Autopsy Case Reports

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Sudden death caused by pulmonary fat embolism in a patient with miliary tuberculosis

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ABSTRACT

An 84-year-old Japanese woman with myelodysplastic syndrome was admitted with pyrexia and dyspnea, but died suddenly during diagnostic evaluation. The autopsy revealed miliary tuberculosis in addition to myelodysplastic syndrome in the bone marrow. The immediate cause of the patient's sudden death was pulmonary fat embolism derived from bone marrow necrosis. This case shows that the infiltration of the myelodysplastic bone marrow by tuberculosis and consequent bone marrow necrosis and fat embolism can be the cause of sudden death. In this article, we report the autopsy results of this unusual cause of sudden death, and discuss tuberculosis-related sudden death with a review of the literature.

Keywords: Tuberculosis; Death, Sudden; Bone Marrow; Necrosis; Embolism, Fat; Autopsy

CASE REPORT

An 84-year-old Japanese woman was admitted with the history of fever (axillary temperature: 38.5°C) and dyspnea. As the patient presented leukocyturia, a urinary tract infection was the working diagnosis. Her past medical history included the diagnosis of diabetes mellitus, and myelodysplastic syndrome (MDS), refractory anemia with excess of blasts in transformation (RAEB-t) diagnosed 5 months ago, and humeral and pelvic fractures that occurred 5 and 4 months ago, respectively. She had been started on cyclosporine (100 mg/day) in addition to receiving blood transfusions after the diagnosis of MDS. The initial laboratory work-up is shown in Table 1. Despite the intravenous treatment with cefmetazole (2 g/day) for 7 days, the fever did not subside. She was found to have some hepatic nodules, up to 15 mm. On the thoracic computed tomography, bilateral pleural effusion and mediastinal lymphadenopathy were detected. Also, the polymerase chain reaction (PCR) of her sputum was positive for *Mycobacterium tuberculosis*, and the diagnosis of tuberculosis (TB) was made. Anti-tuberculous therapy was not started because she suddenly died soon after the diagnosis was made on the 14th hospital day. Immediate antemortem (about 1 hour before death), she was able to talk and eat as usual. However, she developed sinus tachycardia at a rate of 140 beats per minute, followed by ventricular fibrillation, and collapsed. Cardiopulmonary resuscitation was not performed in accordance with the patient's and family's wishes. An autopsy was carried out 90 minutes after death.

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Table 1. Laboratory data on admission

Analyte	Result	NR	Analyte	Result	NR
Leukocyte	3,600 /µL	(3,500-9,000)	Sodium	122 mEq/L	(135-145)
Hemoglobin	9.8 g/dL	(11.5-15.5)	Potassium	4.3 mEq/L	(3.6-4.8)
Hematocrit	24.9 %	(34.0-46.0)	TP	5.8 g/dL	(6.5-8.0)
MCV	112 fL	(83-100)	TB	2.6 mg/dL	(0.4-1.3)
MCH	36.2 pg	(28-34)	CK	18 U/L	(50-170)
MCHC	32.4 g/dL	(32-36)	AST	15 U/L	(10-35)
Platelet	59x10^3 /µL	(150-380x10^3)	ALT	13 U/L	(5-40)
Creatinine	0.45 mg/dL	(0.4-0.8)	LDH	397 U/L	(120-220)
Urea	22 mg/dL	(8.0-20.0)	Chloride	86 mEq/L	(99-107)
Glucose	245 mg/dL	(80-110)	Calcium	8.0 mEq/L	(8.5-10.2)
CRP	16.3 mg/dL	(0-0.35)			

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CK = creatine kinase; CRP = C-reactive protein; LDH = Lactate dehydrogenase; MCH = Mean corpuscular hemoglobin; MCHC = Mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; NR = normal range; TB = Total Bilirubin; TP= Total protein.

AUTOPSY FINDINGS

The liver weighed 790 g (reference range [RR]: 345–1250 g); at the cut surface, scattered yellowish, well-demarcated nodules, measuring up to 15 mm in diameter, were found (Figure 1). Some other larger lesions were also apparent and represented the confluence of the small nodules. Similar nodules, measuring up to 7 mm, were also found in (i) the left and right lungs, which weighed 180 g (RR: 85–500 g) and 210 g (RR: 100–620 g), respectively; (ii) the spleen (weighing 70 g, RR: 70–195 g); (iii) lymph nodes, and (iv) bone marrow.

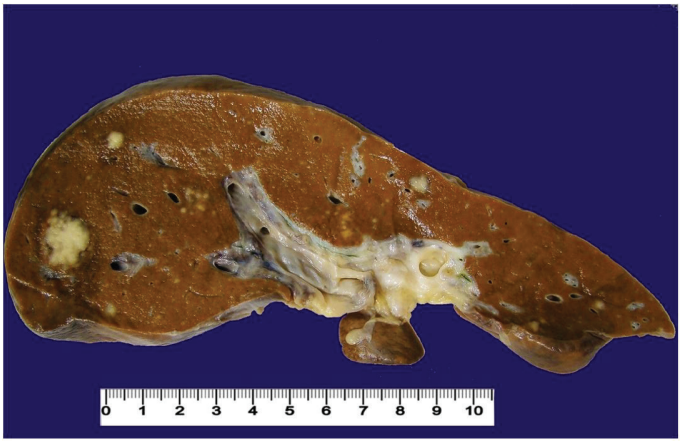

Figure 1. Gross appearance of the cut section of the liver showing some scattered yellowish, well-defined tiny nodules and others of larger size representing their confluence.

Microscopically, the nodules mentioned above were characterized by necrosis, but no Langhans giant cells were identified (Figures 2A, 3B, 5A). Epithelioid cell granuloma was not readily apparent, and the necrosis was surrounded by normal parenchymal cells with mild lymphocytic infiltration (Figure 2A). Ziehl–Neelsen staining revealed the presence of a few acid-fast bacilli (Figures 2B, 4B, 5B). These pathological findings, together with the result of PCR performed antemortem, led to the diagnosis of miliary TB.

Apart from the miliary TB, the bone marrow of the sternum, ribs, and spinal bones showed many blast cells with small megakaryocytes, with hypolobulated nuclei being occasionally identified (Figure 3A). In addition, fat necrosis was observed in many bones (Figure 4B). In a vein near the left rib, a bone marrow embolism was confirmed. In the lungs, widespread pulmonary fat embolisms (PFEs) were evident in the small arteries, arterioles, and capillaries of the interalveolar septa (Figures 5C, 5D, 6). The heart weighed 260 g (RR: 150–480 g), and the gross examination was unremarkable except for left ventricular hypertrophy (20 mm thickness).

Except for PFE, there were no lesions that could have accounted for the patient's sudden death (SD), such as myocardial infarction, myocarditis, or aortic dissection. Therefore, we concluded that the patient died of PFE.

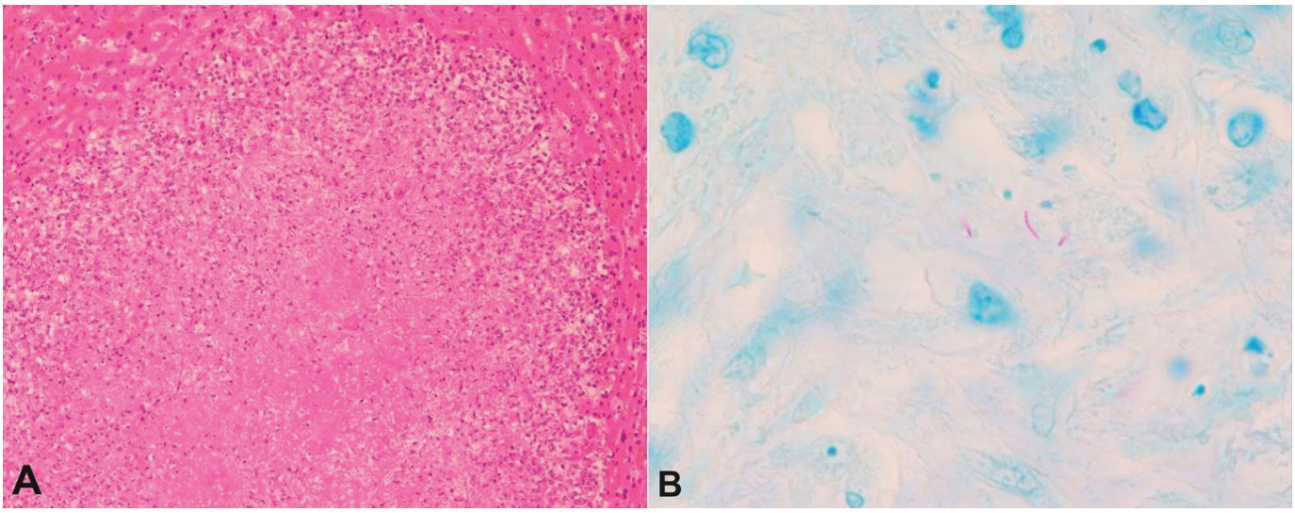

Figure 2. Photomicrographs of the liver. **A –** Necrosis associated with mild lymphocytic infiltration. Note that the epithelioid cells are not readily apparent and Langhans giant cells are absent. The necrosis is surrounded by normal parenchymal liver cells (H&E, 100X). **B –** Ziehl–Neelsen staining demonstrates acid-fast bacilli (1000X).

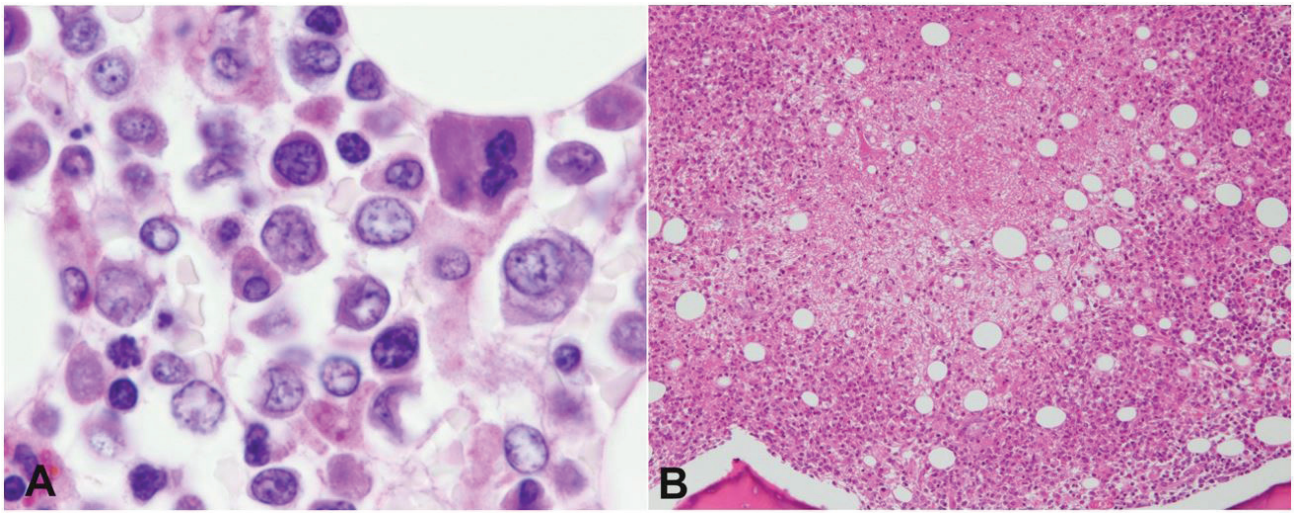

Figure 3. Photomicrographs of the bone marrow. **A –** Hypercellular bone marrow with many blast cells. A hypolobulated micromegakaryocyte is observed (H&E, 1000X), **B –** Necrosis is apparent in the bone marrow (H&E, 100X).

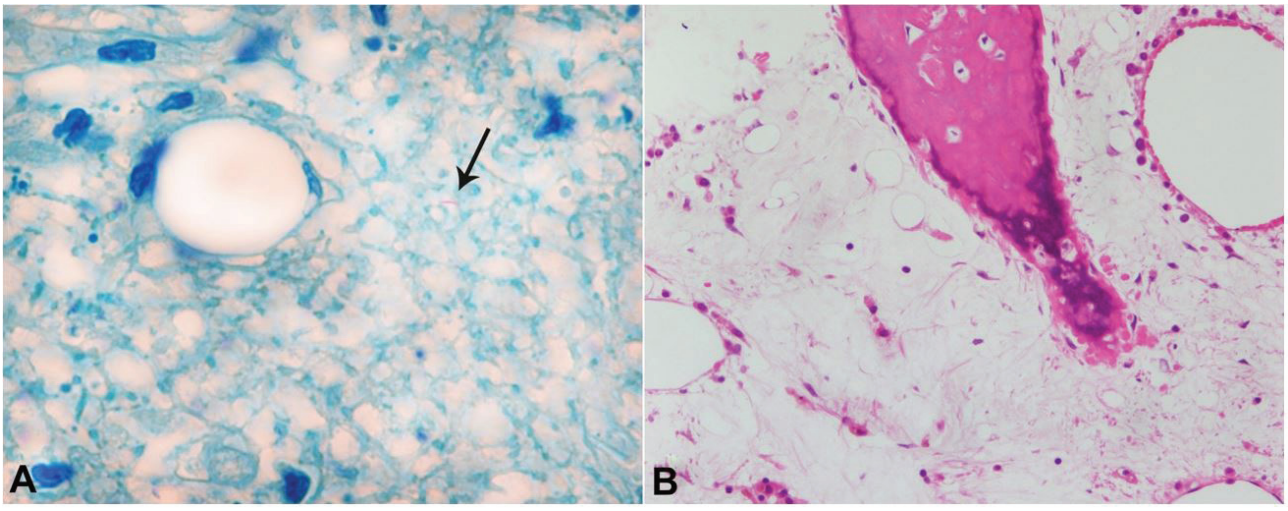

Figure 4. Photomicrographs of the bone marrow. **A –** Note an acid-fast bacillus (arrow) demonstrated by Ziehl-Neelsen staining (1000X), **B –** Necrotic adipose tissue is evident around bone trabecula (H&E, 200X).

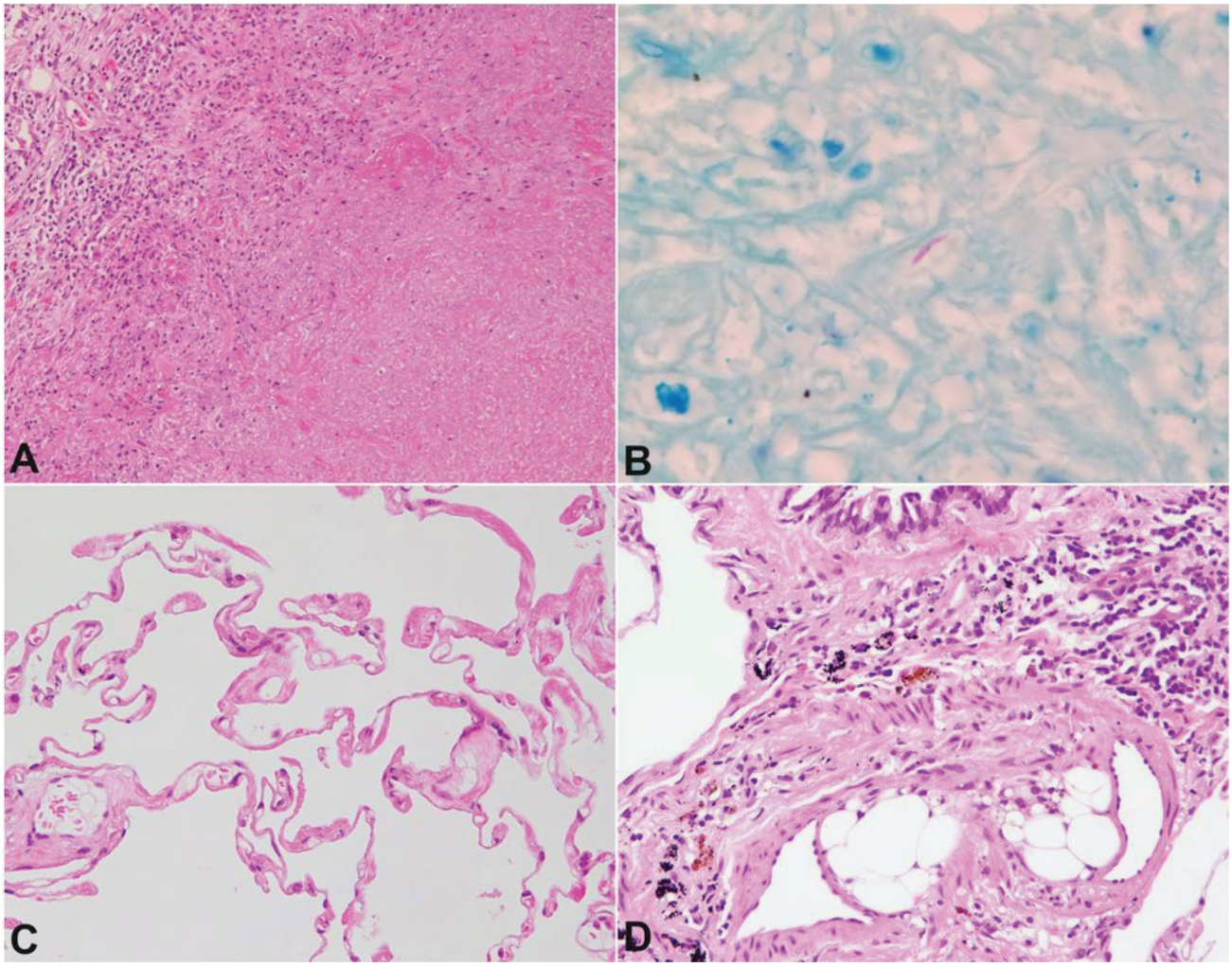

Figure 5. Photomicrographs of the lung. **A –** Necrosis is evident with mild lymphocytic infiltration. Note that features of epithelioid cell granuloma are not readily apparent and Langhans giant cells are lacking (H&E, 100X). **B –** An acid-fast bacillus demonstrated by Ziehl–Neelsen staining (1000X). **C –** Pulmonary fat embolism: Rounded clear vacuoles are apparent within the small pulmonary arterial branches and capillaries of the interalveolar septa (H&E, 200X). **D –** A cluster of fat cells within the small pulmonary artery (H&E, 200X).

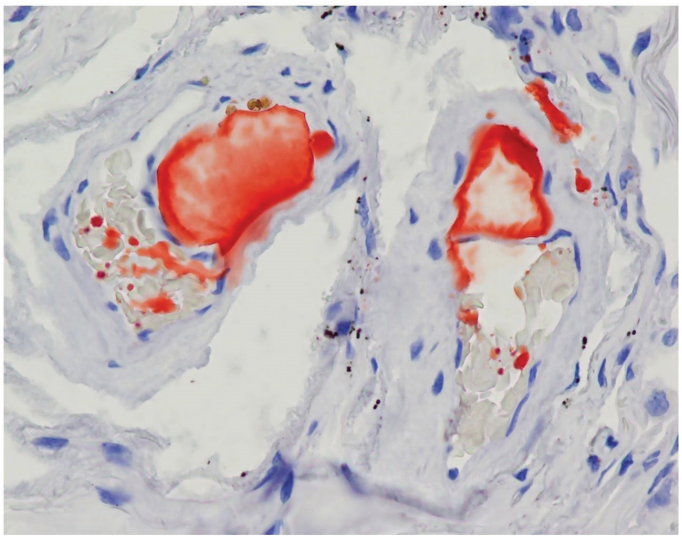

Figure 6. Photomicrograph of the lung. Oil red-O staining demonstrates the fat globules within the pulmonary arterioles (400X).

DISCUSSION

TB, a potentially fatal contagious disease, which is caused by *M. tuberculosis*, can affect virtually any part of the body, but is mainly an infection of the lungs. Immunocompromised individuals—mostly those with cell-mediated immunity—are extremely susceptible. After the primary infection, the tubercle bacilli entrapped in the granulomatous foci can live in a state of microbial persistence for the individual's lifetime. Any factor that disturbs the host immunity may cause endogenous reinfection. Miliary TB stands for the lymphohematogenous spread of the bacilli from the primary foci. In our case, the patient suffered from MDS and diabetes mellitus. In addition, cyclosporine therapy, which induces immunosuppression by means

of impairing T-cell function, must have decreased her cell-mediated immunological competence. As a consequence, a more severe and disseminated form of TB occurred. Indeed, in our case, necrosis was apparent but epithelioid cell granuloma was not readily apparent and Langhans giant cells were absent. The necrosis was surrounded by normal parenchymal cells. Although tubercle bacilli were not numerous, the histopathological features were similar to the histology of "non-reactive TB,"[1] directly reflecting the immunological unresponsiveness of the host. This type of TB is always found in the liver, spleen, and bone marrow.[1]

In the present case, the immediate cause of SD was PFE, which most often follows blunt trauma, such as bone fracture, along with many other causes including severe burns, liposuction, acute pancreatitis, alcoholic fatty liver, sickle cell disease, and panniculitis.[2-6] Bone marrow necrosis (BMN) is another etiology of PFE and is well known to be frequently associated with hematological disorders, such as sickle cell disease, lymphoma, leukemia, and MDS.[5-9] Occasionally, miliary TB can be responsible for BMN.[8-11] The exact pathophysiologic mechanism that causes PFE is unknown. Two theories have been proposed.[2,3] One is the so-called "mechanical theory," according to which large fat droplets are released into the venous system. These droplets accumulate as deposits in the pulmonary capillary beds. Microvascular lodging of droplets further produces local ischemia and inflammation, with concomitant release of inflammatory mediators, platelet aggregation, and vasoactive amines. The other hypothesis, the "biochemical theory," holds that hormonal changes caused by trauma and/or sepsis induce a systemic release of free fatty acids as chylomicrons. Acute-phase reactants, such as C-reactive protein, cause chylomicrons to coalesce and create the physiologic reactions described above. The biochemical theory helps explain non-traumatic forms of PFE. In the present case, the patient suffered from bone fractures, but that was a long time ago before death; moreover, the bone marrow embolism was confirmed near the rib. Additionally, our patient was not submitted to cardiopulmonary resuscitation and therefore no embolic event was elicited by the sternal compression. Thus, we concluded that the PFE was derived from BMN, but not from previous bone fractures. In addition to MDS as a predisposition factor for BMN, we suspect that the miliary TB must have exerted an accelerating effect. BMN and consequent PFE[12] should be recognized as a lethal complication in patients with miliary TB.

Left untreated, TB runs a chronic debilitating course, with cachexia and wasting similar to metastatic cancer, and rarely causes SD. Most physicians do not regard it as a principal cause of SD.[13] However, like our case, some affected patients die suddenly.[14-16] In order to better understand the pathophysiology of tuberculosis-related sudden death (TBRSD), we reviewed the literature and considered probable mechanisms of TBRSD.

TB has a predilection for the pulmonary system, and autopsy studies dealing with TBRSD have indicated that pulmonary TB was the principal lesion in the majority of victims.[14,15] Postmortem examination has revealed miscellaneous pathological findings in lungs, such as tuberculoma, necrotic cavities, miliary TB, abscesses, pneumonia, bronchiectasis, hemorrhage, airway compression, mucoid impaction, pulmonary edema, and pleural adhesions.[13,15,17-22] In many TBRSD cases, respiratory failure is the common pathway leading to death, which has been often demonstrated by extensive pulmonary tissue damage on postmortem examination.[23] The symbiotic relationship between the lungs and the heart means the failure of one leads to the downfall of the other. Thus, in many pulmonary TB patients, respiratory failure leads to cardiac failure; this is the accepted final endpoint leading to death.[23] Alkhuja and Miller[16] reviewed the literature on TBRSD and summarized that the majority of TB patients died from bronchopneumonia (64%) and that massive hemoptysis was the second leading cause (30%). Pulmonary hemorrhage and consequent hemoptysis are the most dramatic clinical presentations in pulmonary TB.[21] Even though a pulmonary lesion is small and localized, hemorrhage can cause SD by hypovolemic shock after profuse bleeding, or by asphyxiation due to hemoaspiration.[18,21,22] Even a small amount of blood can obstruct the airway. A variety of TB presentations with pulmonary hemorrhage are known, such as bronchiectasis, abscesses, scar carcinoma in old TB, the formation of mycetoma in the tuberculous cavity, the rupture of blood vessels inside a tubercular cavity, and fistulas between a major airway and a vessel.[21] Rasmussen's aneurysm—

an inflammatory pseudo-aneurysmal dilatation of a branch of bronchial or pulmonary artery adjacent to a tubercular cavity—is reported to be associated with 5% of tuberculous cavity lesions,[24] and can rupture, leading to massive hemoptysis and SD.[25] Pulmonary TB is often associated with mediastinal lymph node involvement. Such pulmonary and mediastinal TB may extend to the surrounding structures, such as the heart and aorta, and consequently induce lethal complications, as discussed below.

Although its incidence is very low, extrapulmonary TB also can account for SD.[16] In this context, the heart is the most important organ.[23,26] Most patients with cardiac TB are asymptomatic before death, and antemortem diagnosis is extremely rare.[26-31] Cardiac TB is usually secondary to lesions elsewhere in the body. The heart may be involved as (i) a direct extension from intrathoracic lesions; (ii) retrograde lymphatic spread through cardiac lymphatics; and (iii) hematogenous infiltration.[26] Although the pericardium is most commonly involved and myocardial involvement is rare,[23] TB myocarditis is a factor in the majority of TB-related sudden cardiac deaths.[23,26,32-38] The mechanism of SD in TB myocarditis has been hypothesized to be ventricular tachyarrhythmias,[23,26,32-34,37,38] although direct records of ventricular arrhythmia are lacking.[23,26,30,39] When the pericardium is affected by TB, pericarditis and/or cardiac tamponade may develop, and they could be a cause of SD.[31] TB involving the endocardium is extremely rare,[35,40] and SD resulting from endocardial TB has not been reported so far. Once the endocardium is affected, a pedunculated tuberculoma and/or intracavitary mass may develop.[29,40] These mass lesions within a cardiac chamber present an obvious risk for SD because they can cause outflow or inflow obstruction.[29] Also, pulmonary and/or systemic embolization resulting from an intracardiac tuberculous lesion[41] may be responsible for SD. It is very rare for coronary arteries to be affected by TB,[40,41] and subsequent myocardial ischemia accounts for SD. Rodríguez et al.[42] reported the case of a 21-year-old man who suddenly died while playing basketball. His autopsy revealed that the coronary artery was involved by tuberculous granuloma, and showed luminal stenosis. Chow et al.[43] described a TBRSD case of a 12-year-old girl showing coronary ostial obstruction originating from tuberculous aortitis. In addition to the aforementioned cardiac involvement, TB also may be associated with ventricular aneurysm, cardiac rupture, impaired myocardial contractility, dilated cardiomyopathy, congestive heart failure, long QT syndrome, and complete heart block.[26-28,33,39,41,44,45] These cardiac complications should be kept in mind as a probable cause of TBRSD.

Acute blood loss resulting from extrapulmonary TB is another etiology of SD. Vessels affected by TB become fragile and prone to rupture. Both thoracic and abdominal aorta are susceptible to tuberculous involvement. Contiguous invasion from neighboring structures, such as mediastinal lymph nodes, is often observed. Rarely, hematogenous spread (miliary TB) may also occur. Aortic TB is associated with aortitis, aneurysms, dissection, and fistulas with neighboring organs, such as the esophagus.[46-50] These aortic lesions may be responsible for aortic rupture and massive exsanguination, by presenting as hematemesis, hemoptysis, hemothorax, hemoperitoneum, and alimentary tract bleeding (e.g. aorto-esophageal fistula).[48-50] Tuberculous aneurysms of splanchnic and peripheral arteries are also predisposed to massive exsanguination. Tuberculous aneurysms of renal, brachiocephalic, femoral, common iliac, and hepatic arteries have been reported.[51] Beeresha et al.[52] described a 13-year-old boy presenting with SD due to massive intraperitoneal bleeding, in whom the cause of death was an aneurysm rupture of the hepatic artery of tuberculous etiology. Splenic rupture due to splenic TB also has been reported as a cause of hemoperitoneum.[53]

The central nervous system is critical, and any lesions causing rapid functional deterioration of vital foci, such as the brain stem, which controls circulatory or respiratory function, may be responsible for SD. Brain stem tuberculoma[54,55] may be an example of such a condition. Brain TB including tuberculous meningitis can become an underlying pathology of increased intracranial pressure, acute hydrocephalus, brain edema, and epilepsy.[56-58] These neurological disorders are known to be associated with SD.[59] To the best of our knowledge, there has been no case report dealing with brain TB-induced SD, but brain TB may be included in the list of probable causes of TBRSD.[60]

Apart from TB of the critical organs as mentioned above, TB of other sites also can cause SD indirectly by miscellaneous types of pathophysiology. As presented in this manuscript, TB-induced BMN and consequent PFE is just one example. Also, pancytopenia due to BMN is considered to be a risky condition for SD.[10,61] TB of adrenal glands is one of the etiologies

of adrenal insufficiency (Addison disease), which may be responsible for SD. An autopsy case of SD due to adrenal tuberculosis has been reported.[62] Hugar et al.[63] described an SD case due to pathological asphyxia as a result of upper airway obstruction by retropharyngeal abscesses secondary to tuberculous vertebral osteomyelitis (Pott's disease). Hemophagocytic syndrome, with many severe clinical manifestations, such as cytopenia, splenomegaly, and cytokine-mediated multiorgan dysfunction, is fatal unless treated.[64,65] Lam et al.[66] reported a TBRSD case of a 42-year-old man who presented with hemophagocytic syndrome and splenic rupture.

To briefly summarize TBRSD, its causes can be divided into two categories: pulmonary TB and extrapulmonary TB. The former is frequent and SD may be caused by respiratory failure due to bronchopneumonia, pulmonary hemorrhage, and hemoptysis. The latter is rare but includes miscellaneous changes that induce rapid deterioration of the circulation and/or respiration. TB can occur in any part of the human body, and affected organs may be structurally destroyed and physiologically impaired. Therefore, there must be a large spectrum of causes of TBRSD, presumably including examples that have not been reported so far in the literature.

The TB endemic is still a global feature and its spread in the past 3 decades has been facilitated by the acquired immunodeficiency syndrome pandemic and increased drug resistance.[16] International travel and migration may increase the incidence of TB in industrialized countries. The presence of people with TB—especially with far-advanced active caseating and cavitating pulmonary TB—constitutes a public health hazard.[13,18] Therefore, prompt and proper diagnosis is important when patients suffer from or die from TB.[67,68] Especially, in the case of TBRSD, the precise diagnosis is essential through postmortem examination.[18-20,34,36] From the viewpoint of both clinical practice and public health, the accumulation of relevant cases and the analyses of pathophysiology are necessary for a greater understanding of TBRSD.

CONCLUSION

We report the autopsy case presenting as SD due to TB-induced PFE and discuss TBRSD with a review of the literature. Since causes of TBRSD are miscellaneous, the accumulation of studies on TBRSD is necessary for better clinical practice and public health.

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