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Case Report

Intravascular large B-cell lymphoma manifesting as cholecystitis: report of an Asian variant showing gain of chromosome 18 with concurrent deletion of chromosome 6q

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Abstract: Intravascular large B-cell lymphoma (IVLBCL), which involves the lumen of small vessels, is a rare variant of extranodal diffuse large B-cell lymphomas. Herein, we present a case of IVLBCL manifesting as cholecystitis in a 77-year-old Japanese man. He presented with fever, fatigue, and weight loss. Physical examination revealed tenderness of the right upper quadrant. The white blood cell count and C-reactive protein levels were elevated. Computed tomography revealed gallbladder thickening and pericholecystic fluid collection; these observations were consistent with the diagnosis of cholecystitis. Serum soluble interleukin-2 receptor levels were highly elevated, and gallium scintigraphy revealed an abnormal accumulation in the spleen, implying lymphoma. Consequently, G-banding analysis of the patient's bone marrow aspirates revealed the presence of different abnormal clones, including those with gain of chromosome 18 and deletion of chromosome 6q. As cholecystectomy was necessary, a concurrent splenectomy was performed to diagnose the disease definitively. Histopathologically, atypical large lymphoid cells were observed to be localized in the vasculature in both the spleen and gallbladder; the atypical cells expressed high levels of CD20, CD5, and CD10, immunohistochemically. These findings were consistent with IVLBCL. The patient underwent post-operative treatment with rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone. However, a pancreatic fistula developed during chemotherapy, causing left pleural effusion and peritoneal effusion; the patient developed sepsis from multidrug-resistant microorganisms, and subsequently died of multi-organ failure 6 months after the diagnosis. No obvious recurrence of the tumor was found during autopsy. We discuss the characteristic karyotype and immunohistochemical status observed in this case.

Keywords: Intravascular large B-cell lymphoma, Asian variant, gain of chromosome 18, deletion of chromosome 6q, gallbladder, autopsy

Introduction

Intravascular large B-cell lymphoma (IVLBCL), which usually does not present as a mass or lymphadenopathy, is characterized by lymphoma cells that are limited to the lumen of small vessels. According to recent WHO classifications, IVLBCL is defined as a rare variant of extranodal diffuse large B-cell lymphomas [1]; few more than 300 cases have been reported [2]. Generally, IVLBCL can infiltrate the vessels of any organ; minimal extravascular location of lymphoma cells may be observed [1]. The thromboembolic nature of the intravascular lymphoma cells contributes to most of the clinical manifestations, which are non-specific, including constitutional, dermatological, and neurological symptoms [3]. Along with the complications of detecting alterations to the organs, diagnosis is delayed in many patients, which is one of the causes of poor prognosis [4].

Two major clinical variants of IVLBCL are recognized: Western and Asian variants [5]. The most commonly involved sites in the Western variant are the central nervous system (CNS) and skin,

Table 1. Reported cases of intravascular large B-cell lymphoma of the gallbladder

Case No	Age	Gender	Variant	Skin	CNS	Peripheral blood	Immunopheno-type	Diagnosed premortem	Survival
1 [6]	85	Female	Western	No	No	Anemia	N/A	Yes	1 month
2 [7]	N/A	N/A	Western	N/A	N/A	N/A	N/A	Yes	5 months
3 [8]	79	Male	Asian	No	No	Pancytopenia	$CD5^-CD10^-$	No	4 months
4 [9]	64	Female	Western	No	Yes	Anemia	$CD5^-CD10^-$	Yes	5 days
5 [10]	51	Female	Western	No	Yes	Pancytopenia	$CD5^+CD10^-$	Yes	20 days
6 [11]	83	Male	N/A	N/A	N/A	Anemia Absolute lymphopenia	$CD5^+CD10^+$	Yes	3 days
7	77	Male	Asian	N/A	No	N/A	$CD5^+CD10^-$	Yes	5 months

while Asian variants are predisposed to multi-organ failure, hepatosplenomegaly, pancytopenia, and hemophagocytic syndrome [1]. It is quite rare for the gallbladder to be the initial presenting site, with reports of only 6 such cases in the English literature (**Table 1**) [6-11]. Described herein is a case of cholecystitis, which was subsequently diagnosed to be a manifestation of lymphoma cell occlusion of the blood vessels, in a 77-year-old Japanese man. The patient was diagnosed with IVLBCL owing to the lack of lymph node swelling; the spleen was the only other organ involved.

The karytotype anomaly, which involved gain of chromosome 18 with concurrent deletion of chromosome 6q, was one of the more significant cytogenetic findings of this case. Cytogenetic analysis of most IVLBCLs has revealed complex karyotypes, including multiple numerical and structural changes (Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer; http://cgap.nci.nih.gov/Chromosomes/Mitelman). Gain of chromosome 18 is sometimes observed in cases of non-Hodgkin lymphomas (NHLs; Mittelman Database) along with deletion of chromosome 6q [12-14]. Although information regarding chromosomal abnormalities in IVLBCLs is limited owing to poor samples for cytogenetic analyses [15, 16], the characteristic karyotypic observations in our case support the diagnosis of IVLBCL.

Materials and methods

The surgically resected specimens were fixed in 10% buffered formalin for approximately 24 h. Then, 5 mm-thick tissue slices were embedded in paraffin to prepare paraffin blocks. Sections (2.5-μm thick) were cut from each paraffin block for hematoxylin and eosin staining; 4-μm sections were utilized for immunohistochemistry (IHC), and Epstein-Barr virus-encoded small RNA (EBER) were used for *in situ* hybridization. An automated slide stainer (Bench-Mark GX; Ventana Medical Systems, Tucson, AZ, USA) was used to perform IHC; the primary antibodies are listed in **Table 2**. EBER *in situ* hybridization was performed according to the manufacturer's instructions (EBER PNA Probe/Fluorescein, Dako).

Results

A 77-year-old Japanese man presented with fatigue, weight loss, and a febrile history of 4 weeks. Physical examination revealed tenderness of the right upper quadrant; however, there was no neurological deficit. Laboratory examinations revealed bicytopenia (white blood cell count of 10.7×10^9 cells/L, hemoglobin level of 12.0 g/dL, platelet count of 63×10^9 cells/L) and high C-reactive protein level (30.9 mg/dL). A peripheral blood smear review could not detect abnormal cells. Liver dysfunction was also observed based on the following measurements: alkaline phosphatase, 1400 U/L (normal range: 80-260); gamma-glutamyl transpeptidase, 173 IU/L (10-50); glutamic-oxaloacetic transaminase, 200 IU/L (9-32); glutamic-pyruvic transaminase, 69 IU/L (4-37); and total bilirubin, 1.9 mg/dL (0.2-1). Lactate dehydrogenase (LDH) was markedly elevated to 1128 U/L (120-240). There were no electrolyte abnormalities.

Whole-body computed tomography (CT) with intravenous contrast revealed gallbladder thickening, pericholecystic fluid collection without calculus (**Figure 1A**, **1C**), and swelling of the spleen (**Figure 1B**). Neither enlarged lymph nodes, nor abnormal masses were detected. These findings were consistent with a diagnosis of cholecystitis, but further complications were highly probable. The involvement of the central nervous system was not evident.

Table 2. Antibodies used in the present study

Antibody against	Clone	Dilution	Antigen retrieval method	Source
CD3	LN10	1:100	HIER	Novocastra Laboratories, Newcastle upon Tyne, UK
CD5	4C7	1:50	HIER	Dako, Glostrup, Denmark
CD10	56C6	1:100	HIER	Novocastra Laboratories, Newcastle upon Tyne, UK
CD20	L26	prediluted	HIER	Ventana Medical Systems, Tucson, Arizona, USA
bcl-2	124	prediluted	HIER	Ventana Medical Systems, Tucson, Arizona, USA
bcl-6	LN22	1:40	HIER	Novocastra Laboratories, Newcastle upon Tyne, UK
MUM-1	MUM1p	1:50	HIER	Dako, Glostrup, Denmark
Cyclin D1	SP4-R	prediluted	HIER	Ventana Medical Systems, Tucson, Arizona, USA
TdT	SEN28	prediluted	HIER	Nichirei Biosciences, Tokyo, Japan
Ki-67	MIB-1	1:100	HIER	Dako, Glostrup, Denmark

HIER: heat-induced epitope retrieval.

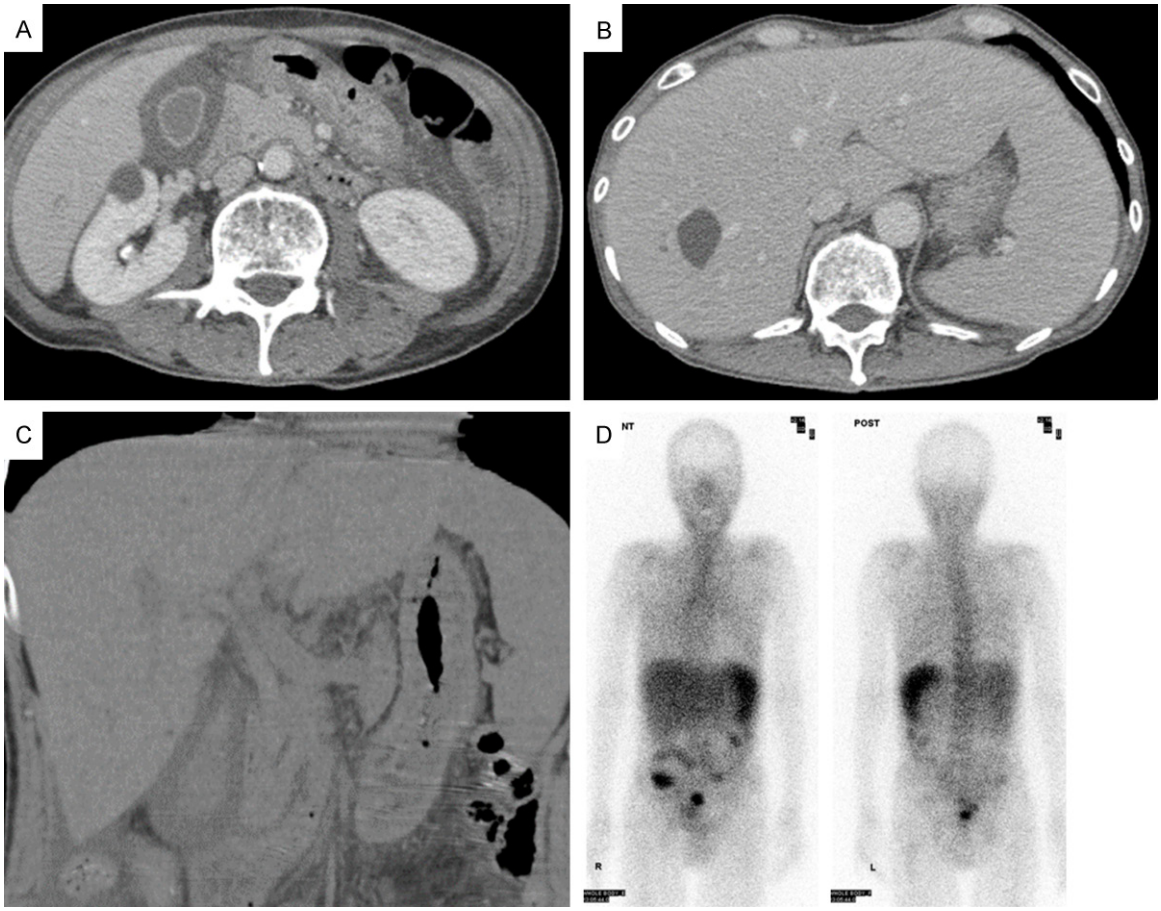

Figure 1. Radiological findings. (A) Contrast-enhanced computed tomography reveals the thickened gallbladder wall, indicating edematous thickening. (B) Computed tomography of another level in the same phase as in (A) showing an enlarged spleen. (C) Longitudinal section of the gallbladder shows no calculus inside it. (D) Gallium scintigraphy reveals accumulation in the spleen; no significant accumulation is evident in other sites.

Tumor screening was carried out in order to exclude malignancy; serum soluble interleukin-2 receptor (sIL-2R) levels were 6530 U/mL. Because of a lack of time for conducting positron emission tomography, gallium scintigraphy was performed as an alternative, which revealed positive findings in the spleen (**Figure 1D**). All the results strongly indicated the presence of lymphoma; subsequently, bone marrow aspiration was performed. Flow cytometry

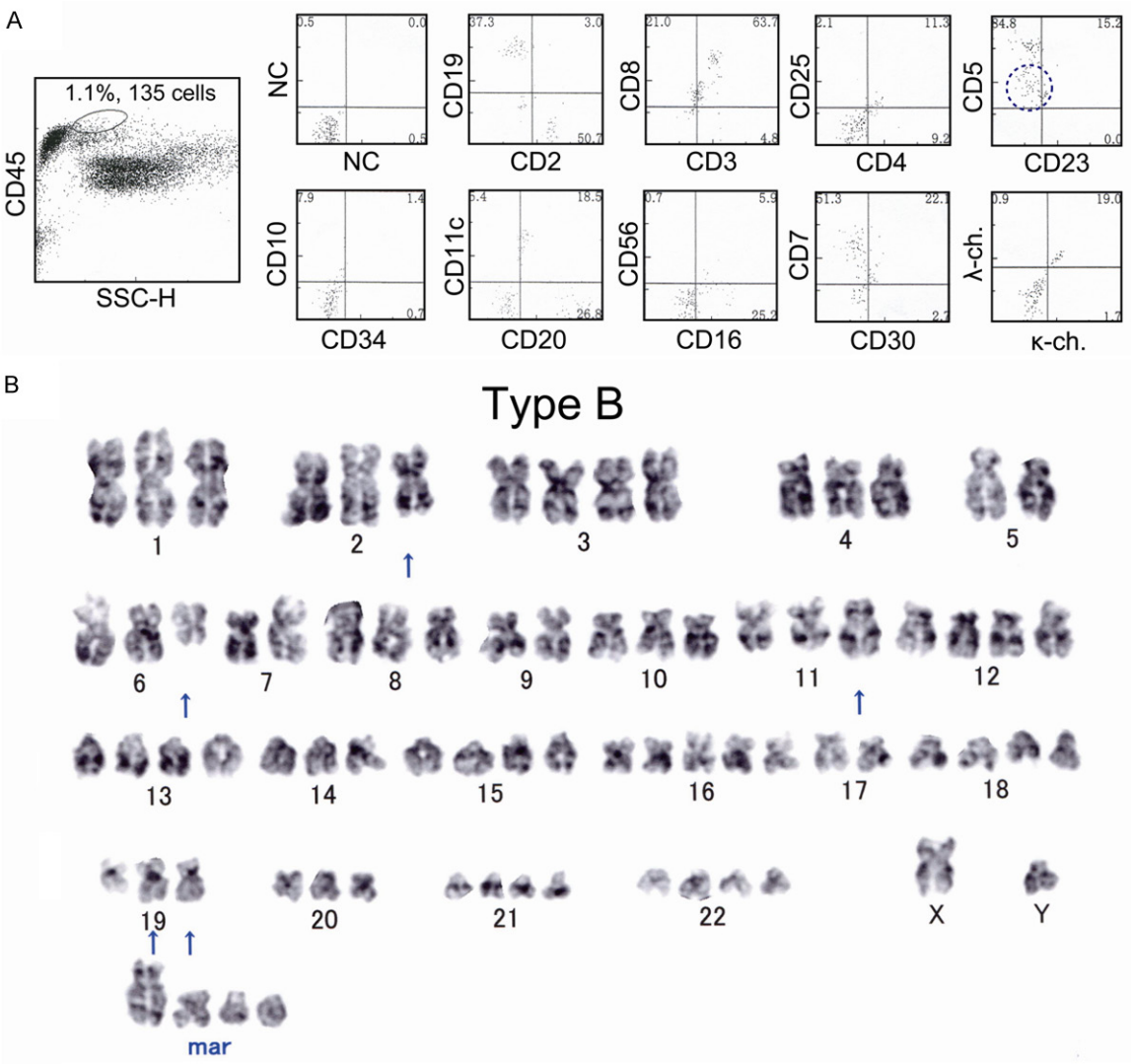

Figure 2. Flow cytometry and G-banding. A. Abnormal cell populations are visible in the encircled area. The encircled CD5-positive population shows CD20 expression. B. Chromosomal abnormalities of type B clones are shown. Arrows indicate structural abnormalities.

(FCM) of the bone marrow identified the following abnormal cell populations: $CD2^-$, $CD3^-$, $CD5^+$, $CD10^-$, $CD19^+$, $CD20^+$, kappa-, lambda- (**Figure 2A**). G-banding analysis of the bone marrow, counting a minimum of 20 cells, included different clones as follows: type A, 47,XY,+8, [1]; type B, 77, XY, -X, add (2) (q21), +3,-5,del (6) (q?), -7, -9, add (11) (q13), +12, +13, +15, +16, -17, +18, add (19) (q13.1) x2, +21, +22, +4mar, [1] (**Figure 2B**); and type C, 46, XY [14]. In addition, 4 subclones derived from type B were observed: 75 [1], and 76 [3]. The bone marrow smear did not reveal any atypical cells. Histopathological examination of a section of the bone marrow clot revealed the presence of sparsely distributed atypical large lymphoid cells (**Figure 4A**), although there was no apparent pattern indicating marrow sinus infiltration. Upon IHC, these atypical cells stained positive for CD20 (**Figure 4B**) and CD5 (**Figure 4C**). Hemophagocytosis was not observed. These findings indicated the presence of lymphoma. The apparent lack of enlarged lymph nodes and abnormal mass suggested the possibility of IVLBCL.

As the patient presented with tenderness in the right upper quadrant, cholecystectomy and splenectomy were performed concurrently. The aim of the splenectomy was to reach a definitive diagnosis, and to determine the IVLBCL subtype. A markedly edematous gallbladder

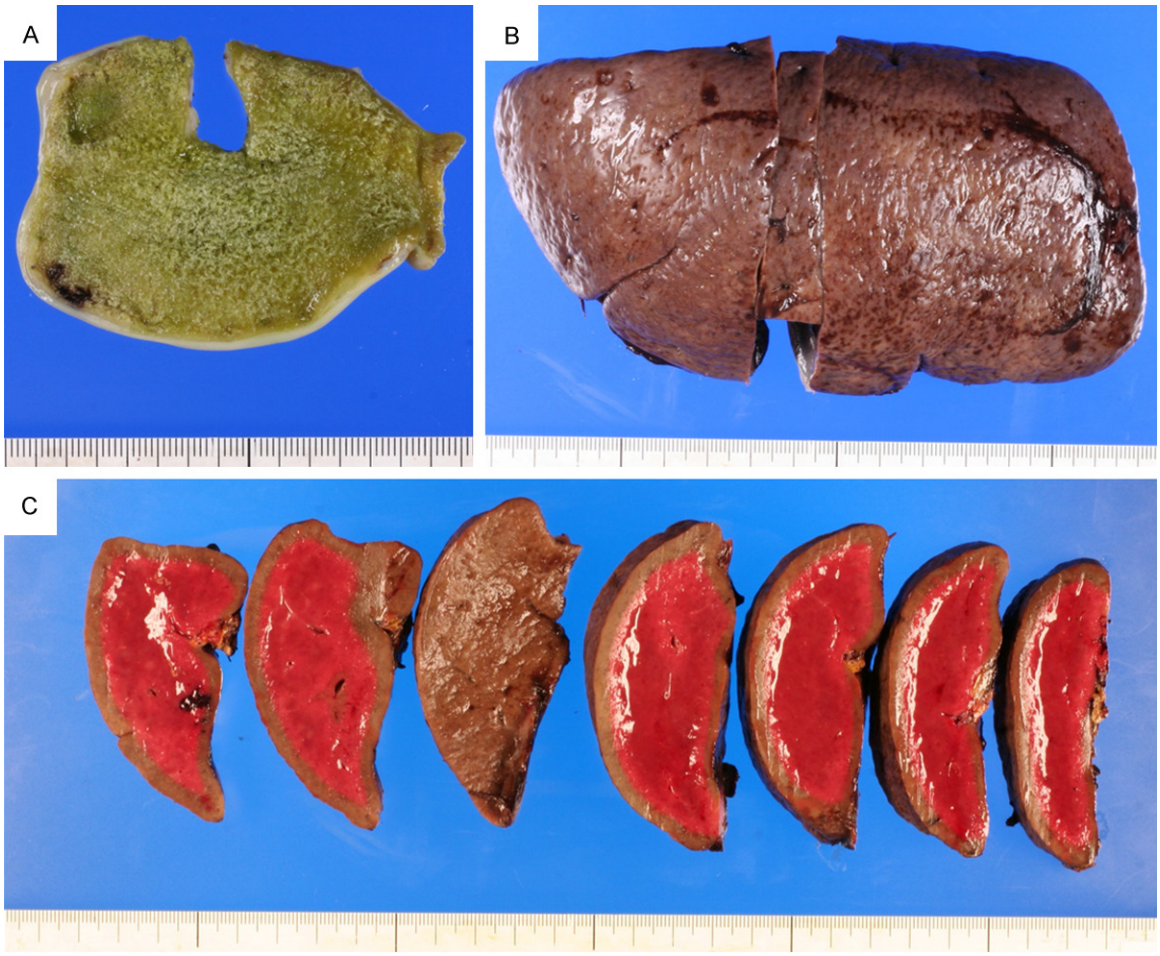

Figure 3. Macroscopic findings. A. The thickened wall of the gallbladder; the incision at the upper rim was created on opening the gallbladder after surgery. B. Swelling of the congested spleen is evident, measuring 14 × 8 × 6 cm. C. Cut surface of the spleen displays no apparent mass.

and a congested spleen were noted during surgical operation; significant lymph node swelling was not evident. Chromosomal analyses and FCM of excised tissue of the gallbladder and spleen revealed no apparent population of abnormal cells. Gross findings of the surgically resected specimens revealed thickening of the gallbladder wall (**Figure 3A**), and enlargement of the spleen, which measured 14 × 8 × 6 cm (**Figure 3B**, **3C**), without the existence of abnormal masses. Histopathological examinations of the gallbladder revealed occluded small vessels especially at the level of muscularis propria (**Figure 4D**). Closer examination showed that the atypical large lymphoid cells were mainly confined to the small vessels (**Figure 4E**). They were strongly immunoreactive for CD20 (**Figure 4F**), CD5 (**Figure 4G**), CD10 (**Figure 4H**), and bcl-2, weakly immunoreactive for bcl-6, and sparsely immunoreactive for MUM-1. Upon IHC, cells were immunonegative for CD3, Cyclin D1, and TdT; cells were also immunonegative for EBER upon *in situ* hybridization. The Ki-67 labeling index was approximately 80%. These findings were all consistent with a diagnosis of IVLBCL. Histopathological findings besides IHC were similar in both the gallbladder and spleen. Lymphoma cells were present in splenic sinusoids rather than in small vessels; the disease was graded as stage IVB.

Following the diagnosis of IVLBCL, the patient underwent 4 cycles of rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone (R-CHOP) treatment, whereupon, the patient recovered his clinical status; C-reactive protein level, liver dysfunction, and LDH levels normalized. Unfortunately, a post-operative pancreatic fistula developed during chemotherapy, caus-

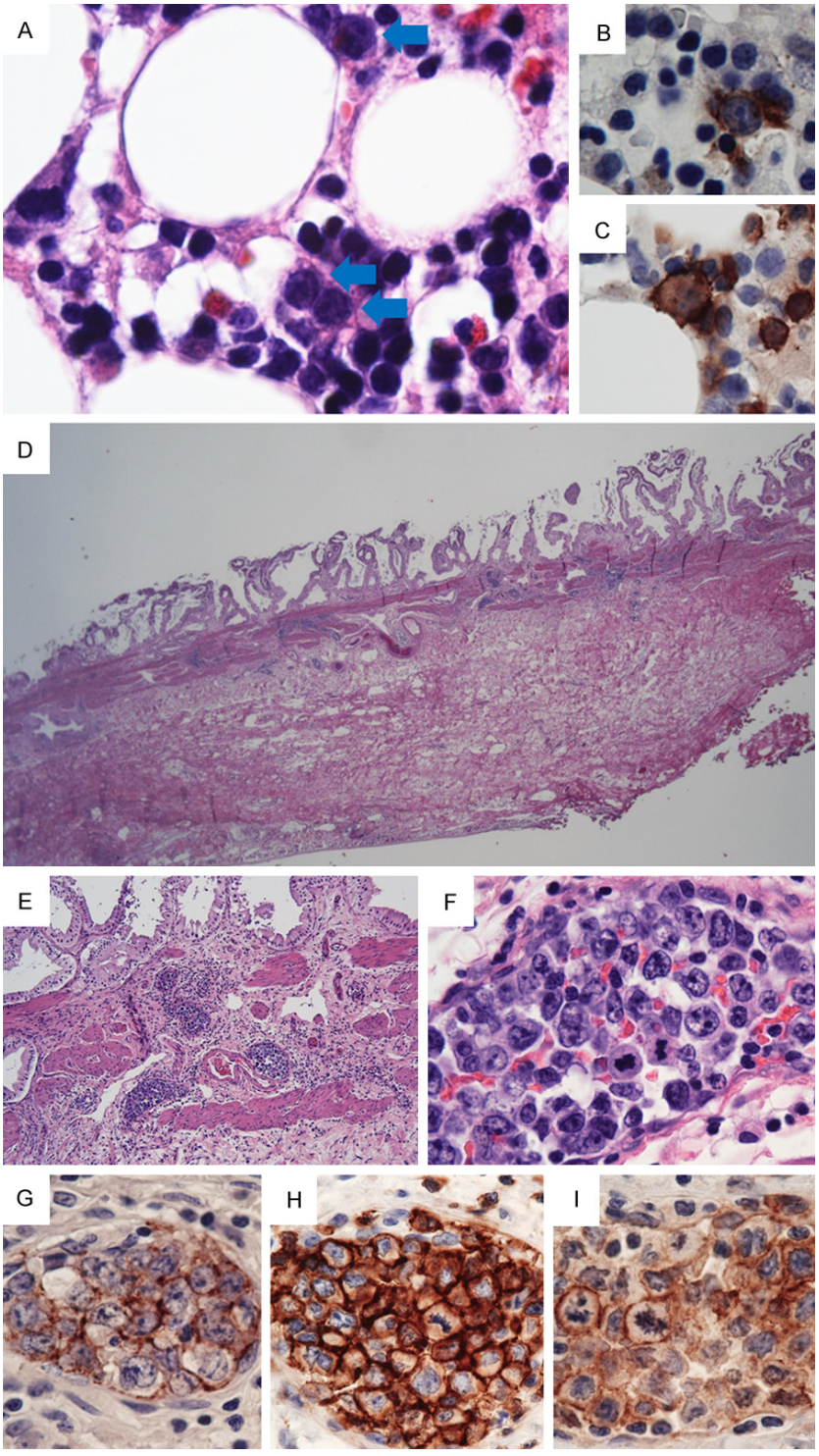

Figure 4. Histopathological and immunohistochemical findings. (A) A section of the bone marrow clot reveals sparsely distributed atypical lymphoid cells (arrows, × 600). (B) An atypical lymphoid cell positive for CD20 is shown (× 600). (C) An atypical lymphoid cell with CD5 immunostaining is depicted (× 600). (D) The wall of the gallbladder, thickened with fibrosis and edema (× 12.5). (E) Small blood vessels near the muscularis propria, predominantly occluded by atypical lymphoid cells (× 200). (F) A small blood vessel, filled with atypical lymphoid cells (× 400). (G-I) Atypical lymphoid cells inside a blood vessel in (G-I) are positive for CD20, CD5, and CD10, respectively.

ing left pleural effusion and peritoneal effusion. As a last resort, total parenteral nutrition was administered via a central catheter in the right inguinal region. The patient developed sepsis with multidrug-resistant *Pseudomonas aeruginosa*, *Enterococcus faecium,* and *Candida glabrata* via the catheter. Upon CT, a large thrombus in the inferior vena cava was revealed, in continuation with the catheter. In spite of intensive treatment, the patient's status continued to decline, and he subsequently died of multi-organ failure, 6 months after the IVLBCL diagnosis.

An autopsy was conducted after obtaining consent from his family. During autopsy, tissue samples were obtained from almost every organ; however, no traces of lymphoma cells were observed. Of note, lymphoma cells were not present in the bone marrow, lymph nodes, CNS, skin, liver, and testis. No visible mass was present outside the organs. It was declared that after 4 cycles of R-CHOP, there was no tumor recurrence for approximately 6 months.

Discussion

The occlusive nature of the intravascular lymphoma cells leads to most of the clinical manifestations of IVLBCL; however, symptoms are non-specific in nature,

and include constitutional, dermatological, neurological manifestations [3]. In English literature, there are only 6 prior reports of patients initially presenting with cholecystitis, which was subsequently diagnosed as IVLBCL (**Table 1**) [6-11].

While diagnosing the underlying disease in this case, the gallium scintigraphy findings of uptake in the enlarged spleen, in conjunction with highly elevated LDH and sIL-2R levels, indicated the presence of lymphoma with involvement in the spleen. As part of the routine protocol, bone marrow aspiration was performed; however, it failed to deliver a definitive histopathological diagnosis of the lymphoma subtype. Splenectomy with cholecystectomy was used to achieve the unequivocal diagnosis of IVLBCL based on the presence of lymphoma cells in the splenic sinusoids and small vessels of the gallbladder, and the lack of a mass. While bone marrow examination is a routine procedure in the diagnosis and work-up of lymphoma, it is not the most efficient way to diagnose IVLBCL [17]. A negative result does not exclude the diagnosis of IVLBCL. In fact, a random skin biopsy from normal-appearing skin is more sensitive in the diagnosis of IVLBCL than bone marrow biopsy. Random skin biopsy, a minimally invasive procedure, revealed positive results in 83% (10 out of 12 cases) of the patients with IVLBCL, as opposed to the lower positive rate during bone marrow biopsy, which showed positive results in only half the patients [18]. Even though random skin biopsy was not necessary in this case, in order to treat the patient's primary complaint of cholecystitis-induced pain in the right upper quadrant, cholecystectomy was necessary; by performing a concurrent splenectomy we were able to attain a definitive diagnosis, as the diagnostic sites had been documented previously [2]. When cholecystitis occurs in an acalculous gallbladder, as in this case, it might be a rare manifestation of IVLBCL [10].

The clinical presentation of splenomegaly and bicytopenia, without apparent symptoms of CNS and skin involvement, was consistent with a diagnosis of the Asian variant of IVLBCL [1], even though hemophagocytic syndrome (HPS) was not observed in this case. In the Asian variant, IVLBCL shows a high degree of association with HPS, particularly in Japanese cases, whereas it is not associated with HPS in the Western variant [3, 4, 19]; HPS was found to occur in 44% (38 out of 87 cases) of Japanese patients and in 19% (7 out of 36) of patients from other Asian countries [19]. In the present case, despite the absence of HPS, other clinical features such as the organs involved, and the race of the patient, supported a diagnosis of the Asian variant.

While CD5 and CD10 were found to be coexpressed with other B-cell markers in 38%, and 13% of the cases, respectively, $CD5^-$ and $CD10^-$ double positivity was observed in 5.2% (5 out of 96) of IVLBCL cases in a large study [2]. Even though FCM failed to identify CD10 expression in our case, it was considered positive based on the results of IHC, as IHC is more effective in detecting CD10 expression than FCM in routine practice. Based on the presence of somatic mutations in variable regions of immunoglobulin heavy-chain genes, it has been suggested that most of IVLBCLs might originate from the post-germinal center (GC) cells [20]. Nevertheless, a minority of the cases probably originate from GC-B-cells [21, 22]. In the present case, the possibility that IVLBCLs originate from GC-B-cells was considered based on the classification by Hans et al. [23], because CD10 was clearly expressed [2]. It is widely known that, in general, the prognosis of IVLBCL is poor [4]; no significant differences were noted for survival among the 3 IVLBCL groups: $CD5^-CD10^-$; $CD5^+CD10^-$; and $CD5^+$ or $CD5^-CD10^+$ [2]. The expression of CD5 or CD10 did not correlate with any significant effects on survival in IVLBCL. The intravascular/sinusoidal growth pattern was a more reliable predictor of poor prognosis than the expression patterns of these markers [2]. The intravascular/sinusoidal growth pattern ensues from defects in the surface receptors for extravascular migration, lack of CD29 and CD54 adhesion molecules, and lack of leukocyte surface glycoprotein CD18 [24].

Of note, cytogenetic findings in this case demonstrated an abnormal karytotype, which involved the concurrent gain of chromosome 18 and deletion of chromosome 6q. The chromosome analysis revealed the presence of a clone with complex abnormalities, which appeared to have expanded to 4 other subclones. The cytogenetic clonal evolution is a known to be a poor prognostic factor in various cancers [25]. Karyotypic data of IVLBCL have

been described in only a few cases, which include a study by Khoury et al. [15]; gain of chromosome 18 was observed in 41% of the cases in the study [15]. Considering the known frequency of gain of chromosome 18 in NHL, which ranges from 15-33%, the higher rate observed in IVLBCL may suggest its involvement in the occurrence of IVLBCL [16]. Meanwhile, deletion of the long arm of chromosome 6 as observed in this case has been described in large series of NHL [12, 13], and has been associated with the full spectrum of NHL [14]. This deletion is one of the most recurrent cytogenetic findings in IVLBCL, and was observed in 59% of 17 cases [15]; it is speculated to have transformed cells into the oncogenic pathway toward IVLBCL in this case. Further studies enrolling more patients are warranted in order to elucidate the karyotypic characteristics that correlate with IVLBCL malignancy and underlie the disease development.

In conclusion. this is the seventh reported case in English literature of IVLBCL that presented as cholecystitis. Its apparent spread was limited to the bone marrow, spleen, and gallbladder. Results of the autopsy revealed that there were no remaining lesions after splenectomy, cholecystectomy, and 4 cycles of R-CHOP. In general, IVLBCL has a poor prognosis; however, within 6 months of diagnosis, the patient died of sepsis, and not of tumor progression. A minor finding indicated that the $CD5^-$ and $CD10^-$positive phenotype originated from GC-B-cells; however, expression of this marker was not found to be correlated with prognosis, while intravascular/sinusoidal growth pattern was found to predict a poor prognosis. Chromosomal abnormalities, specifically the gain of chromosome 18 in conjunction with deletion of chromosome 6q, which possibly led to the initiation of IVLBCL, are important findings. With the absence of information concerning the karyotypic characteristics of IVLBCL, further studies enrolling more patients are anticipated.

Disclosure of conflict of interest

None.

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