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CASE REPORT

Miliary tuberculosis diagnosed by diffuse hepatic uptake on PET/CT and transjugular liver biopsy

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Abstract

The patient was an 81-year-old man. In his 20s, he had been treated with pharmacotherapy for pulmonary tuberculosis for 1 year. He presented to the Department of Respiratory Medicine with a chief complaint of dyspnea. The possibility of respiratory disease appeared to be low, but hepatic impairment was detected. The patient was thus referred to our department. Though the cause of hepatic impairment was unknown, the soluble interleukin-2 receptor level was elevated, suggesting malignant lymphoma. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) revealed diffuse, homogenous, intense FDG uptake in the entire liver, and transjugular liver biopsy confirmed the diagnosis. Histopathological examination revealed an epithelioid granuloma, and auramine staining was positive for bacilli suggestive of tuberculosis. CT revealed diffuse micronodular shadows in the lung, yielding a diagnosis of miliary tuberculosis. Therefore, the patient was prescribed antituberculosis medication by the Department of Respiratory Medicine. His subsequent clinical course was good. The miliary (hepatic) tuberculosis was typical based on the diffuse, homogenous, intense FDG uptake throughout the liver observed on PET–CT.

Keywords Miliary tuberculosis · FDG-PET/CT · Hot liver · Hepatic superscan · Transjugular liver biopsy

Introduction

^{18}F-fluorodeoxyglucose (^{18}F-FDG) is mainly used as a tracer for positron emission tomography (PET)–computed tomography (CT) scans. ^{18}F-FDG, which has a structure similar to that of glucose, is phosphorylated by hexokinase within cells, but not further metabolized, thus accumulating intracellularly. Therefore, ^{18}F-FDG is taken up by regions where glucose uptake is increased. It also accumulates in the normal brain, tonsils, kidneys, and bladder, but is taken up specifically by malignant tumors and inflammatory lesions. We experienced a case with miliary tuberculosis in which FDG-PET/CT, which was originally performed for suspected malignant lymphoma, revealed homogeneous, intense diffuse FDG uptake in the liver. This finding was first reported as hypermetabolic liver (hot liver) by Jeong et al. in 2010 [1]. Subsequently, two case reports were published [2, 3]. Hot liver is considered to be highly characteristic of miliary (hepatic) tuberculosis. In addition, since our patient exhibited coagulopathy, transjugular liver biopsy was performed using a myocardial biopsy needle, thus yielding a definitive diagnosis of miliary tuberculosis.

Case report

An 81-year-old man presented to a clinic with chief complaints of dyspnea and pyrexia. Because hepatobiliary enzyme and total bilirubin (T-Bil) elevations were noted, the patient was admitted to our hospital for detailed examinations. Six months prior to admission, he was found to have right pleural effusion at the Department of Cardiology during follow-up for chronic atrial fibrillation. Because the adenosine deaminase level in the pleural effusion was elevated, at 76.5 U/L, he was referred to the Department of Respiratory Medicine for suspected tuberculous pleuritis. However, tuberculosis bacilli were negative on polymerase

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chain reaction (PCR) assay, sputum smear test, and the QuantiFERON TB (QFT) test. As the inflammatory reaction and pleural effusion subsided, the patient was offered follow-up. As for his medical history, he had received pharmacotherapy in his 20s for pulmonary tuberculosis for 1 year. Moreover, he had been a heavy smoker for 40 years and a heavy alcohol consumer.

Physical findings on admission: his height was 165 cm; body weight, 59.2 kg; body mass index, 21.74 kg/m^2; consciousness, clear; body temperature, 38.4 ºC; blood pressure, 92/45 mmHg; pulse rate, 76 beats/min; arterial oxygen saturation, 97%; He was icteric, anemic and showed arrhythmia, lung vesicular sounds, and liver swelling.

Blood chemistry profile on admission: white blood cells 3.78×10^3/μL, red blood cells 2.98×10^6/μL, hemoglobin 7.1 g/dL, platelets 13×10^4/μL, prothrombin time-international normalized ratio 3.05, prothrombin time (PT) activity 17%, albumin 2.5 g/dL, T-bil 3.8 mg/dL, aspartate aminotransferase 270 IU/L, alanine aminotransferase 99 IU/L, lactate dehydrogenase (LDH) 461 IU/L, γ-guanosine triphosphatase 212 IU/L, blood urine nitrogen 66.7 mg/dL, creatinine 1.76 mg/dL, and C-reactive protein (CRP) 8.09 mg/d. The patient tested negative for hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus antigen, and cytomegalovirus antibody. Both antinuclear antibody and anti-mitochondrial M2 antibody were negative. Carcinoembryonic antigen was 7.1 ng/mL; carbohydrate antigen 19-9, 75.4 U/mL; and soluble interleukin-2 receptor (sIL-2R), 7580 U/mL (Table 1).

While the patient did have alcoholic liver disease, the levels of liver enzymes were within the normal range 2 months prior to admission. Therefore, acute hepatic impairment was suspected. Abdominal ultrasonography on admission showed enlargement of both lobes, with even internal echo. The gallbladder was not swollen. Chest and abdominal plain CT showed no abnormalities in the biliary system, but revealed hepatomegaly and ascites (Fig. 1). The sIL-2R and LDH levels were elevated at 7580 U/mL and 461 U/L, respectively, raising suspicion of malignant lymphoma. Thus, PDG-PET/CT was performed on hospital day 8, revealing intense FDG uptake throughout the liver (SUVmax 6.76), and slight uptake in the lymph nodes near the diaphragm, both lungs, and the pleura (Fig. 2). The patient was taking warfarin 1.5 mg/day for atrial fibrillation. However, PT activity was 66% even after discontinuation of this drug, revealing coagulopathy. On hospital day 13, transjugular liver biopsy was performed using a 6 Fr sheath and a 5.5 Fr myocardial biopsy needle (Fig. 3a). Histopathological examination revealed an epithelioid granuloma with no malignant lesions. Auramine staining was positive for bacilli suggestive of tuberculosis (Fig. 3b–d). On hospital day 15, CT was performed again because of persistent remittent fever and decreased oxygen saturation, revealing diffuse micronodular shadows in both lung fields. The patient was thus diagnosed as having miliary tuberculosis (Fig. 4). On hospital day 16, he was transferred to the Department of Respiratory Medicine for treatment with antituberculosis medications. The patient's subsequent clinical course was initially good. The laboratory tests decreased to nearly normal (AST 26 IU/L, ALT 57 IU/L, LDH 158 IU/L, CRP 0.45 mg/dl) on hospital day 29 and discharged on hospital day 76 (Fig. 4). He completed antituberculosis treatment for 12 months. However, he ultimately died of tuberculous myocarditis 4 months after treatment discontinuation.

Table 1 Laboratory data on admission

Blood count		Biochemistry			
WBC	3.78×10^3	TP	6.8 g/dl	NH3	68 μU/ml
RBC	2.98×10^6/μl	Alb	2.5 g/dl	TSH	0.372 pg/ml
Hb	7.1 g/dl	T-Bil	3.8 mg/dl	FT4	1.41 pg/dl
PLT	13×10^4/μl	D-Bil	3.1 mg/dl	Infection	
Coagulation		AST	270 IU/l	HBsAg	0.0
APTT	74 s	ALT	99 IU/l	HCV-Ab	(–)
PT–INR	3.05	LD	461 IU/l	HIV-Ag	(–)
PT	17%	ALP	798 IU/l	CMV-IgG	≧250
FIB	239 mg/dl	γ-GTP	212 IU/l	CMV-IgM	< 40
Tumor marker		BUN	66.7 mg/dl	HTLV-1Ab	(–)
CEA	7.1 ng/ml	Cre	1.76 mg/dl	EBV-IgG	640
CA19-9	75.4 U/ml	Na	135 mEq/l	EBV-IgM	< 10
AFP	< 2 ng/ml	K	4.4 mEq/l	Antibody test	
sIL-2R	7580 U/ml	Glu	130 mg/dl	ANA	< 40
		CRP	8.09 mg/dl	AMA	1.5

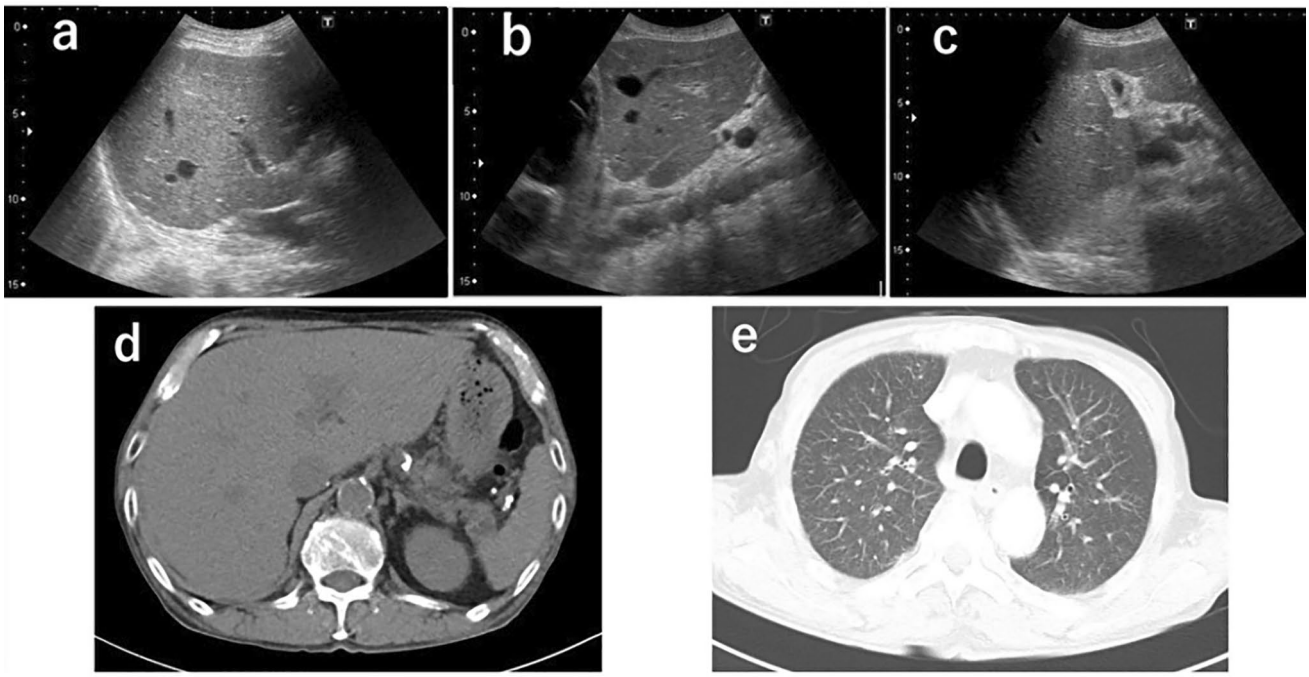

Fig. 1 Abdominal ultrasonography (US) and chest and abdominal plain computed tomography (CT). **a**, **b** US images showing enlargement of both lobes of the liver with even internal echo. **c** US image showing gallbladder with wall thickening. **d** CT image showing hepatomegaly. **e** CT image showing no nodular legions in the lung fields

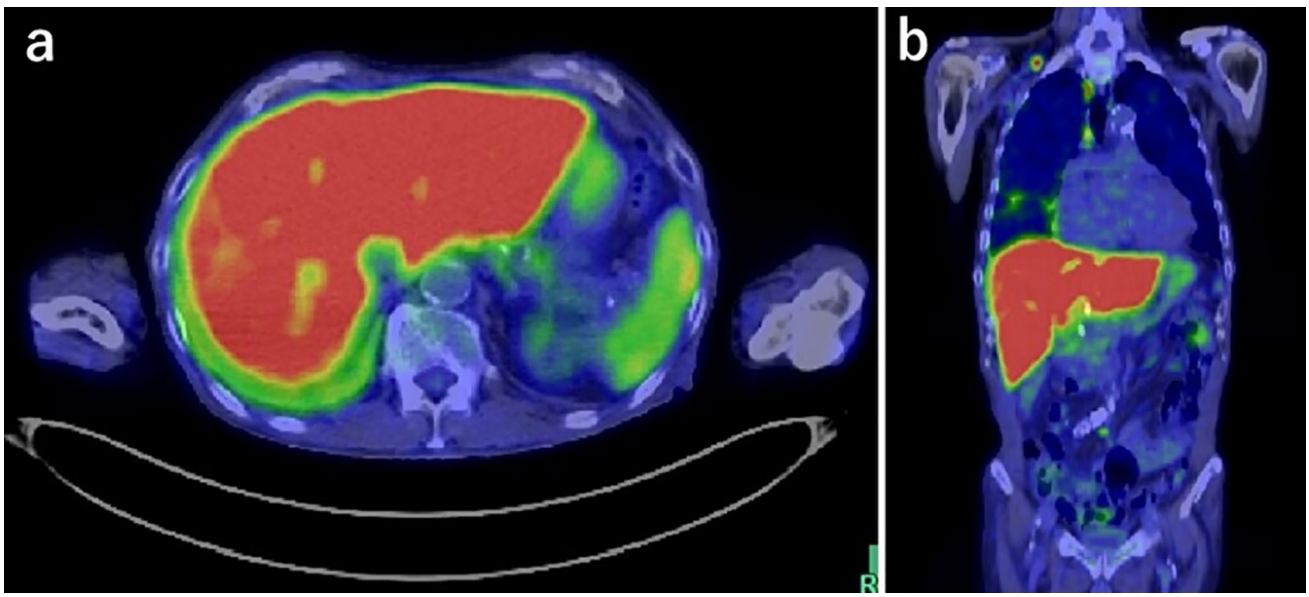

Fig. 2 Positron emission tomography–computed tomography. **a** Homogeneous, intense FDG uptake throughout the liver (SUVmax 6.76). **b** In the coronal section, intense diffuse FDG uptake in the liver and slight uptake in the lymph nodes near the diaphragm, lung fields, and pleura

Discussion

Miliary tuberculosis is characterized by hematogenous dissemination. Patients with hepatic tuberculosis have no specific symptoms, although hepatomegaly, pyrexia, and respiratory symptoms are often reported [4]. Blood tests sometimes reveal normocytic anemia, increased or decreased white blood cells, and pancytopenia [5]. This patient was referred to our department because of pyrexia

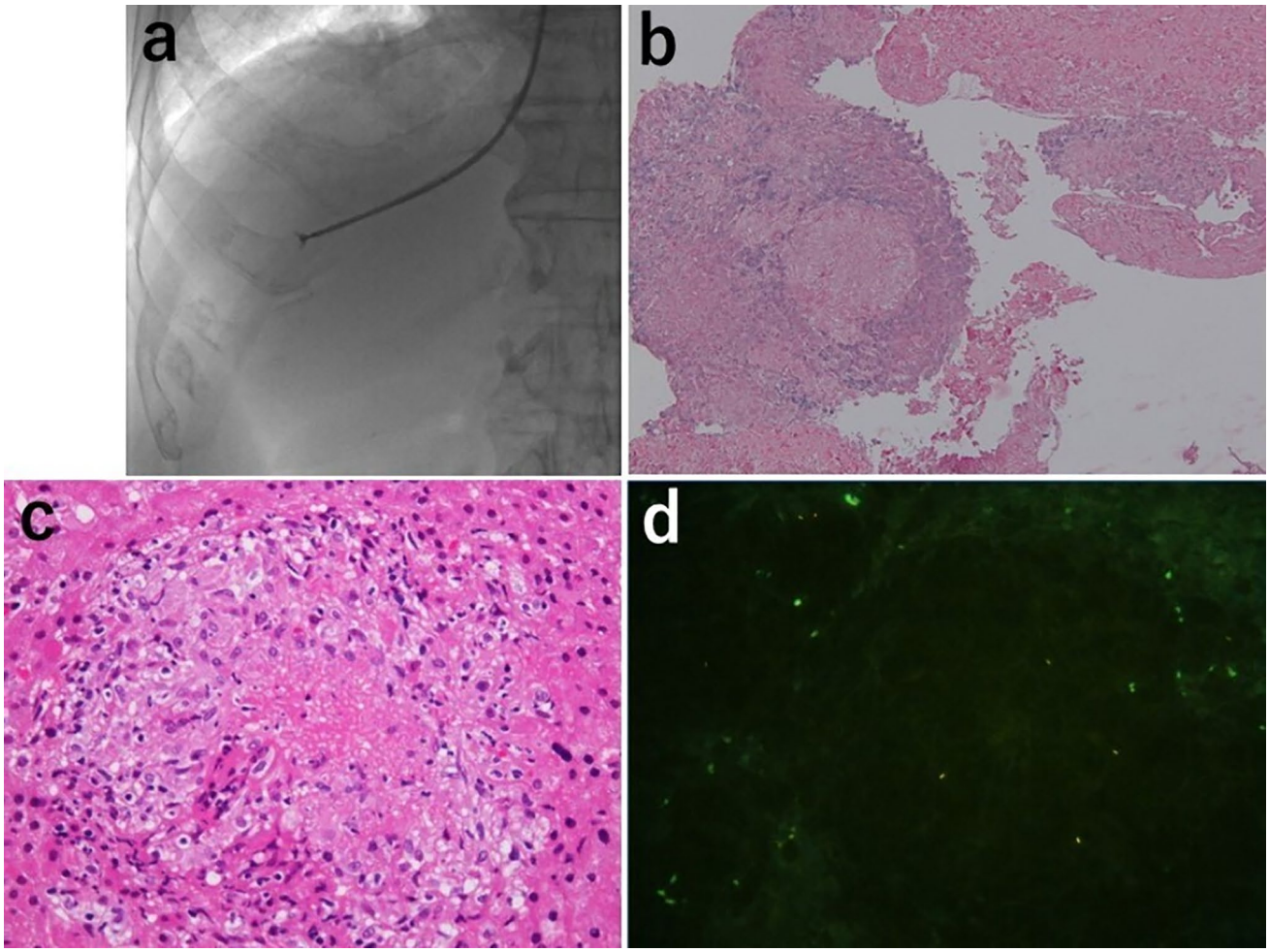

Fig. 3 Transjugular liver biopsy (TJLB) and histopathological specimens. **a** TJLB was performed via the approach from the internal jugular vein using a 6 Fr sheath and a 5.5 Fr myocardial biopsy needle. **b** Hepatic tissue specimen (×4). **c** Hematoxylin and eosin staining showing a caseous granuloma (×400). **d** Auramine staining is positive for acid-fast bacilli (×400)

and hepatic impairment. In addition, anemia and increased CRP were noted. PCR assay, sputum smear test, and the QFT test, performed 6 months prior to admission, were all negative for tuberculosis bacilli. Furthermore, CT on admission showed no abnormalities in the lung fields; thus, tuberculosis was not considered.

Liver biopsy is thought to be the most sensitive diagnostic procedure for miliary tuberculosis. However, acid-fast staining has a positivity rate of 10% for detecting hepatic tuberculous granuloma [6], and the sensitivity rate of the PCR assay for the detection of tuberculosis bacilli is reported to be approximately 56% [7]. When acid-fast staining, tissue culture test, and the QFT test results were combined, the sensitivity rate increased to 96% [8].

Management of miliary tuberculosis is based on the standard treatment for pulmonary tuberculosis and is completed in 6 months [9]. For the present patient, we started ethambutol and rifampicin because of his hepatic impairment. Next, he was treated with a combination of four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) for 1 month. Treatment with isoniazid and rifampicin was continued for six more months. Because the patient was considered to have severe miliary tuberculosis, 12-month maintenance therapy was scheduled.

In general, percutaneous liver biopsy is thought to be contraindicated for cases in which PT activity is less than 70%. In our case, because PT activity was 66% after discontinuation of warfarin, transjugular liver biopsy (TJLB) was considered. TJLB was initially reported by Dotter in 1964 [10] and clinically performed by Hanafee et al. in 1967 [11]. TJLB is a method of obtaining liver tissue by puncturing the liver parenchyma from the hepatic vein side. A biopsy needle is placed via a 7 Fr to 10 Fr sheath in the hepatic vein through the jugular vein. This technique is frequently used in Europe and the USA, but less often in Japan [12, 13]. As a safe alternative to percutaneous liver biopsy, it is performed

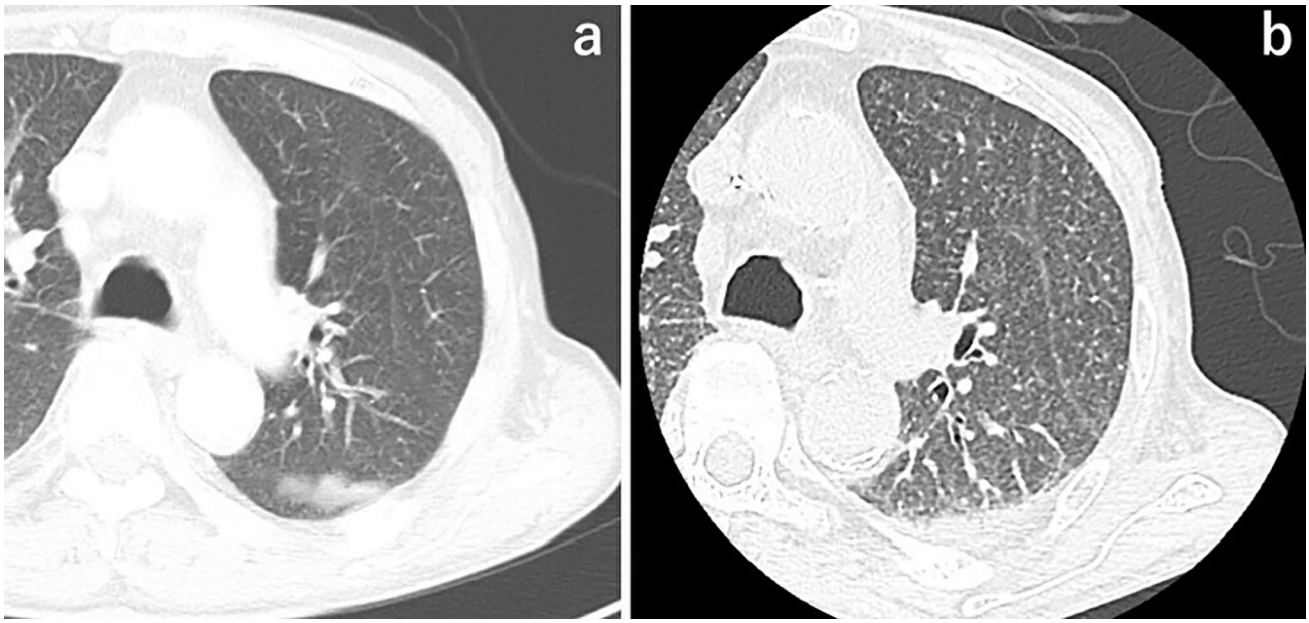

Fig. 4 Sequential changes on chest plain computed tomography. **a** Image showing no abnormalities in the lung fields on hospital day 4. **b** Image showing diffuse nodular shadows in the lung fields on hospital day 16, leading to a diagnosis of miliary tuberculosis

for cases with coagulopathy or ascites [14, 15]. The accuracy of diagnosis is comparable to that of percutaneous liver biopsy, and the quality of the biopsy specimen is not significantly different [16, 17]. Tajima et al. [18] performed TJLB using the 6 Fr sheath and the 5.5 Fr myocardial biopsy needle, instead of the conventionally used 16 G Menghini needle or 18 G True-Cut needle (Fig. 3). This method is indicated mainly for cases with suspected diffuse tumorous lesions, and has been performed to date on ten cases in our institution. It allows collection of sufficient tissue by using a thinner needle.

Massive intraperitoneal bleeding (0.2%) and ventricular arrhythmia (0.05%) are reportedly major complications of TJLB, and death rates were 0.06% and 0.04%, respectively. The same mortality rates associated with percutaneous liver biopsy reportedly range from 0.01 to 0.11% and nearly 0, respectively [14, 19]. Considering the minimal impact on platelet count and PT–INR, TJLB appears to be useful for cases with coagulopathy. In our case, TJLB led to a definitive diagnosis of miliary tuberculosis without complications (Fig. 5).

In this patient, homogeneous, intense uptake was noted throughout the liver on PET–CT using ^{18}F-FDG (Fig. 3). This finding was described as hot liver by Jeong et al. in 2010 [1]. To date, only two cases of miliary tuberculosis have been reported in which histological findings (hepatic tuberculosis) and CT images (hot liver) were both demonstrated. [2, 3].

In three of four reported cases including our present patient, liver dysfunction was a trigger for the detection of miliary tuberculosis. Initially, all four patients were clinically suspected to have malignant lymphoma, and surgical resection or biopsy of the liver led to a diagnosis of hepatic tuberculosis (Table 2).

Diffuse hepatic uptake on PET–CT was previously thought to imply multiple hepatic malignancy. Intense diffuse but multinodular hepatic uptake, which is referred to as hepatic superscan, was reported in cases with Hodgkin's disease [20]. Subsequently, several studies showed hepatic superscan in cases with malignant lymphomas. Multinodular uptake is usually noted on PET–CT for multiple hepatic metastases [21]. For lymphomas, not only multinodular uptake [22], but also various uptake patterns from heterogeneous to relatively homogeneous, intense uptake have been reported [23–25]. However, homogeneous, intense uptake, as seen in our case, is different from previously reported patterns. ^{18}F-FDG is a tracer that accumulates in the inflammatory regions. In our case, FDG was thought to have homogeneously accumulated throughout the liver, which showed diffuse inflammation due to miliary tuberculosis. We consider the PET–CT findings of the liver in our present case to be highly characteristic of miliary (hepatic) tuberculosis.

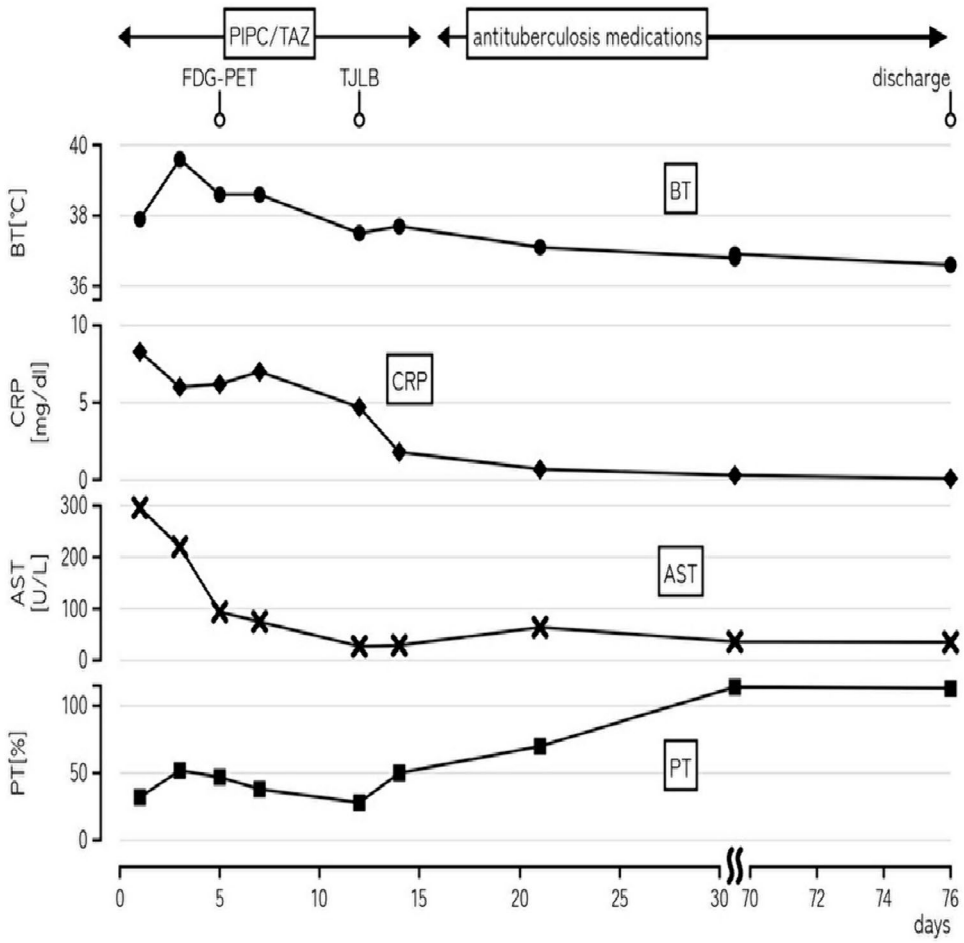

Fig. 5 Clinical course after admission

Table 2 Cases with homogenous, intense diffuse FDG uptake in the entire liver on positron emission tomography–computed tomography

	Author (year)	Age/gender	Diagnostic trigger Laboratory data	PET–CT (FDG uptake)	Clinical diagnosis	Final diagnosis
1	Jeong YJ (2010) [1]	69/F	Hepatosplenomegaly AST 117 IU/l, ALT 113 IU/l, ALP1539 IU/l	Diffuse and extensive in liver, spleen, lymph nodes	Lymphoma	(Splenectomy, liver biopsy) Hepatosplenic Tb
2	Wang SS (2014) [2]	46/M	Fever Hepatosplenomegaly AST, ALT normal, ALP 345 IU/l	Diffuse and extensive in liver	Lymphoma or Tb	(Liver biopsy) Hepatic Tb
3	Vijavakmary B (2020) [3]	56/M	Hepatosplenomegaly ESR 90 mm/h	Diffuse and extensive in liver, lungs, lymph nodes	Liver metastasis (lung cancer) or lymphoma	(Liver biopsy) Hepatic Tb
4	Our case	81/M	Fever Hepatosplenomegaly AST 270 IU/l, ALT 99 IU/l, ALP 798 IU/l, sIL-2R 7580 U/ml	Diffuse, homogeneous and extensive in liver, pleura, lungs, lymph nodes	Lymphoma	(Liver biopsy) Hepatic Tb

Declarations

Conflict of interest Ueta R, Saito A, and Yanase M declare have no conflicts of interest to disclose.

Human/animal rights All procedures followed were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent This study does not contain identifying information on the patient.

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