CASE REPORT

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

Ryusaku Kusunoki¹, Hirofumi Fujishiro¹, Misaki Yoshimura¹, Kiyoka Sawada¹, Shinsuke Suemitsu¹, Masatoshi Kataoka¹, Aya Fujiwara¹, Kousuke Tsukano¹, Satoshi Kotani², Satoshi Yamanouchi¹, Masaki Tanaka², Youichi Miyaoka², Tatsuya Miyake³, Naruaki Kohge¹, Tomonori Imaoka¹, Hideyuki Ohnuma¹, Shunji Ishihara¹ and Yoshikazu Kinoshita⁵

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

(Intern Med 58: 1885-1889, 2019) (DOI: 10.2169/internalmedicine.1995-18)

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/mm³; hemoglobin level, 11.5 g/dL; platelet count, decreased to 6.6×10⁴/μL; increased liver enzyme levels; lactate dehydrogenase (LDH) level, remarkably increased to 633 U/L; D-dimer level, increased to 31.4 μg/mL;

¹Department of Gastroenterology, Shimane Prefectural Central Hospital, Japan, ¹Department of Endoscopy, Shimane Prefectural Central Hospital, Japan, ¹Department of Hepatology, Shimane Prefectural Central Hospital, Japan, ¹Department of Pathology, Shimane Prefectural Central Hospital, Japan and ¹Department of Internal Medicine 2, Shimane University School of Medicine, Japan
Received for publication August 21, 2018; Accepted for publication January 7, 2019
Correspondence to Dr. Ryusaku Kusunoki, ryusakukusunoki@yahoo.co.jp
Table 1. Laboratory Data on Admission.

| Hematology                                      | Reference range | Biochemistry                                      | Reference range |
|------------------------------------------------|-----------------|--------------------------------------------------|-----------------|
| White blood cell count (×10³/mm³)              | 3,300-8,600     | Total bilirubin level (mg/dL)                     | 0.4-1.5         |
| Differential count (%)                         | 9,900           | Direct bilirubin level (mg/dL)                    | 0.0-0.2         |
| Neutrophils                                    | 38-80           | Alanine aminotransferase level (U/L)              | 7-23            |
| Lymphocytes                                    | 16-50           | Aspartate aminotransferase level (U/L)            | 106-322         |
| Monocytes                                      | 2-10            | Lactate dehydrogenase level (U/L)                 | 124-222         |
| Eosinophils                                    | 0-8             | Alkaline phosphatase level (U/L)                  | 106-322         |
| Basophils                                      | 0-3             | Gamma-glutamyl transpeptidase level (U/L)         | 9-32            |
| Red blood cell count (×10¹²/mm³)               | 386-492         | Urea nitrogen level (mg/dL)                       | 8-20            |
| Hematocrit (%)                                 | 35-45           | Creatinine level (mg/dL)                          | 0.46-0.79       |
| Hemoglobin level (g/dL)                        | 11.6-14.8       | C-reactive protein level (mg/dL)                  | 0.0-0.15        |
| Platelet count (×10³/mm³)                      | 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.

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).

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,
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 nervous 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 critically ill patients, and it accounts for 5-14% of all causes of cholecystitis. It 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).

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.

### 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 |
|-----|-----------|---------|-------------------------|-------------|------------------------------------|-------------------|---------|----------|
| 1   | 3         | 64/F    | N/A                     | No          | Yes                                | Cholecystectomy   | None    | 5 days   |
| 2   | 4         | 79/M    | Japanese                | No          | N/A                                | Cholecystectomy   | Chemotherapy | 4 months |
| 3   | 5         | 51/F    | Hispanic                | No          | N/A                                | Cholecystectomy, peripheral blood test | Chemotherapy | 20 days  |
| 4   | 6         | 59/M    | N/A                     | No          | N/A                                | Cholecystectomy, BM, liver biopsy | N/A    | 3 days   |
| 5   | 7         | 83/M    | N/A                     | Yes         | Yes                                | Cholecystectomy, BM biopsy | None    | 6 months |
| 6   | 8         | 77/M    | Japanese                | No          | Yes                                | Cholecystectomy, splenectomy, BM biopsy | R-CHOP | >9 months |
| 7   | 9         | 53/M    | N/A                     | No          | Yes                                | Liver biopsy      | R-CHOP | 21 days  |
| 8   | Our case  | 85/F    | Japanese                | No          | Yes                                | Autopsy           | None    | 21 days  |

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

References
1. Shimada K, Kinoshita T, Naoe T, Nakamura S. Presentation and management of intravascular large B-cell lymphoma. Lancet Oncol 10: 895-902, 2009.
2. Ponzoni M, Ferreri AJ, Campo E, et al. Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. J Clin Oncol 25: 3168-3173, 2007.
3. Flores-Vázquez F, de León-Bojorge B, Ortiz-Hidalgo C, Capurso M. Intravascular lymphoma presenting with clinical features of cholecystitis. South Med J 94: 946-947, 2001.
4. Kuroda N, Mizobuchi M, Shimamura Y, et al. An Asian variant of intravascular lymphoma: unique clinical and pathological manifestation in the gallbladder. APMIS 115: 371-375, 2007.
5. Duan X, Lapus A, Brown RE, Chen L. Intravascular large B-cell lymphoma presenting as cholecystitis and pancytopenia: case report with literature review. Ann Clin Lab Sci 2011; 41: 262-266. Review.
6. Rashidi A, Roullet MR. Intravascular large B-cell lymphoma with leukemic component. Blood 120: 4121, 2012.
7. Yadav S, Chisti MM, Rosenbaum L, Barnes MA. Intravascular large B cell lymphoma presenting as cholecystitis: diagnostic challenges persist. Ann Hematol 93: 1259-1260, 2014.
8. Tajima S, Waki M, Yamazaki H, et al. Intravascular large B-cell lymphoma manifesting as cholecystitis: report of an Asian variant showing gain of chromosome 18 with concurrent deletion of chromosome 6q. Int J Clin Exp Pathol 7: 8181-8189, 2014.
9. Steen ST, Slater ED, Barbaro CE, Huebner ER. An unexpected finding of hepatic lymphoma after emergent cholecystectomy. J Surg Case Rep 2017: rjx051, 2017.
10. Bae J, Lim HK, Park HY. Imaging findings for intravascular large B-cell lymphoma of the liver. Clin Mol Hepatol 21: 295-299, 2015.
11. Abe H, Kamimura K, Mamizu M, et al. Early diagnosis of hepatic intravascular lymphoma: a case report and literature review. Intern Med 53: 587-593, 2014.
12. Indar AA, Beckhamg J. Acute cholecystitis. BMJ 325: 639-643, 2002.
13. Hakala T, Nuutinen PJ, Ruokonen ET, Alhava E. Microangiopathy in acute acalculous cholecystitis. Br J Surg 84: 1249-1252, 1997.
14. Murase T, Yamaguchi M, Suzuki R, et al. Intravascular large B-cell lymphoma (IVLCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CDS. Blood 109: 478-485, 2007.
15. Murase T, Nakamura S, Kawauuchi K, et al. An Asian variant of intravascular large B-cell lymphoma: clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome. Br J Haematol 111: 826-834, 2000.
16. Shimada K, Matsue K, Yamamoto K, et al. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. J Clin Oncol 26: 3189-3195, 2008.