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CASE REPORT

Reactivation of intraabdominal tuberculous lymphadenopathy after drug-eluting beads transcatheter arterial chemoembolization in a patient with hepatocellular carcinoma

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Abstract
Owing to effective treatments and sanitary improvements, the incidence of latent tuberculosis infection (LTBI) has decreased. However, approximately one-quarter of the world's population is thought to have LTBI, and the reactivation of tuberculosis (TB) sometimes occurs in immunocompromised hosts. A 54-year-old man presented with a fever. The patient had past histories of alcoholic and hepatitis C virus-related cirrhosis and hepatocellular carcinoma (HCC). He was treated with drug-eluting beads transarterial chemoembolization (DEB-TACE) for HCC three times, beginning 10 months before his current visit. A computed tomography scan showed enlarged intraabdominal lymph nodes with calcification, and the interferon-gamma release assay for TB infection was positive. The patient was diagnosed with tuberculous reactivation. Anti-TB therapy was administered to the patient, after which we restarted TACE and the TB infection remains controlled. In this case, we presumed that DEB-TACE is associated with the reactivation of TB infection and that anthracycline increases the risk of reactivating TB infection. In summary, we experienced a case of TB reactivation during the clinical course of a patient with HCC who was treated with DEB-TACE. When patients with HCC are treated with TACE, their symptoms, laboratory data, and imaging results should be monitored when latent TB infections are suspected.

Keywords Tuberculosis reactivation · Drug-eluting beads transcatheter arterial chemoembolization · Hepatocellular carcinoma

Introduction

About one-quarter of the world population is thought to have latent tuberculosis (TB) infection (LTBI) [1]. Furthermore, a high prevalence of TB has been estimated in South African and southeast Asian countries, and Japanese people are also at high risk for TB infections compared to people in other developed countries. Among patients with LTBI, reactivation of TB can occur in immunocompromised hosts, such as patients with AIDS, diabetes mellitus, or those who take immunosuppressants, steroids, or cancer chemotherapy [2].

Transarterial chemoembolization (TACE) is a treatment modality for hepatocellular carcinoma (HCC) and offers a survival benefit for patients with advanced stage HCC. However, for conventional TACE (cTACE) therapies, Lammer et al. reported an incidence of 19.4% of treatment-related severe adverse events that were immediately life-threatening, required inpatient hospitalization, resulted in permanent disability, and resulted in death [3]. Recently, the reactivation of tuberculosis has been demonstrated to be a rare complication after TACE for the treatment of HCC [4, 5].

On the other hand, drug-eluting beads TACE (DEB-TACE) has recently been developed as a therapy option for bilobar or recurrent HCC, and this therapy has fewer complications, such as serious liver toxicities and anti-cancer side effects than cTACE. Here, we report a case of TB reactivation showing intraabdominal TB lymphadenopathy during the clinical course of a patient with HCC who was treated

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with several interventions of DEB-TACE. To our best knowledge, this is the first such report to date.

Case report

In January 2014, a 54-year-old man was referred to our department for hepatic tumor examination. His past histories included diabetes mellitus at the age of 30 years and alcoholic and hepatitis C virus (HCV)-related cirrhosis at the age of 42 years. Elevated alpha-fetoprotein level and multiple masses of the liver were demonstrated at nearby hospital, so he was referred to our hospital for further examination. Contrast-enhanced computed tomography (CT) showed a 74 × 63 mm mass, with early phase enhancement and late-phase washout in segments four and eight of the liver, and multiple masses in both lobes (Fig. 1a, b). This image also revealed intraabdominal lymph nodes measuring 10 mm, with calcification (Fig. 1c). The patient was diagnosed with Barcelona Clinic Liver Cancer stage B HCC. Epirubicin-loaded DEB-TACE was performed in May and August 2014. In October, a CT revealed enlarged intraabdominal lymph nodes measuring 20 mm with peripheral enhancement (Fig. 2a, b), and the interferon-gamma release assay for tuberculosis revealed a result of 0.38 IU/ml (cut-off value, 0.10 IU/ml). Differential diagnoses for abdominal lymphadenopathy are malignancy such as metastasis of HCC or malignant lymphoma, inflammatory disease such as Crohn's disease or ulcerative colitis and infectious disease such as human immunodeficiency virus or tuberculosis. In consideration of laboratory data and calcification of lymph nodes, we strongly suspected TB lymphadenopathy. At this time, there was no cytopathological and bacteriological evidence of TB infection, and the third DEB-TACE procedure was performed in November.

In January of 2015, the patient was admitted because of a fever that lasted for 5 days. On admission, laboratory data revealed the following: a white blood cell count of 10,000/μL, a C-reactive protein level of 3.31 mg/dl, and decreased alpha-fetoprotein levels of 2.4 ng/ml (Table 1). The interferon-gamma release assay for tuberculosis was positive (> 8.00 IU/ml), and the CT scan showed more enlarged

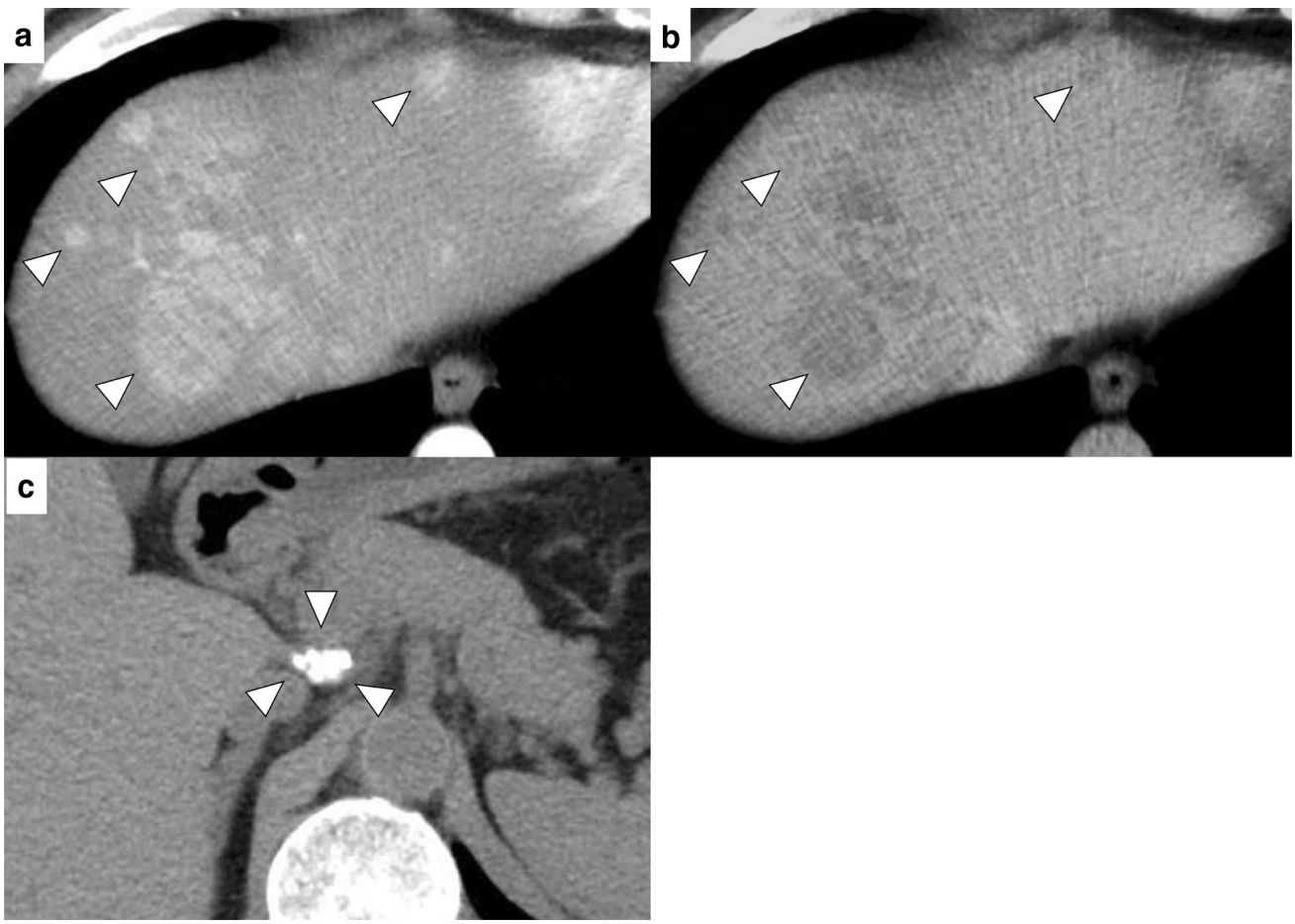

Fig. 1 **a** Contrast-enhanced computed tomography (CT) showed multiple masses with early phase enhancement (arrow heads) and **b** late-phase washout (arrow heads) in both lobes. **c** CT revealed enlarged intraabdominal lymph nodes with calcification (arrow heads)

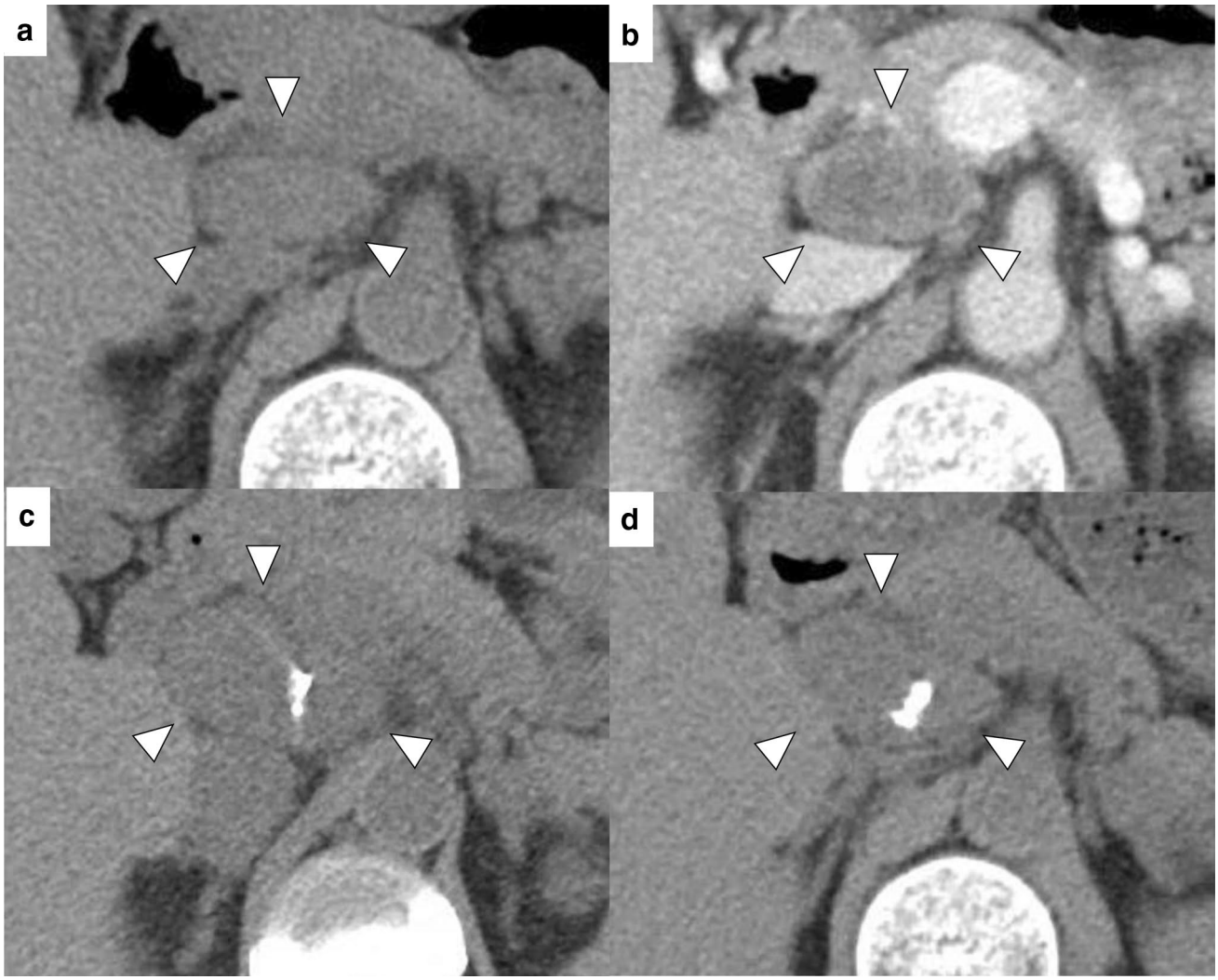

Fig. 2 **a** In October, a CT revealed enlarged intraabdominal lymph nodes measuring 20 mm (arrow heads). **b** The lymph node showed peripheral enhancement by contrast-enhanced CT (arrow heads). **c** Eleven months later CT showed remarkably enlarged intraabdominal lymph nodes (arrow heads) after three times of DEB-TACE procedures. **d** After 3 months of anti-TB therapy, CT results showed a reduction in the size of the intraabdominal lymph node (arrow heads)

intraabdominal lymph nodes (Fig. 2c) with high fluorodeoxyglucose uptake under positron-emission tomography (Fig. 3a). An endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) was then performed. Acid-fast bacilli were identified on Ziehl–Neelsen staining, and PCR of the tissue was positive for mycobacterium TB DNA. Therefore, the patient was diagnosed with reactivated TB lymphadenopathy, and an anti-TB regimen comprising isoniazid, rifampicin, and ethambutol was prescribed for 2 months, followed by isoniazid and rifampicin for 7 months. In 2 weeks, the patient's fever resolved, and 3 months later, CT results showed a reduction in the size of the intraabdominal lymph node (Fig. 2d).

After anti-TB treatment, we restarted the TACE procedure. However, he died of HCC 3 years after his first visit to our hospital. The autopsy shows intraabdominal lymph node enlargement measuring 20 mm (Fig. 3b). Histology showed epithelioid cell granuloma with caseation necrosis (Fig. 3c) that contained typical findings of lymphadenopathy due to TB infection.

Discussion

In this case, TB was reactivated, which manifested as intraabdominal TB lymphadenopathy in a patient with cirrhosis who had received DEB-TACE for advanced stage HCC. This rare, interesting case deserves further discussion.

TB is primarily caused by mycobacterium TB respiratory infection and has been a leading cause of death in the past.

Table 1 Laboratory data on admission

Peripheral blood	
WBC	10,000/μl
Neutrophil	79.0%
Lymphocyte	12.6 %
Monocyte	7.4%
Eosinophil	0.6%
Basophil	0.4%
RBC	261×10^4/μl
Hemoglobin	8.6 g/dl
Hematocrit	25.3%
Platelet	27.2×10^4/μl
Urine chemistry	
Proteinuria	228 mg/dl
Coagulation	
PT-INR	1.07
APTT	33.3 sec
Fibrinogen	629 mg/dl
Chemistry	
Total protein	6.4 g/dl
Albumin	2.2 g/dl
Total bilirubin	0.3 mg/dl
BUN	39 mg/dl
Creatinine	2.69 mg/dl
Glucose	193 mg/dl
Total cholesterol	140 mg/dl
Triglyceride	114 mg/dl
HbA1c	6.2 %
Serology	
CRP	3.31 mg/dl
HBs Ag	(-)
HCV Ab	(+)
AFP	2.4 ng/ml
PIVKA-II	71 mAU/ml

In the middle of the nineteenth century, the incidence of tuberculosis rapidly decreased in developed countries and in Japan, because of effective treatments and sanitary improvements. However, about one-quarter of the world population is still thought to have LTBI, and about 5–10% of LTBI patients have the capacity to develop to TB reactivation in their lifetimes. Reactivation occurs more frequently in immunocompromised states, such as those related to HIV infection, post-organ-transplantation, and diabetes mellitus. Our patient was also at higher risk for TB reactivation because he had cirrhosis, chronic renal failure, and advanced cancer [6].

Recently, DEB-TACE has been developed to improve drug delivery and decrease side effects after TACE. In this case, we selected DEB-TACE for disease control with lower side effects in consideration of bilobar disease with 7 cm in maximum diameter. After three courses of DEB-TACE, we conducted anti-TB therapy, following one course of DEB-TACE and 2 courses of cTACE for further tumor reduction. On the other hand, the drug-eluting beads that are used in DEB-TACE have been designed for sustained anti-cancer drug release. Previous studies have shown that DEB-TACE achieves a high anti-cancer drug concentration in the tumor with a significantly lower plasma drug concentration than cTACE [7, 8]. Theoretically, patients treated with DEB-TACE have lower risk of TB infection reactivation. Therefore, we would like to discuss another mechanism that promotes TB reactivation.

Anthracycline, an anti-cancer drug used in DEB-TACE, was administered in this case. This drug has been commonly used in cTACE for HCC and also for the treatment of breast cancer and leukemia. As a side effect, anthracycline-based chemotherapy is known to cause significant reduction in CD4 + T cells, through the inhibition of IL-2 production [9, 10]. Furthermore, CD4 + T cells are thought to be the important mononuclear cells for the suppressive control of TB infection through the production of interferon-γ, which induces nitric oxide in macrophages [11, 12]. Therefore, we presume that the use of anthracycline for DEB-TACE is closely associated with the reactivation of TB infection, even if the plasma level of this drug is low. In our case, the total lymphocyte count in the peripheral blood significantly decreased after each DEB-TACE procedure (Fig. 4), which might result in the onset of active TB.

In the literature, only eight cases of TB reactivation after TACE have been reported. In these cases, the patients were thought to be treated with cTACE, because the reports did not clearly describe drug-eluting bead procedures. Therefore, this is the first report for a patient with TB reactivation after DEB-TACE therapy. Although DEB-TACE is a newly developed treatment that is associated with lower systemic side effects than cTACE, considering our case, we cannot ignore the risk of the reactivation of TB infection, because anthracycline-based chemotherapy seems very risky, especially for TB reactivation. So, we presume that immuno-suppressive side effect of anthracycline is the main cause for TB reactivation. Furthermore, extended release of anthracycline from drug-eluting beads in DEB-TACE [7] may result in long-lasting immunosuppression and following reactivation of TB after DEB-TACE, even if plasma concentration of anthracycline is low. Therefore, it seems that DEB-TACE could have the same or higher risk for TB reactivation compared to cTACE. As such, in patients with latent TB infections, we should monitor symptoms, laboratory data, and imaging results for potential TB reactivation during TACE procedures, including the newly developed DEB-TACE methods.

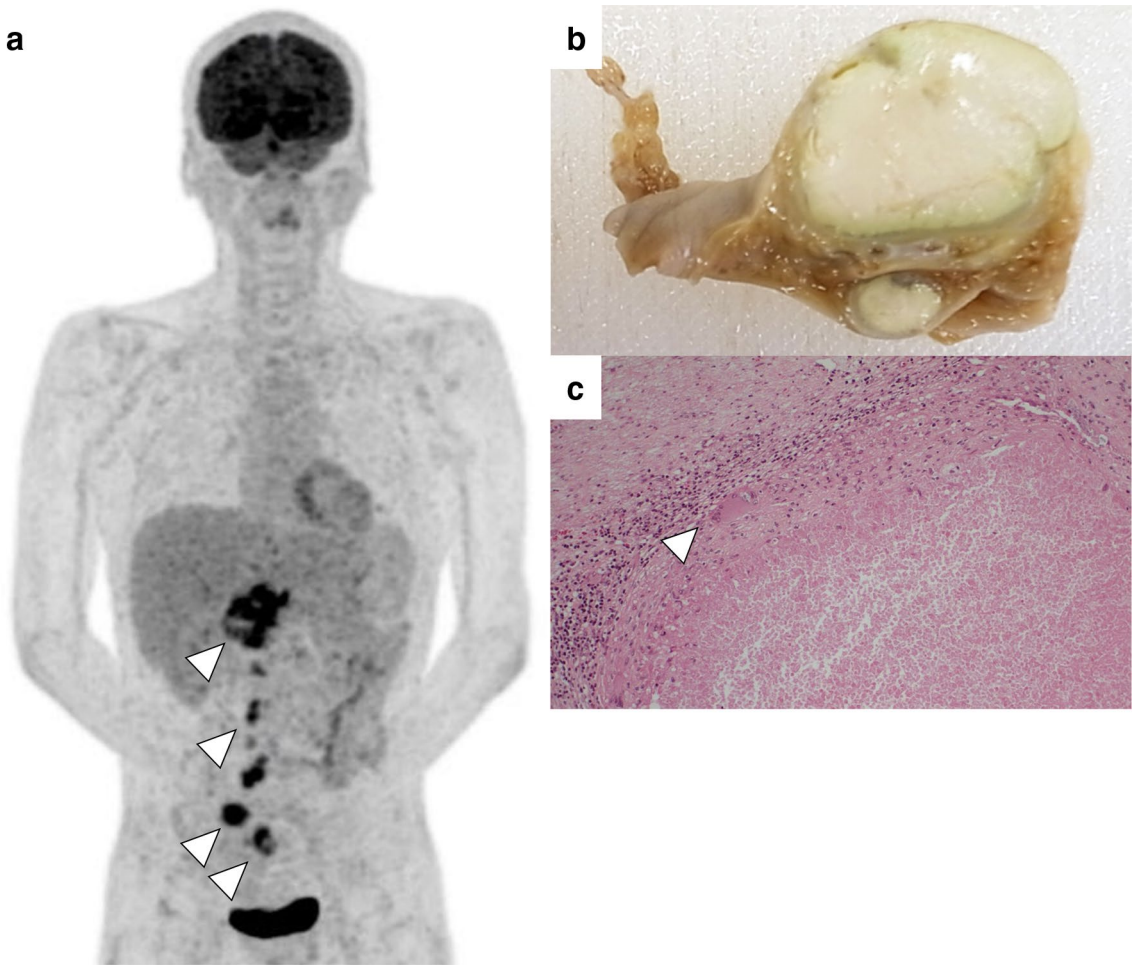

Fig. 3 **a** Those lymph nodes demonstrated high fluorodeoxyglucose uptake under positron-emission tomography (arrow heads). **b** The autopsy showed intraabdominal lymph node enlargement measuring 20 mm in diameter. **c** Histology showed epithelioid cell granuloma with caseation necrosis surrounded by lymphocytes and Langhans' giant cells (arrow head)

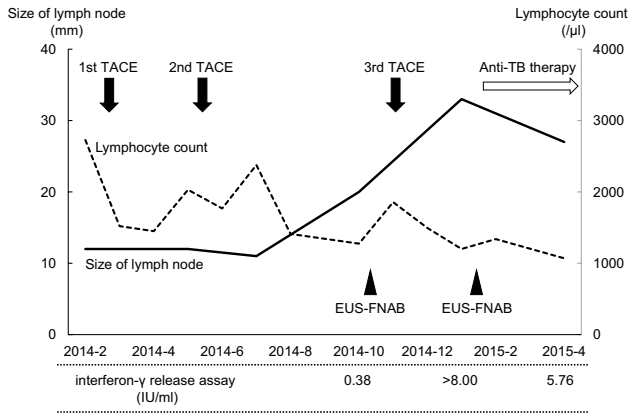

Fig. 4 Clinical course of the patient

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human/Animal Rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its latter amendments.

Informed consent Was obtained from all patients for being included in the study.

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