



A case of liver hilar tuberculous lymphadenitis complicated by biliary stricture diagnosed by endoscopic ultrasound-guided fine-needle aspiration

Nobuhiro Ando¹ · Keisuke Iwata¹ · Kenji Yamazaki¹ · Shogo Shimizu¹ · Junichi Sugihara¹ · Masaki Katayama² · Hitoshi Iwata² · Takuji Iwashita³ · Masahito Shimizu³

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Abstract

This report describes a case of liver hilar tuberculous lymphadenitis complicated by biliary stricture, diagnosed with endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). A 44-year-old woman was referred to our center for further evaluation of abnormal liver function tests. Abdominal ultrasound/contrast-enhanced computed tomography (CT) revealed a 15-mm hypovascular mass with a weakly enhanced margin at the liver hilum. Magnetic resonance cholangiopancreatography revealed dilatation of the intrahepatic bile ducts in the left lobe of liver and gradual narrowing of the left hepatic duct. Biliary stricture associated with enlarged hilar lymph nodes due to metastasis or malignant lymphoma was suspected, but calcification on chest CT and a positive T-SPOT test did not rule out tuberculosis. After transpapillary brush cytology of the bile duct stricture failed to confirm the diagnosis, EUS-FNA of hilar lymph nodes was performed and showed positive for the acid-fast bacillus and polymerase chain reaction for *Mycobacterium tuberculosis* DNA as well as epithelioid granulomas on pathological evaluation. Those findings led to a diagnosis of hilar tuberculous lymphadenitis. The patient is under treatment with antituberculosis drugs. Abdominal tuberculous lymphadenitis is rare and some cases diagnosed as lymphadenopathy of unknown origin have required surgery. EUS-FNA is a safe and minimally invasive diagnostic method in such cases.

Keywords Endoscopic ultrasound-guided fine-needle aspiration · Liver hilar tuberculous lymphadenitis · Biliary stricture

Introduction

Japan is still a moderately affected tuberculosis (TB)-endemic country, with a prevalence rate 3–5 times higher than that in Western developed countries. Recent globalization and resulting increase in intercommunication have also increased the frequency of risk of TB infection. About 85% of all cases of TB infection are pulmonary and the majority of the remaining 15% are tuberculous lymphadenitis in the

neck, with abdominal tuberculous lymphadenitis accounting for only a very small percentage.

Tuberculous lymphadenitis is difficult to diagnose by imaging alone and must be differentiated from metastasis or malignant lymphoma, sarcoidosis, or other similar lesions. The definitive diagnosis of TB infection generally requires bacteriological and/or histological evaluation of the lesion, and tissue sampling via laparotomy or laparoscopy has been performed, especially in patients with suspected hilar lymph nodes [1–4].

The advent of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has enabled minimally invasive tissue sampling from intra-abdominal lymph nodes, with several reports demonstrating the utility of EUS-FNA in diagnosing abdominal tuberculous lymphadenitis [5–11]. We report a case of liver hilar tuberculous lymphadenitis complicated by biliary stricture diagnosed by EUS-FNA and also review the literature concerning abdominal tuberculous lymphadenitis.

✉ Nobuhiro Ando
nobuhiro5091ando@yahoo.co.jp

¹ Department of Gastroenterology, Gifu Prefectural General Medical Center, 4-6-1 Noishiki, Gifu 500-8717, Japan

² Department of Pathology, Gifu Prefectural General Medical Center, Gifu, Japan

³ First Department of Internal Medicine, Gifu University Hospital, Gifu, Japan

Table 1 Laboratory data on admission

WBC	7700/ μ L	TP	7.8 g/dL	CEA	1.2 ng/mL
RBC	451×10^4 / μ L	Alb	4.1 g/dL	CA19-9	173.3 IU/mL
Hb	12.8 g/dL	T-Bil	0.42 mg/dL	DUPAN-2	103 IU/mL
Ht	38.8%	D-Bil	0.15 mg/dL	SPan-1	64 IU/mL
Plt	21.2×10^4 / μ L	AST	30 IU/L	SIL-2R	675 IU/mL
PT	91.1%	ALT	30 IU/L	IgG 4	40 mg/dL
		LDH	156 IU/L	ACE	18.7 IU/L
		ALP	844 IU/L		
		γ -GTP	249 IU/L		
		BUN	15 mg/dL		
		Cre	0.66 mg/dL		
		Na	141 mEq/L		
		K	4.2 mEq/L		
		Cl	108 mEq/L		
		CRP	1.96 mg/dL		

Case report

A 44-year-old woman was referred to our hospital for further evaluation of abnormal liver function tests on health checkup. She was born in the Philippines and came to Japan 12 years prior, with no history of treatment for TB or other remarkable medical history. She had no symptoms including fever, abdominal pain, or icterus.

Blood tests at initial presentation showed increased hepatobiliary enzymes, including alkaline phosphatase of 844 IU/L, gamma glutamyl transferase of 249 IU/L, aspartate aminotransferase of 30 IU/L, and alanine aminotransferase of 30 IU/L, but no evidence of jaundice, with a total bilirubin of 0.42 mg/dL and direct bilirubin of 0.15 mg/dL. The serum levels of tumor markers levels were elevated in CA 19-9 (173.3 U/mL), SPan-1 (64 U/mL), and soluble interleukin-2 receptor (675 U/mL). Immunoglobulin G4 was within the normal range (Table 1).

Abdominal US revealed a 15-mm isoechoic round mass at the liver hilum and dilatation of the intrahepatic bile ducts in the left lobe of liver, with no apparent mass shadow in the liver (Fig. 1). Magnetic resonance cholangiopancreatography showed dilatation of the intrahepatic bile ducts in the left lobe of the liver with gradual compressive narrowing, while no dilatation was observed in the common bile duct or intrahepatic bile ducts in the right lobe of the liver (Fig. 2). On contrast-enhanced abdominal computed tomography (CT), the mass was visualized as a hypovascular tumor with a weakly and persistently enhanced margin and a heterogeneous, low-density content (Fig. 3). The mass was well delineated and showed a slight washout pattern in the equilibrium phase, a finding somewhat different from that of typical bile duct cancers.



Fig. 1 Abdominal US revealed a round, hypoechoic mass at the liver hilum (arrow)



Fig. 2 MRCP showed gradual narrowing of the left hepatic duct at the hilar region (arrow) and dilatation of the intrahepatic bile ducts in the left lobe of liver, but no dilatation of the intrahepatic bile ducts in the right lobe of liver

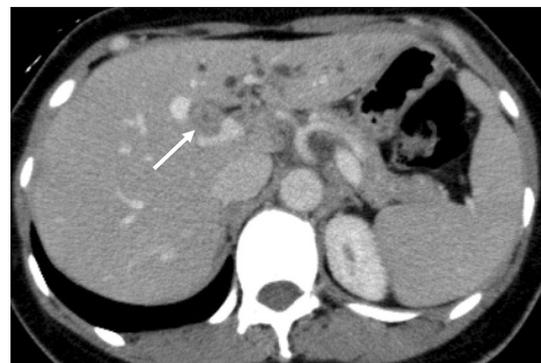


Fig. 3 Contrast-enhanced abdominal CT revealed a hypovascular mass with a persistently and weakly enhanced margin and a heterogeneous, low-density content (arrow)

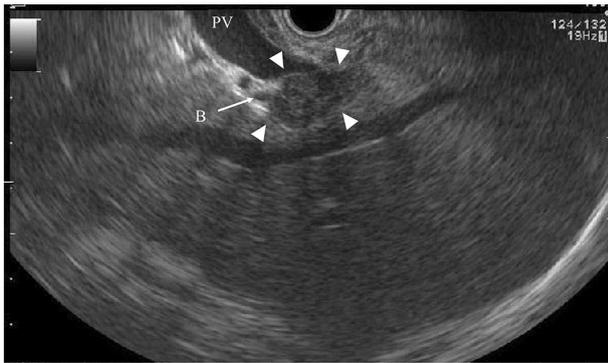


Fig. 4 On EUS, the mass was visualized as a well-delineated, hypoechoic mass with a relatively regular margin and was compressing the bile duct (arrow head). PV Portal vein, B bile duct

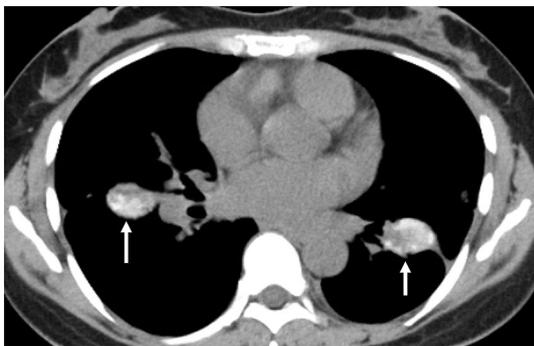


Fig. 5 Chest CT revealed calcified, well-delineated nodular shadows along the border between the left and right lung lobes (arrow)

The left hepatic duct showed tapered narrowing because of the mass, with no other abnormality in the biliary duct. Similarly, no apparent abnormality was detected in the liver, pancreas, or digestive tract. EUS showed no wall thickening of the extrahepatic bile duct and no abnormality in the gall bladder or pancreas. Meanwhile, a well-delineated, hypoechoic mass with relatively regular margin was detected at the liver hilum and was compressing the bile duct, causing dilatation of the upstream duct (Fig. 4).

Based on these findings, we speculated that the enlarged hilar lymph node was responsible for the biliary stricture and performed esophagogastroduodenoscopy and colonoscopy, which revealed no obvious abnormality. On chest CT, although neither cavity formation nor infiltrative shadow was detected in the lung field itself, multiple calcified, well-delineated nodules were detected along the border between the left and right lobes (Fig. 5). Despite no history of treatment for TB and negative results in the sputum acid-fast bacillus (AFB) and polymerase chain reaction (PCR) assay for *Mycobacterium tuberculosis* DNA, a positive T-SPOT® test did not rule out the possibility of TB infection as a cause of the enlarged hilar lymph nodes. Endoscopic retrograde

cholangiopancreatography was then performed and revealed short length stricture at the left hepatic duct of the liver hilum. Transpapillary biopsy of the bile duct stenosis was attempted, but was resulted in failure due to difficulty in advancing a biopsy forceps into the stenotic site. Only brush cytology was then performed and a 7-Fr, 12-cm plastic stent (Flexima™ Plus; Boston Scientific Japan, Tokyo, Japan) was deployed at the stricture. Brush cytology of the stenotic bile duct showed no evidence of malignancy.

Even if T-SPOT® test is positive, it cannot distinguish between past and present infection with the *M. tuberculosis*. Therefore, because the enlarged hilar lymph nodes were considered to be associated with typical metastatic disease or malignant lymphoma, we considered that direct tissue sampling from enlarged hilar nodes is first priority. To confirm the diagnosis, we performed EUS-FNA of the enlarged hilar lymph nodes after sufficient informed consent. Three passes of FNA were performed using a 19-gauge FNA needle (Sono Tip® Pro Control; Medi-Globe GmbH, Achenmühle, Germany) with a 10-cc suction technique and completed without any adverse events. The obtained tissue samples were positive for the AFB and PCR assay for *M. tuberculosis* DNA, and pathologically characterized as containing multiple epithelioid granulomas with caseous necrosis (Fig. 6). These findings strongly suggested hilar tuberculous lymphadenitis and an associated biliary stricture, and anti-TB therapy with four standard drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) was started. A few weeks later, *M. tuberculosis* was isolated from the culture of the obtained tissue, leading to the final diagnosis of hilar tuberculous lymphadenitis. CT performed after 1 month of anti-TB therapy showed reduced size of both hilar lymph nodes and pulmonary nodules. We also removed the biliary stent and verified improvement of the stricture by endoscopic retrograde cholangiopancreatography after the completion of treatment.

Discussion

The majority of TB patients in the global population are in Africa and Asia. In Asia, the prevalence of TB remains high, especially in Southeast Asian countries, such as the Philippines, Indonesia, and Vietnam. In Japan, the corresponding prevalence is as low as 13.9 per 100,000 people as of 2016 [12], although increased intercommunication with neighboring countries of recent date has led to an increasing prevalence of TB among foreign residents in Japan. Therefore, TB infection should be considered in the differential diagnosis in patients with certain underlying diseases or national origins. *Mycobacterium tuberculosis* most commonly infects the lung, followed by lymph nodes in the lung hilum and neck. Intra-abdominal tuberculous lymphadenitis is a relatively rare form of TB, and tuberculous lymphadenitis with

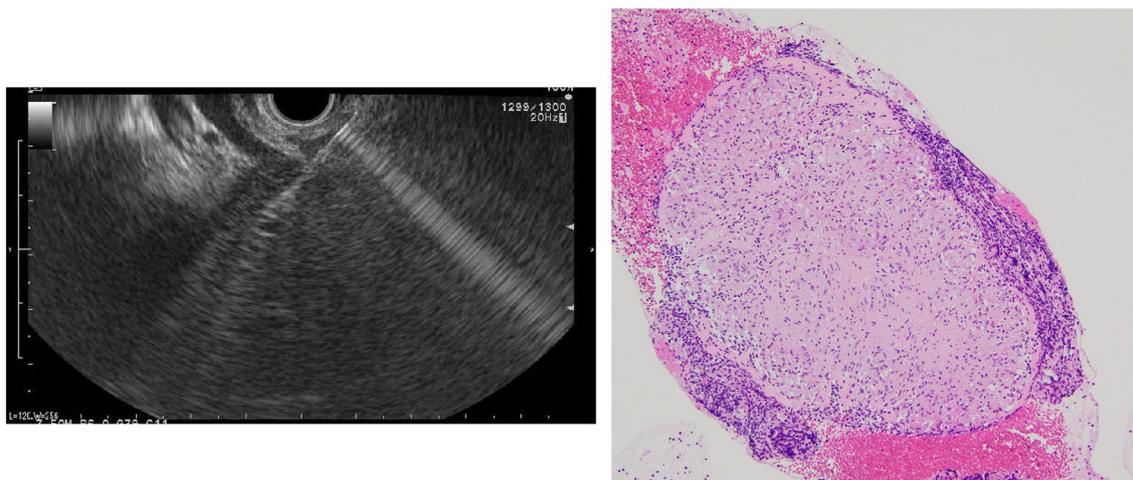


Fig. 6 (Left) An EUS image during EUS-FNA using a 19-G FNA needle. (Right) Histopathological findings of EUS-FNA sample characterized as containing multiple epithelioid granulomas with caseous necrosis (hematoxylin and eosin stain, $\times 100$)

secondary biliary stricture at the liver hilum, as seen in the present patient, appears to be even rarer. We searched the PubMed databases (2000–2017) for similar case reports using the keywords ‘liver hilar’ and ‘Tuberculous lymphadenitis’, and there was a total nine cases (male 6/female 3, median age 44 years; range 20–70 years) including present case (Table 2) [1–4, 8]. The median size of the hilar lymph node was relatively large, 31 mm, and seven cases had symptoms such as jaundice and abdominal pain. Conversely, one might say that our case was asymptomatic because the size of the lymph node was as small as 15 mm.

Lymphadenopathy can be seen in a wide variety of diseases, ranging from benign diseases, such as reactive lymphoid hyperplasia and sarcoidosis, to malignant diseases, such as multi-organ metastases and malignant lymphoma.

It is therefore not always easy to differentiate tuberculous lymphadenitis from these diseases. Yang et al. reported a so-called “ring enhancement pattern,” characterized by a heterogeneous low-density area corresponding to caseous necrosis at the center of the mass and an irregular enhancement pattern reflecting inflammatory vascular proliferation in the periphery, as a typical contrast-enhanced CT finding of tuberculous lymphadenitis that could be seen in 88% of patients [13].

While there are no established diagnostic criteria for abdominal tuberculous lymphadenitis, Cantrell et al. have proposed that the definitive diagnosis of tuberculous lymphadenitis in the neck can be made when at least three of the following six criteria are met: (1) a mass in the neck, (2) positive tuberculin test, (3) histopathological evidence

Table 2 The cases of tuberculous lymphadenitis at the liver hilum

Author	Year	Age	Sex	Symptom	LN size (mm)	Method	Granulomatous inflammation	PCR assay for TB	AFB or culture for TB
Poon	2001	20	M	Jaundice Body weight loss	40	Surgical	+	NA	–
	2001	34	M	Jaundice Anorexia	30	Surgical	+	+	–
Saluja	2007	35	M	Jaundice	NA	Surgical	NA	NA	NA
	2007	70	M	Jaundice	NA	Surgical	NA	NA	NA
	2007	55	F	Jaundice	NA	Surgical	+	NA	NA
Garcia	2011	49	F	Jaundice Abdominal pain	32	EUS-FNA	+	–	+
Muñelo	2013	29	M	Jaundice Abdominal pain	40	Surgical	+	NA	+
Wakasugi	2015	49	M	None	26	Surgical	+	+	NA
Present case	2018	44	F	None	15	EUS-FNA	+	+	+

of caseating granuloma, (4) the presence of AFB in biopsy tissue, (5) positive AFB culture from the biopsy tissue, and (6) response to anti-TB treatment [14]. This also suggests that the diagnosis of TB infection should not be made simply by clinical symptoms, imaging findings, and non-invasive tests, such as T-SPOT® test, but should be made in a more comprehensive manner by combining these tests with bacteriological testing of the lesion and histological diagnosis. In fact, in previous reports, the diagnosis of abdominal tuberculous lymphadenitis was made by biopsy of suspected intra-abdominal lymph nodes under laparotomy or laparoscopy. As shown in Table 2 especially for liver hilar lymphadenitis, surgical tissue sampling was performed in seven of eight cases, excluding the present case [1–4, 8]. In the present case, we also strongly suspected tuberculous lymphadenitis from the fact that the patient was a foreign resident from a severely affected TB-endemic country, with a positive T-SPOT® test, imaging findings, and negative cytology of the bile duct, but decided to collect tissue samples from the lesion to obtain a definitive diagnosis.

EUS-FNA has been widely used to obtain tissue sample from lesions around the upper intestine as a reliable, safe, and minimally invasive procedure after the initial report by Vilmann et al. [15], and its application is expanding from diagnosis to treatment. EUS-FNA allows for real-time aspiration of a lesion under guidance with a high-resolution ultrasound image and thus enables easy and safe tissue sampling from even a small lesion. An enlarged lymph node that can be approached from the digestive tract is therefore considered as a good indication of a pancreatic tumor and an intestinal submucosal tumor. Yasuda et al. reported that EUS-FNA with a 19-G needle provided a diagnostic yield of 98% and complication rate of 1% for intra-abdominal and mediastinal lymphadenopathy and concluded that EUS-FNA is a safe, minimally invasive, and accurate diagnostic method for lymphadenopathy of unknown cause, and can be substituted for more invasive tests [16]. On the other hand, Song et al. performed EUS-FNA in patients with pancreatic/peripancreatic TB and reported that 61.9% were histologically diagnosed as having a granulomatous lesion, 66.7% tested positive in the PCR assay for *M. tuberculosis* DNA, 26.7% tested positive in the AFB, and 37.5% tested positive for *M. tuberculosis* in the culture, giving a diagnostic yield of 76.2% with EUS-FNA [7]. This report suggested greater difficulty in diagnosing TB infection compared to diagnosing metastasis or malignant lymphoma.

It is thought that one of the reasons for the difficulty in diagnosing TB infection is the bacteriological proof of TB from the lesion. The AFB smear test can detect TB bacteria most quickly, but is not sensitive enough to determine the viability or identification of bacteria. In contrast, the culture test is the only way to determine the presence/absence and activity of live bacteria, as well as the identification

and drug sensitivity, but requires weeks to months of time before results are available. The PCR assay for *M. tuberculosis* DNA is not suitable for determining the viability of bacteria, but can be done in a few hours and is more sensitive than the AFB smear test. This test is therefore gaining popularity [17]. The PCR assay using tissues obtained minimally invasively by EUS-FNA may be able to start anti-TB therapy earlier than invasive procedures such as laparotomy or laparoscopy.

We experienced the case of a patient with enlarged hilar lymph nodes in which tuberculous lymphadenitis was strongly suspected and confirmed by EUS-FNA and subsequent histological and bacteriological examination of the collected samples. TB infection is still commonly encountered in Japan. Tuberculous lymphadenitis, although rare, should be considered in the differential diagnosis of enlarged abdominal lymph nodes. The diagnosis of tuberculous lymphadenitis requires histological and bacteriological testing of the lesion, and thus always requires sample collection. EUS-FNA should be actively performed in patients with abdominal lymphadenopathy of unknown cause, as it can be performed safely and minimally invasively in these patients and can greatly contribute to the accurate diagnosis of tuberculous lymphadenitis.

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 1975, as revised in 2008(5).

Informed consent Informed consent was obtained from all patients to be included in study.

References

1. Poon RT, Lo CM, Fan ST, et al. Diagnosis and management of biliary obstruction due to periportal tuberculous adenitis. *Hepato-gastroenterology*. 2001;48:1585–7.
2. Saluja SS, Ray S, Pal S, et al. Hepatobiliary and pancreatic tuberculosis: a two decade experience. *BMC Surg*. 2007;7:1–9.
3. Fernández Muínelo A, Salgado Vázquez M, Núñez Fernández S, et al. Obstructive jaundice secondary to liver hilar lymph node tuberculosis. *Cir Esp*. 2013;91:611–2.
4. Wakasugi M, Tanemura M, Mikami T, et al. Liver hilar tuberculous lymphadenitis successfully diagnosed by laparoscopic lymph node biopsy. *Int J Surg Case Rep*. 2015;10:191–4.
5. Ahlawat SK, Charabaty-Pishvaian A, Lewis JH, et al. Pancreatic tuberculosis diagnosed with endoscopic ultrasound-guided fine needle aspiration. *JOP*. 2005;10:598–602.
6. Itaba S, Yoshinaga S, Nakamura K, et al. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of peripancreatic tuberculous lymphadenitis. *J Gastroenterol*. 2007;42:83–6.

7. Song TJ, Lee SS, Park DH, et al. Yield of EUS-guided FNA on the diagnosis of pancreatic/peripancreatic tuberculosis. *Gastrointest Endosc.* 2009;69:484–91.
8. Macías-García F, Iglesias-García J, Abdulkader I, et al. Tuberculous lymph node at the porta hepatis: diagnosis by EUS-guided FNA. *Gastrointest Endosc.* 2011;74:437–9.
9. Furuhashi H, Abe H, Yoshizawa K, et al. A case of peripancreatic tuberculous lymphadenitis diagnosed by endoscopic ultrasound-guided fine-needle aspiration. *Clin J Gastroenterol.* 2014;7:68–73.
10. Kim JB, Lee SS, Kim SH, et al. Peripancreatic tuberculous lymphadenopathy masquerading as pancreatic malignancy: a single-center experience. *J Gastroenterol Hepatol.* 2014;29:409–16.
11. Yamada R, Inoue H, Yoshizawa N, et al. Peripancreatic tuberculous lymphadenitis with biliary obstruction diagnosed by endoscopic ultrasound-guided fine-needle aspiration biopsy. *Intern Med.* 2016;55:919–23.
12. <http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkyoku/0000175603.pdf>. Accessed 6 Dec 2017.
13. Yang Z, Sone S, Min P, et al. Distribution and contrast enhanced CT appearance of abdominal tuberculous lymphadenopathy. *Nihon Igaku Houshasen Gakkai Zasshi.* 1997;57:567–71.
14. Cantrell RW, Jansen JH, Reid D. Diagnosis and management of tuberculous cervical adenitis. *Arch Otolaryngol.* 1975;101:53–7.
15. Vilmann P, Jacobson GK, Henriksen FW, et al. Endoscopic ultrasonography with guided fine-needle aspiration biopsy in pancreatic diseases. *Gastrointest Endosc.* 1992;38:172–3.
16. Yasuda I, Tsurumi H, Omar S, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy for lymphadenopathy of unknown origin. *Endoscopy.* 2006;38:919–24.
17. Gan HT, Chen YQ, Ouyang Q, et al. Differentiation between intestinal tuberculosis and Crohn's disease in endoscopic biopsy specimens by polymerase chain reaction. *Am J Gastroenterol.* 2002;97:1446–51.