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【 CASE REPORT 】

Intravascular Large B-cell Lymphoma Mimicking Hepatobiliary Infection: A Case Report and Literature Review

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Abstract:
Intravascular large B-cell lymphoma (IVLBCL) frequently involves the hepatobiliary system, but its clinical course and pathophysiology are still not fully known. We herein describe a case of IVLBCL mimicking acute hepatobiliary infection. An 85-year-old woman was admitted because of fever and epigastric pain, and she was diagnosed to have acute acalculous cholecystitis based on gallbladder wall thickening with fluid collection. The gallbladder swelling regressed within several days, and areas of intrahepatic hypoperfusion appeared. Inflammation continued despite treatment with antibiotics, and she died within 21 days. An autopsy examination revealed IVLBCL. IVLBCL can present as acute cholecystitis with an improvement in the imaging findings and the presence of a subsequent liver mass.

Key words: intravascular large B-cell lymphoma, acalculous cholecystitis

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is characterized by the selective growth of tumor cells in the lamina of small vessels of various organs, usually without lymphadenopathy (1, 2). IVLBCL frequently involves the hepatobiliary system (3-11), but its pathophysiology and clinical course are still not fully known. We herein describe a case of IVLBCL mimicking hepatobiliary infection that manifested as acute acalculous cholecystitis with an improvement of the imaging findings followed by the onset of liver mass formation.

Case Report

An 85-year-old woman was admitted to our hospital because of fever for 1 week and she had also fractured her leg during a fall. She complained of epigastric tenderness and left leg pain. She had been previously diagnosed as having dementia. Her body temperature was 40.1°C and blood pressure was 116/68 mmHg. Hepatosplenomegaly and superficial lymph node swelling were not detected on palpation. The laboratory findings were as follows: white blood cell count, 9,900/mm^3; hemoglobin level, 11.5 g/dL; platelet count, decreased to 6.6×10^4/μL; increased liver enzyme levels; lactate dehydrogenase (LDH) level, remarkably increased to 633 U/L; D-dimer level, increased to 31.4 μg/mL;

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Table 1. **Laboratory Data on Admission.**

Hematology	Reference range		Biochemistry	Reference range	
White blood cell count (/mm^3)	3,300-8,600	9,900	Total bilirubin level (mg/dL)	0.4-1.5	1.5
Differential count (%)			Direct bilirubin level (mg/dL)	0-0.2	0.3
Neutrophils	38-80	75	Alanine aminotransferase level (U/L)	7-23	31
Lymphocytes	16-50	14	Aspartate aminotransferase level (U/L)	106-322	58
Monocytes	2-10	9	Lactate dehydrogenase level (U/L)	124-222	633
Eosinophils	0-8	0.5	Alkaline phosphatase level (U/L)	106-322	434
Basophils	0-3	1	Gamma-glutamyl transpeptidase level (U/L)	9-32	48
Red blood cell count (×10^4/mm^3)	386-492	375	Urea nitrogen level (mg/dL)	8-20	7
Hematocrit level (%)	35-45	34.4	Creatinine level (mg/dL)	0.46-0.79	0.59
Hemoglobin level (g/dL)	11.6-14.8	11.5	C-reactive protein level (mg/dL)	0-0.15	7.09
Platelet count (×10^4/mm^3)	15-35	6.6			
Prothrombin time (s)	11-14	13.6			
Prothrombin time-international normalized ratio	0.8-1.2	1.21			
Activated prothrombin time (s)	25-36	30.6			
D-dimer (μg/mL)	0-0.8	31.4			

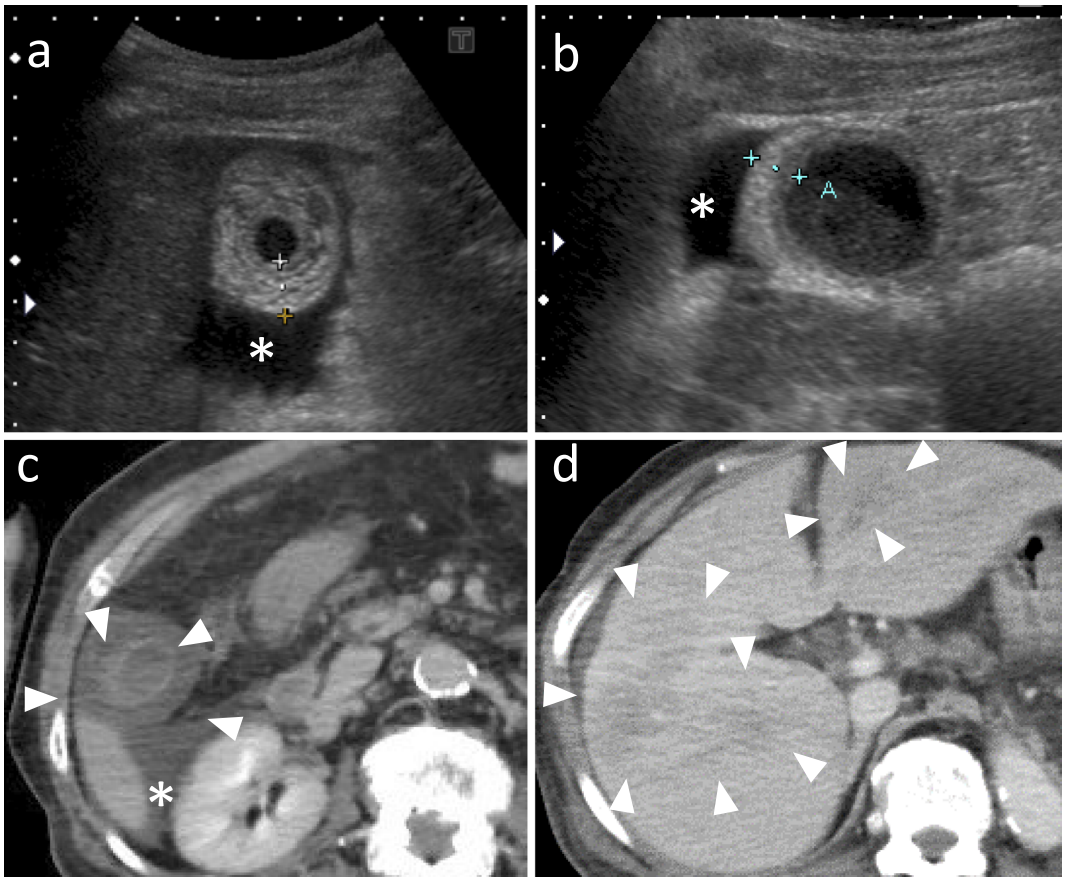

Figure 1. **Imaging studies of the hepatobiliary system. (a) Ultrasonogram revealing an extremely thickened gallbladder wall and fluid collection (∗) on admission. (b) The thickness of the gallbladder wall regressed 5 days after admission. (c) A computed tomography scan showing an extremely thickened gallbladder wall (arrowheads) and fluid collection (∗) on admission. (d) A hypovascular area of the liver is shown (arrowheads) 9 days after admission.**

prothrombin time-international normalized ratio, 1.21; and C-reactive protein level, increased to 7.09 mg/dL (Table 1). No atypical cells were detected in the peripheral blood. Abdominal ultrasonography (US) and computed tomography (CT) examinations revealed gallbladder wall thickening and fluid collection without gallstones (Fig. 1a and c). A con-

trast enhanced CT study on admission revealed no abnormal findings in the liver. Neither lymphadenopathy nor hepatosplenomegaly was detected, and the blood culture results were negative.

She was treated with a course of antibiotics, but fever and thrombocytopenia persisted. A US examination showed a regression of the gallbladder wall thickness within 5 days after admission (Fig. 1b). A CT examination 9 days after admission also showed a regression of gallbladder wall thickness; however, hypovascular areas in the liver newly appeared (Fig. 1d). She was diagnosed to have acute acalculous cholecystitis, followed by an infectious liver abscess. A fluid collection area for drainage was not detected, and cholecystectomy was too invasive because her general condition was very poor. She died 21 days after admission (Fig. 2).

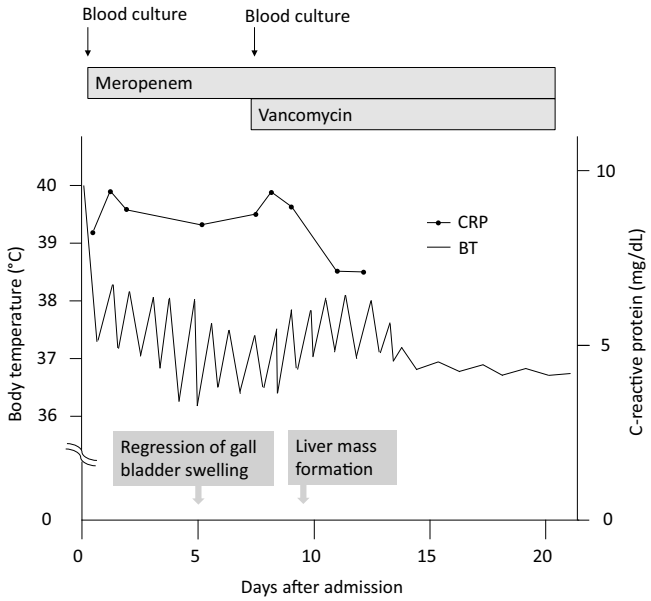

Figure 2. **The patient's clinical course. BT: body temperature, CRP: C-reactive protein**

A necropsy examination of the abdominal organs was performed. The gallbladder was moderately swollen, and all layers of the gallbladder wall were thickened. The small veins in the mucosa and submucosa were filled with large atypical lymphocytes (Fig. 3a and b). Liver masses were unclearly demarcated (Fig. 3d). Microscopically, sinusoids and hepatic veins in the liver mass were also invaded with atypical lymphocytes (Fig. 3e). Atypical lymphocytes were CD20 (+) (Fig. 3c and f), CD79a(+), BCL6(+), MUN1(+), CD3 (+), CD10(-), IMP3(-), EBV-LMP1(-), and CD56(-) according to the immunohistochemical examination. The postmortem diagnosis was IVLBCL. The bone marrow, kidney, spleen, stomach, and small intestine were also affected by the tumor cells. Ultimately, we determined the cause of death as being due to IVLBCL which had invaded her entire body.

Discussion

We noticed two important clinical findings in this case. First, IVLBCL can manifest as acute acalculous cholecystitis with an improvement in the imaging findings, and second,

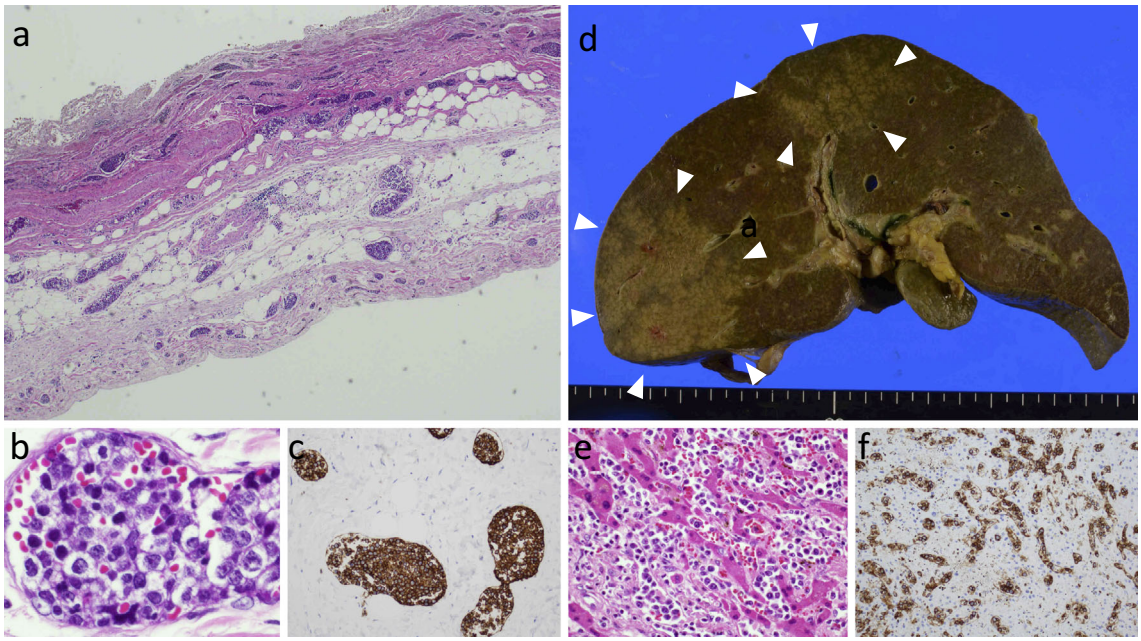

Figure 3. **Pathological findings. (a-c) Microscopic findings of the gallbladder. (a) Thickened gallbladder wall and small vessels are filled with lymphoid cells. (b) Large lymphoid cells with atypical nuclei are observed. (c) Lymphoma cells are positive for CD20. (d-f) Pathological findings of the liver. (d) Macroscopic findings of the liver showing unclear segmental lesions (arrowheads). (e) Sinusoids in the segmental lesion are filled with lymphoma cells. (f) Lymphoma cells are positive for CD20.**

Table 2. Clinical Features of Intravascular Large B-cell Lymphoma of the Gallbladder.

No.	Reference	Age/ sex	Ethnicity of the cohort	Skin lesion	Imaging findings of the gallbladder			Diagnostic method	Therapy	Survival
					Wall thickening	Fluid collection	Gallstones			
1	3	64/F	N/A	No	Yes	No	No	Cholecystectomy	None	5 days
2	4	79/M	Japanese	No	N/A	N/A	N/A	BM biopsy	Chemotherapy	4 months
3	5	51/F	Hispanic	No	N/A	N/A	No	Cholecystectomy, peripheral blood test	Chemotherapy	20 days
4	6	59/M	N/A	No	N/A	N/A	N/A	Cholecystectomy, BM, liver biopsy	N/A	N/A
5	7	83/M	N/A	No	Yes	Yes	Yes	Cholecystectomy, BM biopsy	None	3 days
6	8	77/M	Japanese	No	Yes	Yes	No	Cholecystectomy, splenectomy, BM biopsy	R-CHOP	6 months
7	9	53/M	N/A	No	Yes	No	No	Liver biopsy	R-CHOP	>9 months
8	Our case	85/F	Japanese	No	Yes	Yes	No	Autopsy	None	21 days

F: female, M: male, N/A: not available, BM: bone marrow, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

subsequent acute liver mass formation can occur.

IVLBCL infiltrates the small vessels of many organs, and its tendency of invasion for two ethnic subgroups is different. In a European cohort, IVLBCL predominantly affects the skin and central nerves system. In contrast, in an Asian cohort, IVLBCL predominantly affects bone marrow, resulting in hemophagocytic syndrome, and it more often affects the hepatobiliary system (1, 2). Cholecystitis is a rare initial symptom of IVLBCL, as only 7 cases of this symptom have been reported in English literature (3-9). The imaging features of IVLBCL with cholecystitis include gallbladder wall thickening and fluid collection, usually without gallstones (Table 2).

Acute cholecystitis is mostly associated with cholelithiasis which induces an obstruction of the cystic duct, increases the intraluminal pressure, and together with cholesterol supersaturated bile, triggers an acute inflammatory response (12). Acute acalculous cholecystitis usually occurs in critically ill patients, and it accounts for 5-14% of all causes of cholecystitis (12). Ischemia of the gallbladder appears to play an important role in the pathogenesis of acute acalculous cholecystitis. Regarding the microangiographic findings, in acute acalculous cholangitis, deficits in the microcirculation were observed; in contrast, in gallstone-associated cholecystitis, luxuriant microcirculation was found (13). In the present case, local circulation disturbance by lymphoma cells and systemic immunodeficiency induced acute acalculous cholecystitis. Subsequent antibiotic administration might have been responsible for the regression of gallbladder wall thickening. To our knowledge, this is the first case of IVLBCL with a spontaneous imaging improvement of acute cholecystitis.

IVLBCL can manifest with an acute liver mass. Liver invasion of IVLBCL was reported to occur more frequently in an Asian cohort (55%) than in a Western cohort (26%) (2). The imaging characteristic of liver IVLBCL has been reported as hepatomegaly in many cases. A heterogeneous liver invasion pattern was reported in only a few case reports (10, 11). A tumor invasive lesion indicates a low attenuated area by contrast-enhanced CT or magnetic resonance imaging, with no mass effects on adjacent structures (10). A wedge-shaped low blood flow lesion induced by tumor thrombotic effects has also been reported (11). Positron emission tomography-CT is useful for differentiating the tumor invasive lesions from the thrombotic lesions (11). In the present case, low attenuated areas of the liver on the enhanced CT study were consistent with areas of tumor cell invasion found in the necropsy examination.

The unique characteristic of IVLBCL is that it invades only the small vessels, and the induced ischemic condition can result in many possible clinical manifestations which occur in various organs other than the gastrointestinal system, such as the brain or lung (1, 2). Physicians should therefore consider IVLBCL if an elderly patient complains of consistent fever, pancytopenia, disseminated intravascular coagulation, and a high LDH level. Furthermore, the serum ferritin and soluble interleukin 2 receptor levels tend to be highly elevated in patients with IVLBCL. If these clinical findings suggest that the patient has IVLBCL, then an organ biopsy is mandatory, and the organs that the physician selects for biopsy are key to making an accurate diagnosis. The most relevant diagnostic site seems to be the bone marrow (14). Tumor cell involvement with a sinusoidal pattern and hemophagocytosis in a bone marrow biopsy specimen are characteristic in an Asian cohort (15). The liver is another biopsy site for diagnosing IVLBCL, and a target biopsy should be considered based on the imaging findings as described above. Cholecystectomy is an invasive procedure for diagnosing IVLBCL; 5 patients diagnosed as having IVLBCL by cholecystectomy have been reported, and only 1 patient was subsequently treated with chemotherapy (Table 2). Although a random skin biopsy was reported to be effective in a European cohort, its use still remains controversial in an Asian cohort.

The prognosis of patients with IVLBCL treated by rituximab-containing chemotherapy was reported to be as follows: the 2-year overall survival was 66%, and the progression-free survival was 56% (16). These data suggest that rituximab-containing chemotherapy in patients with IVLBCL is as effective as in those with diffuse large B-cell lymphoma. Making a timely and accurate diagnosis is essential for patients with IVLBCL, because appropriate treatment can improve the clinical outcomes.

The authors state that they have no Conflict of Interest (COI).

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