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Short Communication

EBV positive DLBCL, NOS

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Abstract

Epstein-Barr virus positive DLBCL, NOS (EBV + DLBCL, NOS) occurs in apparently immunocompetent patients usually older than 50 years, which can also occur in younger patients and has a worse prognosis than EBV negative tumors. EBV + DLBCL, NOS has a broader morphological spectrum. Here the clinicopathological of EBV positive DLBCL will be discussed.

Keywords
EBV positive DLBCL; immunophenotype; Cytogenetics

Identity

Other names
Senile EBV-associated B-cell lymphoproliferative disorder; age-related EBV+ lymphoproliferative disorder; EBV-associated B-cell lymphoproliferative disorder of the elderly.

Clinics and pathology

Disease

EBV+ diffuse large B-cell lymphoma (DLBCL), NOS was initially described by Oyama et al in 2003 (Oyama et al, 2003). The 2008 monograph included "EBV-positive DLBCL of the elderly" as a provisional entity. These tumors occur in apparently immunocompetent patients usually older than 50 years and have a worse prognosis than EBV negative tumors. But EBV+ DLBCL have been increasingly recognized in younger patients, with a broader morphological spectrum and better survival than initially thought. This new information has led to substitution of the modifier "elderly" with "not otherwise specified" (EBV+ DLBCL, NOS) in the updated classification (Swerdlow, et al, 2008. Swerdlow, et al, 2016. Nicolae A, et al, 2015. Uccini S, et al, 2015. Ok CY, et al. 2013).

Phenotype/cell stem origin

The neoplastic cells are of B-cell lineage, expressing the pan B-cell antigens CD19, CD20, CD22, CD79a, and PAX5 and are negative for pan T-cell antigents. Immunoglobulin light chain restriction may be difficult to demonstrate, except in cases with immunoblastic or plasmablastic features in which cytoplasmic Ig can be assessed. Plasmacytoid cases can be weakly positive or negative CD20. EBV+ DLBCL of the elderly usually has an ABC immunophenotype being MUM1/IRF41 and CD102 and usually BCL6. BCL-2 and CD30 are usually positive, and CD15 is negative. It is speculated that either there is a change in B-cell population during aging or there is putative pathological specificity of EBV in elderly patients with DLBCL. Most cases displayed a striking shift to an ABC immunophenotype with prominent activation of NF-kB pathway (Swerdlow, et al, 2008. Swerdlow, et al, 2016).

Epidemiology

The median age of patients with EBV+ DLBCL is 71 years (range, 50-91 years), however, younger patients can be affected. There is a slight male predominance, with a male to female ratio of 1.4 :1. There is a higher prevalence of EBV+ DLBCL among East Asians (8.7%-11.4%) compared with 5% in Western countries. The definitive criterion for EBV positivity in EBV+ DLBCL remains under discussion (Swerdlow, et al, 2008).

Clinics

EBV+ DLBCL is characterized by higher age distribution and an aggressive clinical course with a median survival of 2 years in Asian patients. Initial reports emphasized that EBV+ DLBCL of the elderly commonly involved extranodal sites. Site of primary extranodal involvement include the skin, soft tissue, bones, nasal cavity, pharynx/hypopharynx, tonsils, tongue, lung, pleura, stomach, liver, spleen, peritoneum, cecum, and bone marrow. Patients with EBV+ DLBCL of the elderly have a poorer overall survival and progression-free survival than patients with Activated B-cell-like (ABC) -type EBV-negative DLBCL in older European patients (Swerdlow et al, 2008).

Pathology

Two morphologic subtypes of EBV+ DLBCL have been recognized: polymorphic and monomorphic. Both subtypes may include large transformed cells or immunoblasts, as well as HRS-like giant cells and may demonstrate increased mitotic activity and areas of geographic necrosis.

The polymorphic subtype displays a broad range of B-cell maturation, and lesions are composed of centroblasts, immunoblasts, and plasmablasts with a variable component of admixed reactive cells, including small lymphocytes, plasma cells, histiocytes, and epithelioid histiocytes.

The monomorphic subtype of EBV+ DLBCL of the elderly is composed of monotonous sheets of large transformed B cells. Cases of EBV+ DLBCL of the elderly also can have a mixed pattern with intermingled polymorphic/and monomorphic areas, suggesting that the subtypes represent 2 ends of a morphologic spectrum.

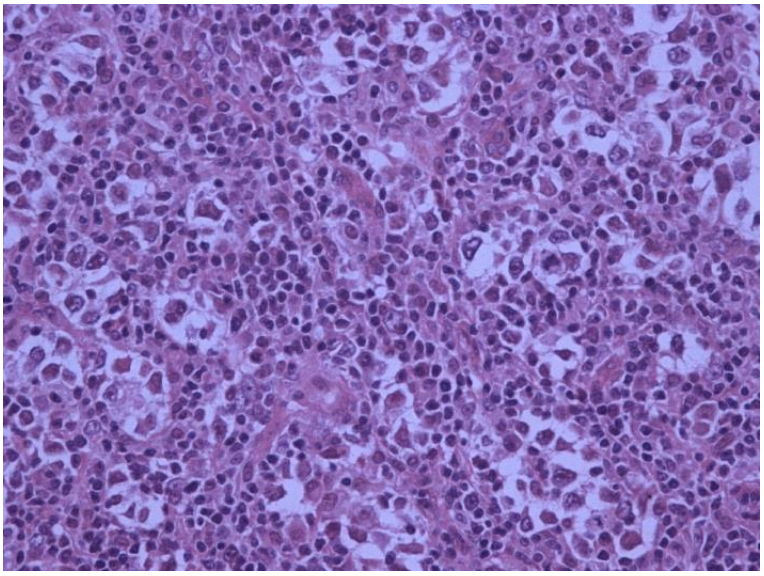

Figure1. EBV+ DLBCL, polymorphic subtype. A broad range of B-cell maturation, composed of centroblasts, immunoblasts, and plasmablasts with a variable component of admixed reactive cells (HE staining).

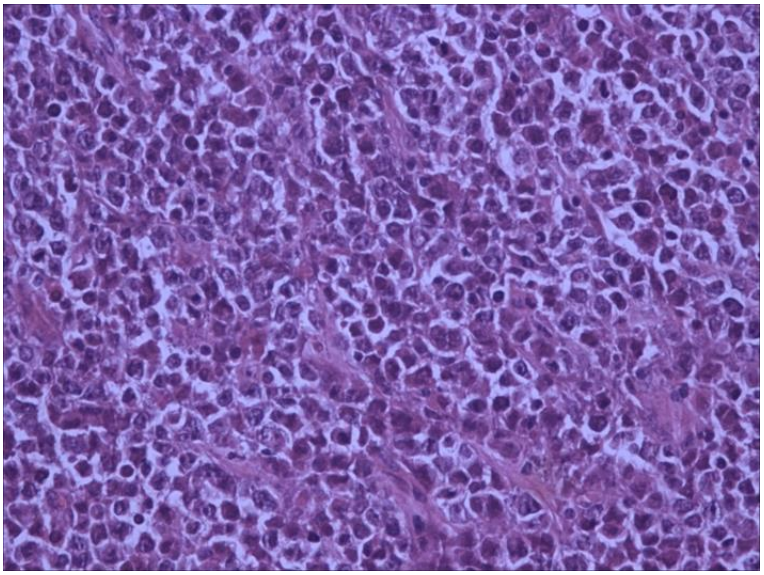

Figure 2. EBV+ DLBCL, monomorphic subtype. Sheets of large transformed B cells HE staining).

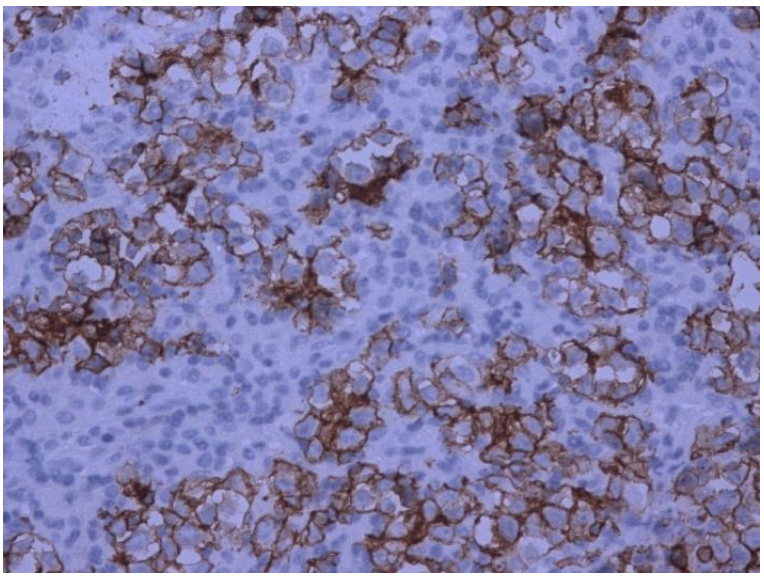

Figure 3. The lymphoid cells are positive for CD20.

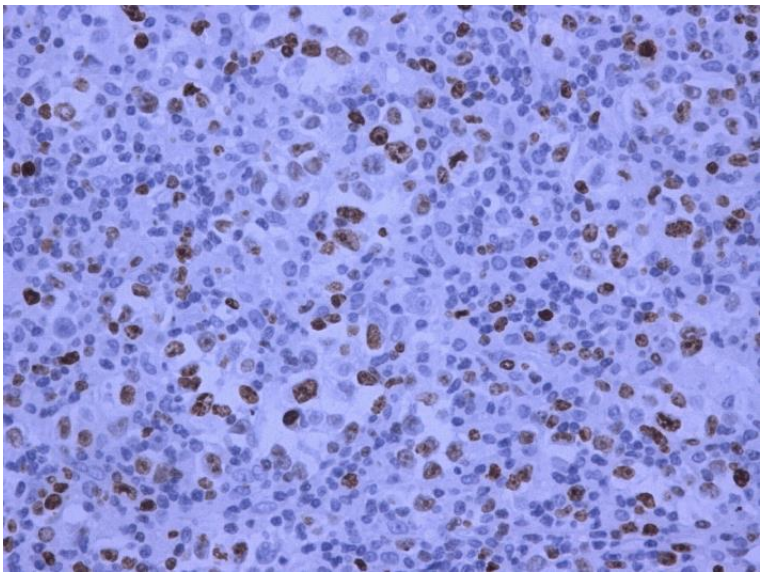

Figure 4. The lymphoid cells are positive for EBER (In situ hybridization).

Treatment

EBV+ DLBCLs, including EBV+DLBCL of the elderly, respond more poorly to treatment with a poorer outcome compared with patients who have EBV-negative DLBCL. Novel therapeutic approaches need to be considered for patients with EBV+ DLBCL. Possible therapeutic approaches include (1) EBV-specific adoptive immunotherapy; (2) miRNA-targeted therapy; (3) combination therapy based on EBV lytic phase induction followed by exposure of the tumor cells to antiherpsvirus drugs (Swerdlow et al, 2008. Swerdlow, et al., 2016). Less toxic treatment strategy such as a cell therapy for EBV-specific viral antigens will be needed and should be evaluated in clinical trials (Oyama T et al., 2007).

Prognosis

Young patients present with nodal disease and have a good prognosis (Nicolae A et al., 2015). The International prognostic index (IPI) and the Oyama score can be used for risk-stratification. The Oyama score includes age >70 years and presence of B symptoms. The expression of CD30 is emerging as a potential adverse, and targetable, prognostic factor (Castillo JJ et al., 2018). In contrast to non-Western populations, the North American population had a low prevalence of EBV+ DLBCL that did not convey an adverse prognosis. A history of immunosuppression, while known to be a risk factor for the development of diffuse large B-cell lymphoma, did not affect subsequent prognosis (Tracy SI et al., 2018).

Cytogenetics

Note

Only a few genetic studies on cases of EBV+DLBCL have been performed. The immunoglobulin genes are monoclonally rearranged in most cases, with clonality of EBV also usually detectable using EBV terminal repeat regions probes and molecular techniques. IGH-mediated translocations are uncommon (15%). However, these analyses were restricted to single loci (IGH, IGK, IGL, PAX5, MYC, BCL2, and BCL6). Given the presence of a low number of genomic aberrations in EBV+ DLBCL, it has been suggested that immunosenescence coupled with the EBV oncogenic properties is sufficient, and additional chromosomal alterations are therefore usually not needed for lymphomagenesis.

Although viral miRNA constitutes only 2% of all miRNA in EBV-positive DLBCL, the viral miRNAs share seed sequence homology with cellular miRNA. It also becomes evident that EBV miRNAs have evolved to target multiple cellular pathways rather than a single pathway. Interestingly, cellular miRNAs are modulated by viral proteins. MIR155 has been shown in DLBCL, especially in the ABC subtype, and can be induced by PDLIM7 (LMP1) via the NF-kB pathway (Swerdlow, et al ,2008. Ok CY, et al. 2013).

A study showed that the gene expression profiling and microRNA profiles of younger patients with EBV+ DLBCL is similar to older patients (Ok CY, et al. 2015).

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