

EBV-positive intravascular large B-cell lymphoma of the liver: a case report and literature review

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Case Report

Keywords: Intravascular large B-cell lymphoma, IVLBCL, Liver, EBV, Case report

Posted Date: June 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-16787/v3>

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Version of Record: A version of this preprint was published at Diagnostic Pathology on June 8th, 2020.
See the published version at <https://doi.org/10.1186/s13000-020-00989-x>.

Abstract

Background Intravascular large B-cell lymphoma (IVLBCL) is an extremely rare subtype of diffuse large B-cell lymphoma that most commonly involves the central nervous system, skin, and bone marrow. To our knowledge, Epstein-Barr virus (EBV)-positive IVLBCL in the liver has never been reported in the literature.

Case presentation We report a case of a 65-year-old Chinese man with complaint of fever for 18 days. No obvious abnormality was found by physical examination. Laboratory findings were notable for anemia, thrombocytopenia, and elevated level of serum lactate dehydrogenase. Bone marrow on smear, biopsy, and flow cytometry revealed no lymphoma. Imaging studies showed a slightly lower density lesion in the liver with high fluorodeoxyglucose uptake and hepatosplenomegaly. Percutaneous liver biopsy revealed clustering of large atypical lymphocytes within the hepatic sinusoids. Immunohistochemically, these lymphoma cells were positive for CD20, PAX-5, MUM-1, BCL-6 and CD5, but negative for CD3 and CD10. Besides, Epstein-Barr virus-encoded RNA was detected in tumor cells by in situ hybridization. BCL-2, BCL-6 and MYC genes were intact tested by fluorescence in situ hybridization analysis. The patient was diagnosed as IVLBCL and died after 1 month of hospitalization without receiving immunochemotherapy.

Conclusions IVLBCL of the liver is a highly rare lymphoma with nonspecific manifestations and dismal prognosis. Full recognition of its clinicopathological features will help to better diagnose this disease.

Background

Intravascular large B-cell lymphoma (IVLBCL) is a rare variant of extranodal diffuse large B-cell lymphoma (DLBCL) characterized by the selective growth of lymphoma cells within the lumina of small to medium-sized blood vessels, particularly in capillaries [1]. The clinical manifestations of IVLBCL are various and may vary based on geographic origin of the patients. Two major patterns of IVLBCL have been described: a Western form which displays a relatively high frequency of central nervous system (CNS) and skin involvement, and an Asian form which predominantly shows bone marrow involvement, fever, hepatosplenomegaly, and thrombocytopenia [2-4]. However, IVLBCL of the liver is distinctly uncommon and has been rarely described.

Here we report the first case of hepatic IVLBCL with EBV-positivity diagnosed by percutaneous liver biopsy. Based on literature review, we described and summarized the clinicopathological features of IVLBCL of the liver, and discussed the connection of EBV and disease prognosis.

Case Presentation

A 65-year-old Chinese man with complaint of high spiking fever of unknown origin for 18 days was admitted to Xiangya Hospital, Central South University, Hunan, China. The medical history of the patient was not remarkable. No obvious abnormality was found by

physical examination, including lymphadenopathy, skin lesions, or abnormal neurological signs. Abnormal laboratory findings were as follows: red blood cells, 3.0 ($4.3\text{-}5.8 \times 10^{12}$ /L); platelets, 91 ($125\text{-}300 \times 10^9$ /L); hemoglobin, 85 (130-175 g/L); serum albumin, 25 (40-55 g/L); serum lactate dehydrogenase (LDH), 2,300 (109-245 U/L); C-reactive protein (CRP), 139 (0-8 mg/L); ferritin, >2,000 (10-240 mg/L); alanine aminotransferase (ALT), 109 (9-50 U/L); aspartate aminotransferase (AST), 160 (15-40 U/L). All numbers in parentheses mentioned above indicated the reference interval. The patient underwent an exhaustive infectious disease work-up including viral hepatitis, cytomegalovirus, herpes simplex virus, and human immunodeficiency virus, and all of the results were negative. Besides, the result of DNA quantitative study of EBV was undetectable. Bone marrow on smear, biopsy, and flow cytometry revealed no evidence of lymphomatous cells. Abdominal computed tomography (CT) showed a slightly lower density lesion of 11.5×4.8cm in the right liver lobe (Fig. 1a) with hepatosplenomegaly. Positron emission tomography-computed tomography (PET-CT) revealed abnormal fluorodeoxyglucose (FDG) uptake in the liver without other organ involvement (Fig. 1b). Ultrasonography-guided percutaneous liver biopsy was performed under the impression of a suspected unusual malignant tumor.

Histologically, the hepatic sinusoids were markedly expanded by the selective proliferation of atypical lymphocytes (Fig. 2a & b). Under higher magnification, these neoplastic lymphoid cells were large in size with round to oval-shaped nuclei, vesicular chromatin, prominent nucleoli, and scant cytoplasm (Fig. 2c). Fibrin thrombus and mitotic figures could be easily found. Immunohistochemical staining revealed the tumor cells were positive for CD20 (Fig. 2d), PAX-5, MUM-1, BCL-6 and CD5, and negative for CD3, CD10, CD56, CD38, CD138, MPO, BCL-2, HHV8, CyclinD1, and SOX11 (See Supplementary Fig. 1). The Ki-67 proliferation index was estimated to be 80%. The intravascular growth pattern of tumor cells was confirmed by CD31 staining of the endothelial cells (Fig. 2e). The results of immunohistochemical staining were summarized in Table 1. In addition, the neoplastic cells were positive for Epstein-Barr virus-encoded small RNA (EBER) by in situ hybridization (Fig. 2f). Fluorescence in situ hybridization (FISH) tests were performed on formalin-fixed, paraffin-embedded tissues using *BCL-2*, *BCL-6* and *MYC* dual-color break-

apart probes (Abbott Molecular Inc., USA), and no obvious split signals were observed with each probe (Fig. 3).

Based on these findings, the patient was diagnosed as IVLBCL of the liver with EBV-positivity. The patient was treated with antibiotics initially, and then dexamethasone and supportive treatment. However, the patient's symptoms couldn't be obviously relieved. Because of the rapidly deteriorating general conditions, the patient died from the disease after 1 month of hospitalization without receiving immunochemotherapy.

Table 1 List of antibodies

Antibody	Clone	Dilution	Source	Result
CD20	L26	Ready-to-use	Maixin China	+
PAX-5	ZP007	Ready-to-use	Zhongshan China	+
MUM-1	EP190	Ready-to-use	Zhongshan China	+
BCL-6	MX042	Ready-to-use	Maixin China	+
BCL-2	bcl-2/100/D5	Ready-to-use	Zhongshan China	-
CD3	UMAB54	Ready-to-use	Zhongshan China	-
CD5	UMAB9	Ready-to-use	Zhongshan China	+
CD10	UMAB235	Ready-to-use	Zhongshan China	-
CD56	MX039	Ready-to-use	Maixin China	-
CD38	SPC32	Ready-to-use	Zhongshan China	-
CD138	EP201	Ready-to-use	Zhongshan China	-
MPO	/	Ready-to-use	Zhongshan China	-
CD31	UMAB30	Ready-to-use	Zhongshan China	-
HHV8	13B10	Ready-to-use	Zhongshan China	-
CyclinD1	EP12	Ready-to-use	Zhongshan China	-
SOX11	MRQ-58	Ready-to-use	Zhongshan China	-
Ki-67	MX0006	Ready-to-use	Maixin China	80%

Discussion

IVLBCL has been described in an increasing number of reports, mostly single case report and small series. It primarily affects elderly individuals with a slight predominance in men, and can progressively involve any organ without involvement of lymphoid tissues and peripheral blood [5, 6]. Patients with IVLBCL usually present with a wide range of clinical manifestations that are generalized and nonspecific, or localized and related to the involved organ [4]. Most of the symptoms and signs might be related to

organ dysfunction caused by occlusion of small vessels or capillaries. Due to the absence of significant mass lesions or lymphadenopathy, the clinical picture is further complicated and a timely diagnosis is very challenging.

Previously, one-half of IVLBCL cases were made by post-mortem [2]. With the improvement of awareness of this entity, most patients were diagnosed by bone marrow biopsy and skin biopsy from positive skin lesions or random skin biopsy [4, 7]. In our case, bone marrow biopsy revealed no evidence of lymphoma infiltration, and random skin biopsy was not performed because of a low index of suspicion of IVLBCL. Therefore, a biopsy from an affected organ is necessary. Significantly, PET-CT is a powerful tool for the early diagnosis of IVLBCL by identifying indicated sites for biopsy because these patients usually show high FDG uptake in involved organs [8, 9]. With the review of literature, liver biopsies can be performed using percutaneous, transjugular, or laparoscopic approaches, and each method has advantages and disadvantages [10]. Because of the absence of severe coagulopathy, ultrasonography-guided percutaneous liver biopsy was performed in our patient. Up to present, only 12 cases of IVLBCL diagnosed by liver biopsies have been described in the literature [10-21]. The clinical and immunohistochemical features of the reported cases and our case are summarized in Table 2 [See Additional File 1].

The patients with hepatic involvement of IVLBCL were predominantly men (11/13, 84.6%). The age of the patients ranged from 42 to 79 years, with a mean age of 61 years. With the exception of 2 cases from the West [14, 18], the remaining 11 cases were reported from Asia. Due to the limited number of reported cases, whether IVLBCL of liver is more prevalent among Asian populations is unclear. Lymphoma infiltration of bone marrow was detected in 4/13 patients (30.8%). The common clinical presentations were fever (7/12, 58.3%), anemia (7/12, 58.3%), thrombocytopenia (6/12, 50.0%), hepatomegaly and/or splenomegaly (8/12, 66.7%), and high levels of serum LDH (9/12, 75.0%). The ferritin and liver enzymes levels were elevated in 6 of 12 cases tested (50.0%). The clinical manifestations were variable and nonspecific, but indicative for suspected IVLBCL of the liver. The definitive diagnosis was mainly based on its typical morphologic and immunohistochemical features.

The histopathological findings presented in our case were consistent with those described in previous reports. IVLBCL of the liver was characterized by the infiltration of large atypical lymphocytes cells in the hepatic sinusoids. The neoplastic cells are typically positive for B-cell markers as CD20 and PAX-5, and a subset of cases may co-express the T-cell marker CD5 [22]. According to the algorithm of Hans et al. [23], our case was classified as the non-germinal center B-cell-like subtype (positive for BCL-6 and MUM-1, negative for CD10). Notably, EBV-positive nuclear signals were detected by in situ hybridization in our case. Although EBV-positive diffuse large B-cell lymphoma was listed as a distinct subtype of DLBCL in the revised World Health Organization (WHO) classification [1], no study focusing on EBV expression in IVLBCL has been reported. In addition, data for EBV-expression was not available in 11/12 previously reported cases, and only a case showed EBV-negativity detected by in situ hybridization [12]. The EBV-positivity rate might be higher than actual, as negative cases were less likely to be reported. It has been well established that latent EBV infection is causative of B-cell lymphoma [24]. Our case implied that EBV

infection might be an important risk factor for poor prognosis of IVLBCL, like as the DLBCL. In the previously reported cases of hepatic IVLBCL, molecular characteristics of the tumor cells were not mentioned and need further investigation.

IVLBCL usually shows an aggressive clinical course with a poor prognosis. Specifically, a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone with the recombinant anti-CD20 antibody rituximab (R-CHOP) is the most commonly used regimen to improve the outcome of IVLBCL [25]. Unfortunately, our patient died before treatment could be administered because of rapid disease progression.

Conclusion

In summary, we described a rare case of IVLBCL in the liver diagnosed too late to treat the patient because of a low index of suspicion. We want to emphasize that nonspecific clinical manifestations as fever, anemia, and thrombocytopenia with markedly elevated level of serum LDH should raise the suspicion for IVLBCL and it is crucial to get histology promptly. The difficulties and delays in diagnosis often result in the poor prognosis which makes it urgent need to better understand this lymphoma. Further studies will be required to clarify the mechanisms underlying the involvement of the liver in patients with IVLBCL.

Abbreviations

IVLBCL: Intravascular large B-cell lymphoma; EBV: Epstein-Barr virus; PAX-5: Paired box protein 5; MUM-1: Multiple myeloma oncogene 1; MPO: Myeloperoxidase; DLBCL: Diffuse large B-cell lymphoma; CNS: Central nervous system; LDH: Lactate dehydrogenase; CRP: C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PET-CT: Positron emission tomography-computed tomography; FDG: Fluorodeoxyglucose; EBER: Epstein-Barr virus-encoded small RNA; FISH: Fluorescence in situ hybridization; WHO: World Health Organization; R-CHOP: Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Declarations

Acknowledgments

We thank the Department of Pathology, Xiangya Hospital, Central South University, Hunan, China for assistance with pathological diagnosis.

Funding

Not applicable.

Availability of data and materials

All data generated or analyzed during this case are included within the article.

Authors' contributions

LQJ collected the clinical data and drafted the manuscript. LJH and YKD made the pathological diagnosis. PY, XY, SSY, ZJ, and ZX offered assistance in image selection. WJP made revision to the final manuscript and provided the funding support. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This case study was approved by the Institutional Ethics Committee of Xiangya Hospital Central South University, Hunan Province, China.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the consent form is available for review by the Editor of Diagnostic Pathology.

Competing interests

The authors declare that they have no competing interests.

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Figures

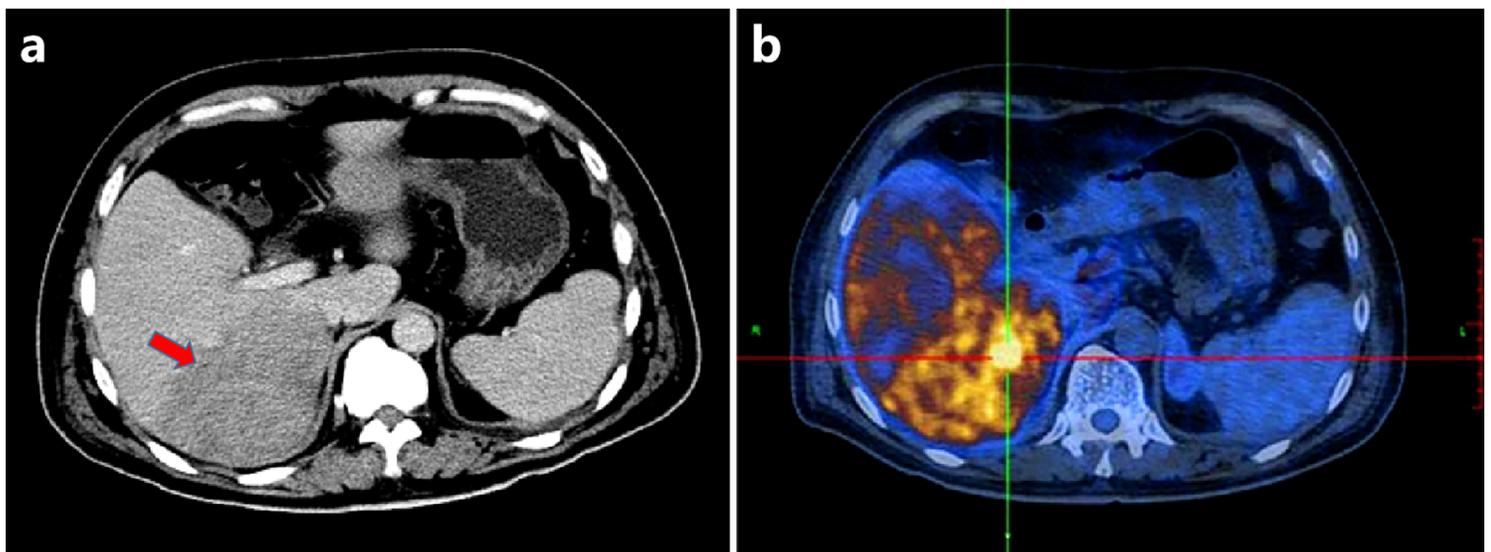


Figure 1

a. Abdominal CT showed a slightly lower density lesion of 11.5×4.8cm (arrow) in the right liver lobe with hepatosplenomegaly. b. PET-CT revealed abnormal fluorodeoxyglucose uptake in the liver.

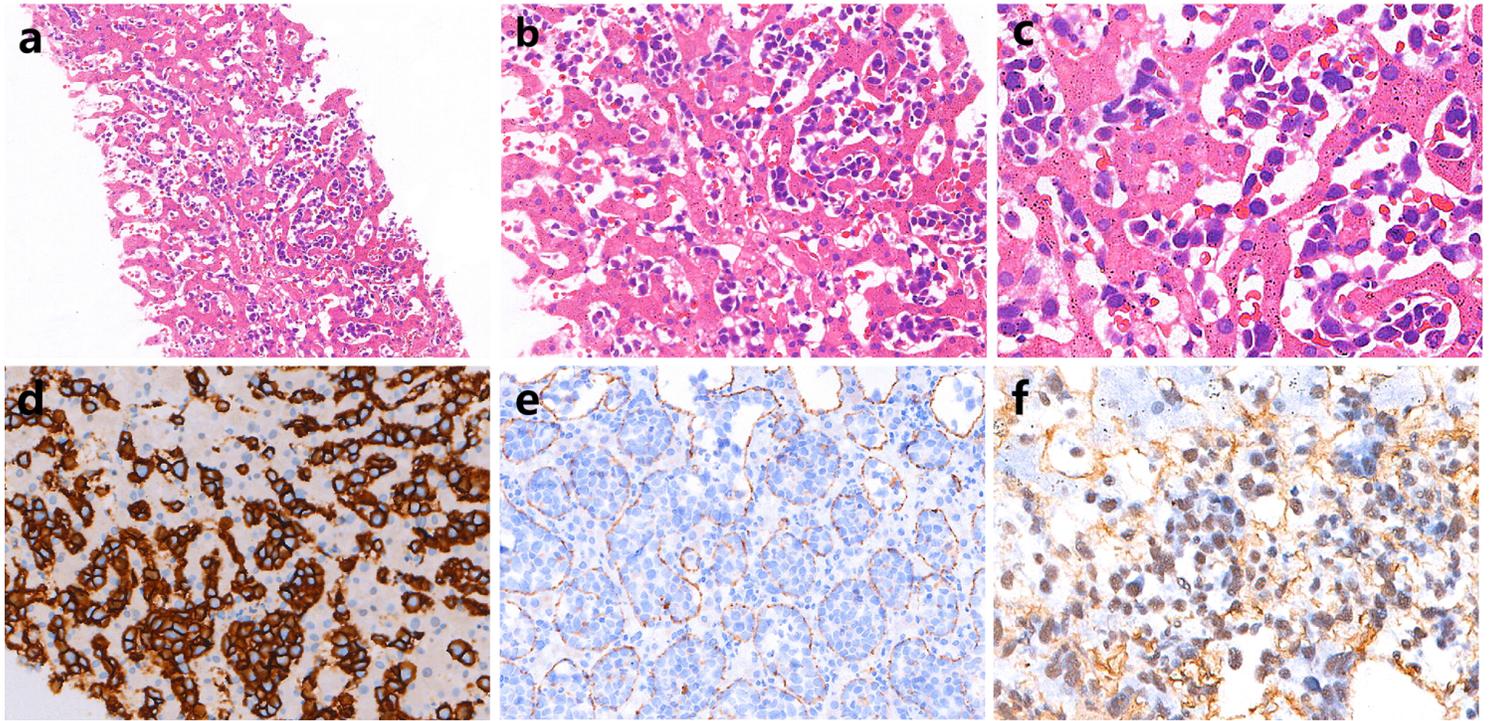


Figure 2

a & b Histopathology analysis showed the hepatic sinusoids were markedly expanded by the selective proliferation of atypical lymphocytes (a: magnification $\times 100$ and b: magnification $\times 200$). c. The neoplastic cells were large in size with round to oval-shaped nuclei and scant cytoplasm (magnification $\times 400$). d. The tumor cells were positive for CD20 (magnification $\times 200$). e. CD31 immunohistochemical staining highlights the intravascular growth pattern of tumor cells (magnification $\times 200$). f. The neoplastic cells were positive for EBER by in situ hybridization.

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