A case of disseminated tuberculosis after the initiation of hemodialysis

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Abstract A 67-year-old man with diabetes mellitus, chronic kidney disease, chronic heart failure, and amputation of the left lower limb was admitted to our hospital with decreasing renal function. On admission, he was started on hemodialysis. He simultaneously developed a urinary tract infection, infected necrotic wound of the right lower limb, and pneumonia, and was treated with broad-spectrum antibiotics. Although his general condition improved, fever and anorexia persisted and jaundice worsened. He died 138 days after admission. Autopsy revealed granulomas in the lungs, liver, and spleen. Cultures revealed *Mycobacterium tuberculosis*, leading to the diagnosis of disseminated tuberculosis.

Keywords Disseminated tuberculosis · Extrapulmonary · Hemodialysis · End-stage renal disease · *Mycobacterium tuberculosis*

Introduction

Tuberculosis (TB) is a common life-threatening infection worldwide, especially in developing countries, with the total number of cases still increasing in the African, Eastern Mediterranean, and Southeast-Asian regions [1]. Compared with the general population, immunocompromised patients, such as those with end-stage renal disease (ESRD) requiring hemodialysis, have a 6–25-fold increased risk of developing TB [2–4]. In addition, TB diagnosis is difficult in hemodialysis patients because of

the high incidence of extrapulmonary infections. We experienced a case of disseminated TB in a hemodialysis patient that was only detected at autopsy. The findings of the present case are consistent with the high incidence of TB during the early stages of hemodialysis reported previously [5], emphasizing the importance of screening for this infection in such patients.

Case report

A 67-year-old man presented with dyspnea and edemas of the extremities. His past medical history included diabetes mellitus diagnosed in 2000 that required insulin therapy, atrial fibrillation, cerebral infarction with right hemiplegia in 2001, acute myocardial infarction, and above-knee amputation of the left lower limb in 2009, resulting from arteriosclerosis obliterans and a diabetic foot. The patient had no known allergies and had a negative smoking history, but had a long history of alcohol abuse. One month prior to presentation, he was discharged from another hospital after undergoing treatment for heart failure; however, heart failure recurred and he was admitted to our hospital in 2011 for further treatment. A routine physical examination revealed the following findings: height, 169 cm; body weight, 75.1 kg; body temperature, 36.9 °C; heart rate, 107 beats/min with irregular rhythm; and blood pressure, 123/79 mmHg. No heart murmur or lung abnormalities were detected on auscultation. There was no abdominal bulge or tenderness in the abdomen and bowel sounds were normal. He had an above-knee amputation stump on his left lower limb, and his right foot had a necrotic wound. He had moderate pitting edema in the lower limbs.

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Table 1 Laboratory findings on admission

Occult blood	(2+)	AST	98 IU/l
Protein	(2+)	ALT	114 IU/l
	2890.4 mg/day	LDH	385 IU/l
Sediment		gGTP	68 IU/l
Red blood cell	50–99/HF	ALP	472 IU/l
White blood cell	10–19/HF	T.Bil	0.5 mg/dl
		AMY	23 IU/l
Peripheral blood		CK	51 IU/l
White blood cell	12580/ μ l	BUN	79.9 mg/dl
Neut	79 %	Cr	3.22 mg/dl
Baso	1.5 %	Na	140 mEq/l
Eosino	10.5 %	K	4.4 mEq/l
Mono	4.5 %	Cl	101 mEq/l
Lymph	3.5 %	Ca	8.4 mg/dl
RBC	$297 \times 10^4/\mu$ l	iP	4.8 mg/dl
Hemoglobin	8.9 g/dl	CRP	7.8 mg/dl
Hematocrit	27.6 %	Blood glucose	200 mg/dl
Platelet	$24.5 \times 10^4/\mu$ l	Hb A1c	7.4 %

g-GTP gamma-glutamyl transpeptidase; HbA1c hemoglobin A1c

Laboratory tests showed the following: hemoglobin 8.9 g/dl; white blood cell count, 12580/ μ L; serum C-reactive protein, 7.8 mg/dL; alanine aminotransferase, 114 international units (IU)/L; aspartate aminotransferase, 98 IU/L; alkaline phosphatase, 472 IU/L; and total bilirubin, 0.5 mg/dL (Table 1). Assays for hepatitis B markers as well as anti-hepatitis C virus antibody and anti-human immunodeficiency virus (HIV) antibodies were all negative. Chest X-ray revealed a clear lung field with a moderate amount of bilateral pleural effusion and a cardiothoracic ratio of 62 %. A plain computed tomography (CT) scan showed mild pleural effusion, mild ascites, and mild cervical lymphadenopathy, but showed no abnormal findings in the lung fields (Fig. 1a). Echocardiography showed no abnormal findings in the liver or spleen.

We initiated treatment for heart failure with diuretics and isosorbide dinitrate. The patient soon developed fever, malaise, and anorexia, with a positive culture of *Pseudomonas aeruginosa*, confirming the diagnosis of a urinary tract infection. Antibiotics were started, but his renal function worsened (i.e., serum creatinine level increased significantly from 3.08 mg/dL on admission to 8.02 mg/dL). On day 37 after admission, he was started on incident hemodialysis, after which the body water was removed slowly. Antibiotics were administered for the treatment of the urinary tract infection. A culture of a swab from the necrotic wound on his right foot was positive for *P. aeruginosa*. Therefore, his right lower limb was amputated above the knee. His general condition and laboratory

Fig. 1 Radiographic findings. **a** A plain computed tomography (CT) scan on the 31st day showed no abnormal findings in the lung field. **b** A plain CT scan on the 108th day showed a 5-mm nodule lesion on the right lung field

results improved after surgery, except that a low fever persisted. On day 80, the patient developed jaundice and his liver function deteriorated. On day 121, his gamma-glutamyl transpeptidase and alkaline phosphatase levels were 152 and 1638 IU/L, respectively. CT scan revealed a consolidated lesion extended across the lower lung fields and a single 5-mm nodule lesion in the right lung field, along with moderate pleural effusion and ascites. Lymphadenopathy showed no change (Fig. 1b). Bacterial pneumonia was diagnosed following the culture of methicillin-resistant *Staphylococcus aureus* from the sputum, and appropriate antibiotic therapy was initiated. CT consolidated lesions in the lungs improved and fever decreased shortly after treatment; however, the patient's condition worsened gradually, and he developed a spiking fever. The patient died on day 138 of admission because of shock.

Autopsy revealed the presence of yellow nodular lesions in both lungs (Fig. 2a), some of which had formed

Fig. 2 Autopsy findings. **a** Yellow nodule lesions in both lungs. **b** Yellow nodules formed granulomas from Langhans-type giant cells

granulomas. Ziehl–Neelsen staining of these lesions showed Langerhans-type giant cells and acid-fast bacteria (Fig. 2b). *Mycobacterium tuberculosis* was subsequently cultured. The liver and spleen were also found to contain yellow nodular lesions, and liver fatty metamorphosis was detected. On the basis of these findings, a diagnosis of disseminated TB was made.

Discussion

We report an incident hemodialysis patient with disseminated TB that was only detected at autopsy. TB is a critical disease for nephrologists because infection is the leading cause of death among incident dialysis patients [6] and the mortality rate of TB in prevalent dialysis patients is higher than that in the general population [7]. In addition, the diagnosis of TB in dialysis patients is difficult because of the high rate of extrapulmonary (i.e., disseminated) TB [8].

The known risk factors of developing TB are underweight, drug use, tobacco and alcohol abuse, malignancy, diabetes, renal disease, HIV infection, corticosteroid, tumor necrosis factor (TNF) inhibitors or therapy, and transplantation [9]. In a multicenter clinical trial in Greece by Christopoulos et al. [10], the investigators showed that

elderly (aged ≥ 70 years), underweight, tuberculin-positive, hemodialysis (≤ 12 months duration) patients with diabetes and fibrotic lesions are at risk of developing TB.

The diagnosis of TB is often difficult in patients with dialysis because of prevailing extrapulmonary involvement and nonspecific symptoms. The incidence of extrapulmonary TB is high, with a rate of 50–85 % in hemodialysis patients [11–13], and it can involve many organs [14, 15]. The most common extrapulmonary sites of infection include the lymphatic system, gastrointestinal tract, and genitourinary tract, as well as the pleura in patients with pleural effusion, pericardial effusion, and military TB.

Disseminated TB shows atypical presentation and non-specific symptoms. The clinical features of disseminated TB in hemodialysis patients are fever of unknown origin, anorexia, night sweats, lymphadenopathy, pleural effusion, pericardial effusion, and weight loss [16]. These symptoms are similar to those observed in patients with uremia.

Many abnormal laboratory findings are also observed. Anemia is seen in approximately 50 % patients, with the majority having a normal white blood cell count, although leukopenia and leukocytosis can also occur. The erythrocyte sedimentation rate and other acute-phase reactants are elevated in the majority of patients. In addition, disseminated TB is often difficult to identify on radiography during the early stages.

In cases of suspected pulmonary TB, chest X-rays and sputum analysis are important; however, in patients with disseminated tuberculosis who do not have active pulmonary disease, identifying the mycobacterial organism may be extremely difficult by sputum analyses [16]. Alternative methods include obtaining pleural, ascitic, cerebrospinal, or peritoneal dialysis fluid analysis or biopsy of lymph nodes, pleura, bone marrow, or other tissues for smears and culture. It is important to recognize that positive bacterial confirmation is not obtained in up to 20 % of patients with a clinical diagnosis of TB [14].

The value of blood tests for the diagnosis of TB infections has been described previously. A meta-analysis of the general population has suggested that interferon gamma release assays (IGRAs) should not be used to diagnose active TB, and that TB should only be diagnosed by microbiological approaches [17, 18]. Segall et al. [19], on the other hand, summarized the value of IGRAs for active TB infection in hemodialysis patients. The sensitivity and specificity of QuantiFERON-TB Gold (QFT-G) [20] and T-SPOT.TB tests [21] were both shown to be high. Thus, IGRAs can be useful supplementary tools for the diagnosis of active TB infection in hemodialysis patients.

The patient in the present study had no recent exposure to TB, suggesting reactivation as a possibility. He was subsequently hospitalized and he developed anorexia and fever shortly thereafter. Although hemodialysis was

performed and antibiotics were administered, his symptoms deteriorated. This time course of illness also suggests reactivation of TB. We initially thought that these symptoms were caused by uremia, the infected necrotic wound on the right foot, or drug-induced hepatitis; in retrospect, we believe that reactivation of TB should have been considered. A QFT-G test might have been positive if it was checked; however, there is at least one case where active TB infection of a hemodialysis patient yielded a negative QFT-G result [22]. Because the diagnosis of TB infection is based on clinical symptoms, diagnosis is sometimes difficult.

To conclude, the diagnosis of TB infections can be challenging, especially in extrapulmonary TB infection cases, because of nonspecific clinical symptoms. Nephrologists should be wary of TB infection so that patients are diagnosed correctly.

Conflict of interest The authors have declared that no conflict of interest exists.

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