory values WBC/CRP/ALB/ALP
1	81/F	lumbar pain, slight fever	myocardial infarction, hypertension	interstitial pneumonia, myelitis	m-PSL (pulse)	4,390/5.10/(−)/(−)
2	86/F	slight fever, dyspnea	apoplexy, hepatitis C virus (+)	congestive heart failure, DIC	antibiotics	4,800/11.5/(−)/(−)
3	79/F	dyspnea	diabetes mellitus, chronic renal failure	anemia, lymphadenopathy	antibiotics	4,700/3.3/2.8/219
4	86/F	lumbar pain, anorexia	old TB, surgery for cervical carcinoma	TB (Gaffky 2)	anti-TB drug	6,160/5.23/2.9/258
5	78/M	fever	old TB, hypertension, gout	interstitial pneumonia	m-PSL (pulse) antibiotics	3,140/3.0/3.8/485
6	41/F	coma	liver dysfunction, hepatitis B virus (+)	meningitis, tuberculosis (Gaffky 1)	anti-TB drug	8,000/3.1/2.2/441
7	41/F	coma	Unknown, tuberculin skin test (−)	meningitis, TB (Gaffky 2)	anti-TB drug, PSL	22,600/4.5/4.3/339

WBC, white blood cell count (/mm3); CRP, C-reactive protein (mg/dL); ALB, albumin (mg/dL); ALP, alkaline phosphatase (mg/dL); M, male; F, female; m-PSL, methylprednisolone; TB, tuberculosis; PSL, prednisolone; DIC, disseminated intravascular coagulation; (+), positive; (−), not confirmed

Table 2 Autopsy findings in cases of miliary tuberculosis

Patient	Granulomas containing multinucleated giant cells	Old tuberculosis (calcification)	Bacteria by Ziehl-Neelsen	Underlying disease	Cause of death
1	lung, liver, spleen, kidney bone marrow, adrenal gland	(−)	(+)	liver cirrhosis	tuberculosis infection
2	lung, liver, spleen bone marrow, adrenal gland	(+) lymph node	(+)	benign renal sclerosis lung tumorlet	tuberculosis infection
3	lung, liver, spleen, bone marrow, lymph node	(−)	(+)	diabetic glomerulosclerosis, nephritis	tuberculosis infection
4	lung, liver, spleen, kidney, bone marrow, lymph node	(+) lung apex, pleura	(+)	fatty liver, chronic cholecysitis	tuberculosis infection
5	lung, liver, spleen, kidney, bone marrow, adrenal gland, heart, esophagus	(+) pleura	(+)	(−)	tuberculosis infection
6	lung, liver, spleen, kidney, adrenal gland, lymph node, meninges, brain, peritoneum	(−)	(−)	liver cirrhosis	tuberculosis infection
7	bone marrow, adrenal gland, lung, liver	(+) lymph node	(−)	paravertebral abscess	tuberculosis infection

guidelines of the Declaration of Helsinki (1975).

Results

Clinical characteristics of the 7 patients are shown in **Table 1**. The main chief complaints were fever of unknown origin (in 3 of 7 [43%] patients), cough or dyspnea (in 3 of 7 [43%] patients), and lumbar pain (in 2 of 7 [29%] patients). Two patients (28.6%) presented with TB meningitis-induced coma. The WBC counts were greater than 10,000 cells/mm^3 in all cases but 1 (patient 7). Levels of CRP were <10 mg/dL in all cases but 1 (patient 2), and albumin levels were low (<3.0 mg/dL) in all cases but 2 (patients 5 and 7). There was no marked alkaline phosphatase elevation in all patients. Underlying diseases included liver dysfunction (in 2 of 7 patients [29%]), associated autoimmune disease (in 2 of 7

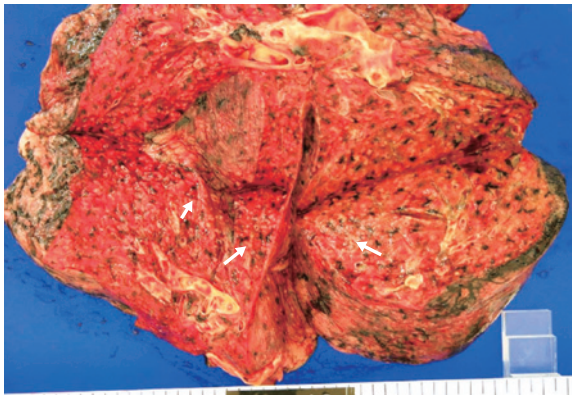

Fig. 1 Macroscopic appearance of miliary tuberculosis at autopsy. Cut section of the lung shows yellowish lesions 1 to 2 mm in diameter **(arrows)** which resemble millet or rice seeds (case 4).

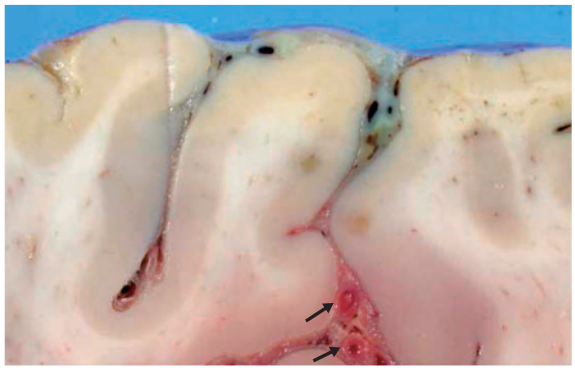

Fig. 2 Cut section of the brain shows diffuse white lesions and swelling of blood vessels **(arrows)** around the subarachnoid area, indicative of meningoencephalitis with vasculitis (case 6).

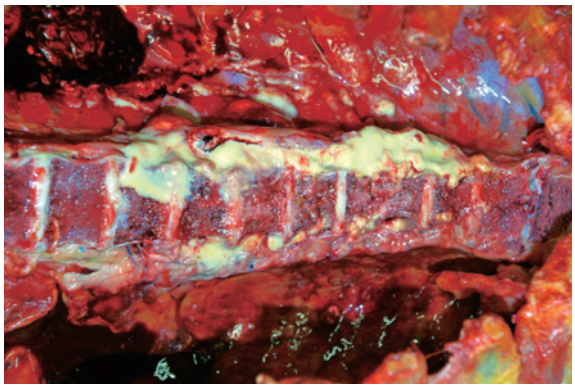

Fig. 3 Macroscopic appearance of the vertebrae at autopsy in a case of tuberculosis meningitis. Numerous yellowish paravertebral abscesses are seen (case 7).

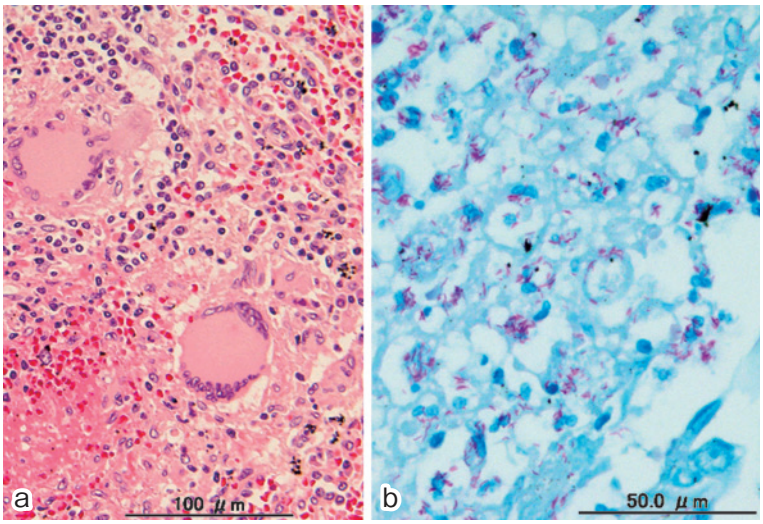

Fig. 4 Histologic details (case 4).

a. Granulomas containing multinucleated (Langhans) giant cells are present in the splenic area.

b. Ziehl-Neelsen acid-fast staining reveals numerous red bacilli in the pulmonary area.

patients [29%]), and chronic renal failure (in 2 of 7 patients [29%]). Two of 7 (29%) patients had a confirmed history of TB infection or radiologic evidence of old TB. Two (29%) of the patients had been treated with methylprednisolone pulse therapy for interstitial pneumonia or radiologic indications of interstitial lung disease. Prednisolone was used to relieve brain edema in 1 of the 2 patients in whom TB meningitis was diagnosed (patient 7). The 2 patients with TB meningitis were treated with anti-TB drugs, and a third patient (patient 4) was also treated with anti-TB drugs, but only 1 day before death. In cases 1 and 7, computed tomography of the chest had been performed just before death. However, the typical findings of multiple irregular and nodular pulmonary vessels corresponding to miliary TB were not present. Four of 7 (57%) patients were treated with antibiotics for an elevated WBC count and CRP level. The QFT-G test had been performed in 1 case and was positive (patient 7). The QFT-G test was not performed in other cases because it had not been introduced in Japan before 2004.

Autopsy findings are shown in **Table 2**. Active TB was not diagnosed in 4 of 7 (57%) patients before autopsy. *M. tuberculosis* was detected in the sputum of the other 3 (43%) patients before death. Postmortem examination included thoracotomy and ventrotomy in all cases. Craniotomy was also performed in cases 6 and 7. On macroscopic examination, lesions the size of millet seeds (1–2 mm) (**Fig. 1**, arrows) were seen on cut sections of the lung (**Fig. 1**), liver, and spleen. These were sometimes accompanied by caseating necrosis. Lymph node swelling was seen in some cases.

Diffuse distribution of hemorrhagic subarachnoid to subcortical lesions with edematous enlargement of blood vessels was observed (**Fig. 2**). Also, a muddy yellow subvertebral abscess was seen in case 7 (**Fig. 3**).

Calcified lesions indicative of old TB were found in 4 of 7 (57%) patients. In 1 of these patients, a calcified lesion was found at the pulmonary apex, and involvement of the hilar lymph nodes or pleura was seen in 3 cases. Various histologic features of nonreactive exudative inflammation were seen, and granulomas with Langhans giant cells containing nuclei in a horseshoe-like arrangement were seen both with and without caseous necrosis (**Fig. 4a**) in hypervascular organs or tissues, such as the lung and liver, in 100% of cases, the spleen in 86%, bone marrow in 86%, the kidneys in 57%, lymph nodes in 43%, the adrenal glands in 71%, the brain in 14%, the heart in 14%, and the esophagus in 14%. The bacillus was confirmed in 71% of cases by Ziehl-Neelsen staining (**Fig. 4b**). Underlying diseases were liver cirrhosis in 29%, and chronic renal failure in 29%. Causes of death were TB infection in all cases. Although no granulomas containing Langhans giant cells were observed in the subarachnoid or subcortical area in case 7, TB meningitis was diagnosed because results a polymerase chain reaction test of the cerebrospinal fluid were positive for *M. tuberculosis*.

Discussion

Although fever of unknown origin was generally an important symptom in this miliary patient series[17], it was difficult for the clinicians to make a correct diagnosis because the fever was thought to have originated not from active TB but from the patients' underlying diseases[8]. In our present autopsy series of numerous tuberculous granulomas in multiple organs, calcified lesions indicative of old TB were found in 57% of patients, indicating a re-emergence of latent TB infection[13]. It is prudent for clinicians to screen seriously ill patients for latent TB before pursuing immunosuppressive therapy or chemotherapy to prevent secondary TB infection[17]. Of particular note in the autopsy series was the predominance of female patients. Although we do not know the specific reason(s) for the unbalanced sex ratio, we suspect that it is due to the number of women with autoimmune disease treated by immunosuppressive drugs. Miliary TB is characterized by caseous necrosis or nonreactive exudative inflammation. When a patient with a history of TB has been treated with methylprednisolone, mature neutrophils already present in the bone marrow are released into the peripheral blood, where they compensate for the

depletion of T-cell function to produce nonreactive exudative inflammation (abscess)[13,14]. These changes portend an impaired immune response to the TB infection, leading to rapidly progressive dissemination of tubercle bacilli into the circulation. Liver cirrhosis or chronic renal failure could be an important factor in early dissemination because macrophage depletion in patients with hepatorenal disease is associated with decreased activity of the reticuloendothelial system[18]. A depressed host defense system and rapid bacillus dissemination impede the characteristic histologic anti-TB reaction[1].

In our autopsy series, granulomas containing Langhans giant cells were confirmed in the lung in 100% of cases, the liver in 100% of cases, and bone marrow in 86% of cases, regardless of age or treatment type. Kinoshita *et al.*[19] and Escobedo-Jaimes *et al.*[20] have reported that bone marrow biopsy or smear is useful for diagnosing miliary TB because bone marrow biopsy of the superior iliac spine does not depend on the patient's breath-holding ability or the need for administration of coagulation factors (as in liver biopsy)[21,22]. The fact that active TB was not diagnosed in 57% of our patients before autopsy points to the need for physicians to have a basic understanding of the likelihood of miliary TB. Educating young physicians to suspect TB is important; a delay in diagnosis of miliary TB can be fatal[15]. There are many reports of TB infection. However, the majority of diagnoses have depended on statistical or molecular analysis, which is not practical for most physicians. There are few reports of the general pathologic features of numerous granulomas in multiple organs, i.e., of miliary TB.

In conclusion, because it is a life-threatening disease in compromised hosts, miliary TB should be considered in seriously ill patients with an underlying disease, such as liver cirrhosis and chronic renal failure, particularly in older patients (>70 years) with a history of TB who have undergone immunosuppressive therapy.

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