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Commentary

EBV-positive Intravascular Large B-cell Lymphoma

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EBV-positive intravascular large B-cell lymphoma

Intravascular large B-cell lymphoma (IVLBCL) is a rare and specific variant of diffuse large B-cell lymphoma (DLBCL) [1,2]. Epstein-Barr virus (EBV)-positive IVLBCL is particularly rare and highly aggressive. Up to present, only a few cases of EBV-positive IVLBCL have been reported in the literature. Here, we would like to further explore its clinicopathological and molecular features to ensure the awareness and accurate diagnosis of this entity.

We have performed an extensive literature search for the reported cases of IVLBCL. A total of 5 cases of IVLBCL with EBV-positivity have been reported in the literature [3-6]. These cases were carefully reviewed to extract essential clinicopathological data. The clinical and immunohistochemical features of EBV-positive IVLBCL are summarized in Table 1. The patients were 3 males and 2 females, with an average age of 59 years ranging from 42 to 73 years. All 5 cases were initially diagnosed in the extranodal sites included liver [3], uterus, ovary [4], testis [5], kidney, and brain [6]. Only one case was diagnosed by autopsy and confirmed central nervous system involvement [6]. There was no skin lesion in all 5 patients. Depending on the organ involved, the clinical presentations were variable and nonspecific. Laboratory findings revealed level of lactate dehydrogenase (LDH) was markedly elevated in 3 of 4 patients examined. And 3 of 5 patients underwent bone marrow biopsies which revealed no lymphoma infiltration. Histopathologically, all 5 cases demonstrated selective proliferation of large lymphoma cells within the lumina of small vessels or sinuses. Immunohistochemistry staining results showed these tumor cells were positive for B-cell markers (such as CD20) but negative for CD3. In this series, 4 of 5 cases also weakly expressed CD5 antigen. According to the study on 96 patients with IVLBCL from Japan, 36 cases (38%) were positive for CD5 [7]. All findings of the 5 cases were consistent with the diagnosis of IVLBCL.

The mechanism of intravascular localization of neoplastic cells in IVLBCL is incompletely understood due to the rarity of this entity. Most investigation have demonstrated that tumor cells of IVLBCL uniformly lacked expression of adhesion molecules, such as CD29 (β-1 integrin) and CD54 (ICAM-1), which may inhibit migration of neoplastic cells through vessel walls [8]. Unfortunately, lack of expression of adhesion molecules was not detected in the 5 cases or the detection result was not informative. Significantly, the neoplastic cells of these cases were positive for EBV-encoded RNA (EBER) by *in situ* hybridization.

EBV was the first oncogenic virus ever identified, and EBV infection has been associated with a number of malignancies [9]. In the 2017 revised World Health Organization (WHO) classification of lymphomas [1], EBV-positive DLBCL, not otherwise specified (NOS), was designated as a distinct clinicopathological entity. Of note, detection of EBER was considered standard for diagnosis. However, EBV has been rarely demonstrated in IVLBCL. According to the largest study, a total of 59 of 96 cases with IVLBCL were performed molecular analysis by using *in situ* hybridization on EBV, and all cases showed that neoplastic cells were negative for EBER [7]. From the extensive literature review, we have found a few cases of IVLBCL were demonstrated EBV infection by using polymerase chain reaction (PCR) on EBV, while tumor cells were negative for

Case	Age (y) /Sex	Sites	Clinical symptoms	Skin lesion	CNS symptoms	Laboratory findings	Imaging features	BM	Immunohistochemistry				EBER ISH	Treatment	Outcome (months)
									CD20	CD3	CD5	CD10			
1 [3]	65/M	Liver	Fever	No	No	Thrombocytopenia, hypoalbuminemia, anemia, and high levels of CRP, LDH, ferritin, ALT and AST.	Hepato-splenomegaly and a low density lesion in the liver	No	+	–	+	–	+	ND	Died (1)
2 [4]	42/F	Uterus and bilateral ovaries	General fatigue, genital bleeding and weight loss	No	No	Anemia, elevated levels of CRP and sIL-2R	Huge uterine myoma	No	+	–	+	–	+	R-CHOP	Alive (10)
3 [5]	56/M	Testis	Fever, disorientation and testicular pain	No	No	NR	A small nodular lesion in the epididymal region	No	+	–	–	ND	+	R-CHOP and radiotherapy	Alive (20)
4 [6]	73/M	Kidney	Double vision	No	Yes	High level of LDH	NR	NR	+	–	+	ND	+	CHOP	Alive (71)
5 [6]	58/F	Brain	Demention and quadriplesia	No	Yes	High level of LDH	NR	NR	+	–	+	ND	+	ND	Died (3)

M: Male; F: Female; CNS: Central Nervous System; NR: Not Reported; ND: Not Done; CRP: C-reactive Protein; LDH: Serum Lactate Dehydrogenase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; sIL-2R: Soluble Interleukin 2 Receptor; BM: Bone Marrow involvement; EBER: Epstein-Barr virus-encoded RNA; ISH: In situ Hybridization; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CHOP: Rituximab combined with CHOP

Table 1: Clinicopathological features of previously reported cases of EBV-positive IVLBCL.

EBER by *in situ* hybridization or the result was not available in the original article [6,10-12]. Besides, we have also found a rare case of primary intra-aortic EBV-positive large B-cell lymphoma, which was confirmed pathologically at autopsy [13]. In spite of sharing a common feature of intravascular selective growth, this entity is distinct from IVLBCL histopathologically, which is characterized by the selective growth of neoplastic cells within the lumina of small to medium-sized blood vessels [2]. Therefore, it is controversial whether this case should be included in the entity of IVLBCL. However, the positive expression of EBV in tumor cells by *in situ* hybridization and the rapidly deteriorating clinical process of the patient have successfully attracted our attention.

The etiology and the risk factors of IVLBCL have remained uncertain. The EBV infection has been reported to be associated with an increased risk of DLBCL (NOS) [9], while the association between the EBV infection and IVLBCL remains unknown. The fact that all 5 cases showed evidence of EBV infection lends support to the association of this entity to viral illness. The available literature on this subject is scant, and this association needs to be explored further. In addition, immunodeficiency is an independent risk factor for the development of lymphoproliferative disorders. Of the 5 patients, there was one patient who was immunosuppressed owing to azathioprine therapy for autoimmune hepatitis [5], resulting in rapid onset of local and systemic symptoms. Therefore, lymphomas in this setting may be more aggressive clinically.

Of the 5 patients with EBV-positive IVLBCL, only 3 patients received the lymphoma treatment regimens which included cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or rituximab combined with CHOP, and had a complete remission at least initially. The other 2 patients died from the disease because of the rapidly deteriorating general conditions, with a survival time ranging from 1 to 3 months. Due to the rarity of this entity and lack of representativeness, the prognosis of EBV-positive IVLBCL could not be well evaluated. To establish the therapeutic strategy for the patients with EBV-positive IVLBCL, further observation and many more case analyses may be necessary.

EBV-positive IVLBCL is extremely rare and aggressive. Full recognition of its clinicopathological features and improvement of the diagnostic awareness may help to promote proper treatment.

Conflicts of Interests

The authors have no conflicts of interest to declare.

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