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LYMPHOID NEOPLASIA

Comment on Nicolae et al, page 863

The expanding spectrum of EBV$^+$ lymphomas

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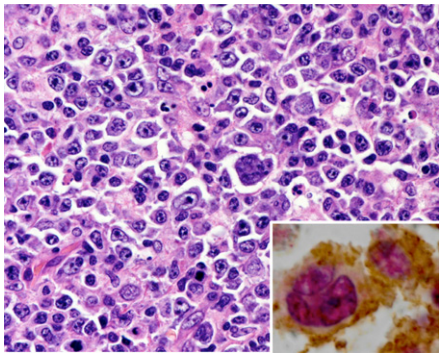
In this issue of *Blood*, Nicolae et al at the National Cancer Institute describe a series of Epstein-Barr virus–positive (EBV$^+$) diffuse large B-cell lymphomas (DLBCLs) in young patients (median age 23 years) without known immunodeficiency.[1]

This suggests a paradigm shift from the prevailing dogma that EBV$^+$ DLBCL is limited to the elderly. The original name, senile EBV-associated lymphoproliferative disorder,[2] implied a relationship to the weakness of old age. The World Health Organization (WHO) in 2008 adopted a less pejorative term, EBV$^+$ DLBCL of the elderly, which still rankled many patients and their treating physicians because old age was defined as >50 years.[3] The current study indicates that in addition to senescence of the immune system in older individuals, a similar spectrum of lymphoma occurs in young immunocompetent patients, possibly related to alterations in the immune environment, which in turn may be modulated by EBV. Cases of EBV$^+$ large B-cell lymphomas (LBCLs) showed high programmed death ligand 1 (PD-L1) positivity in the tumor cells (see figure) and expression of PD-L1 and indoleamine 2,3-dioxygenase in the microenvironment, and it is postulated that these factors contribute to dysregulation of immune checkpoints and tumor immune escape.



Lymph node biopsy from a patient with EBV$^+$ LBCL. The cells are pleomorphic including the presence of Hodgkin-like cells. Inset, the neoplastic B cells are positive for PAX5 (red nuclear stain) and strongly express PD-L1 (brown), which may inhibit the host antitumor response. Hematoxylin and eosin, original magnification ×250; inset, double immunostain for Pax5 (red) and PD-L1 (brown).

Diagnosis of EBV-related DLBCL may be problematic due to the variable histologic appearance and overlap with other EBV-related lymphoid proliferations.[4-6] The lymphoma may be nodal or extranodal, and many patients have a high International Prognostic Index with a prognosis that is inferior to that of EBV-negative (EBV$^-$) DLBCL even when adjusted for age. Geographical necrosis is common, and there is a histologic continuum from polymorphous to diffuse proliferation of large cells. Histologic features may overlap with Hodgkin lymphoma, and polymorphous cases are similar to those seen in the posttransplantation setting. In addition to DLBCL-not otherwise specified, cases in young patients described by Nicolae et al had a T-cell/histiocyte-rich LBCL–like or gray zone appearance. The malignant cells are variably positive for EBV-encoded small RNAs (EBERs), EBV latent membrane protein 1 (LMP1), and EBV nuclear antigen 2 (EBNA2), with EBV latency pattern II or III. Those in the younger age group were predominantly latency type II. Latency II (LMP1$^+$, EBNA2$^-$) is a pattern more in keeping with an immunocompetent patient. LMP1 was expressed in most tumor cells. A requirement for the diagnosis is that the malignant cells rather than the background inflammatory cells express EBV. The lymphomas usually have a non–germinal center B or activated B-cell phenotype (CD10$^-$, IRF4/MUM1$^+$). There is clonal rearrangement of immunoglobulin genes, which may help differentiate neoplastic proliferations from reactive hyperplasia and infectious mononucleosis of the elderly.

Cases that histologically resemble EBV$^+$ DLBCL occasionally present in the oropharynx and skin with localized sharply circumscribed mucocutaneous ulcers. They are more common in older female patients, some of whom have been treated with methotrexate for rheumatoid disease.[7-9] Histologically, there is surface ulceration and a polymorphous lymphoid proliferation that includes atypical immunoblasts that can resemble Hodgkin cells, and a brisk inflammatory reaction at the base of the ulcer. The lesions tend to remain indolent without progression, but may recur. By contrast, patients with secondary cutaneous involvement by systemic EBV-related lymphoproliferative disorder do poorly.

In contrast with older individuals, the younger patients described by Nicolae et al had predominantly nodal disease and had a favorable outcome. The term "of the elderly" is no longer valid with reference to EBV$^+$ LBCL, and it is likely that it will be eliminated in the update of the WHO

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classification which is in progress.[10] This study provides an argument for screening cases of DLBCL for EBV (EBER, LMP1, and possibly EBNA2) in young as well as elderly or immunosuppressed patients.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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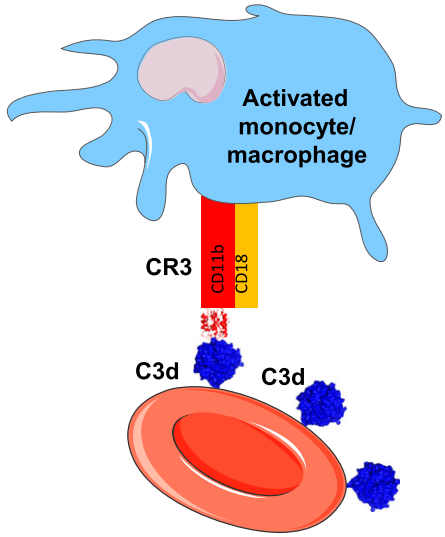

PNH erythrocytes from eculizumab-treated patients

Mechanism of C3dg-CR3–mediated erythrophagocytosis. The erythrocytes of patients with PNH and treated with eculizumab are opsonized by C3dg. C3dg serves as a ligand of CR3, facilitating the erythrophagocytosis by activated monocytes and potentially by macrophages. The cell shapes in the figure are taken from Servier Medical Art database (http://www.servier.fr/smart/banque-dimages-powerpoint). The atomic coordinates of the integrin I domain of the CR3-C3d complex (Protein Data Bank ID code 4M76) and the C3d domain taken out of it are used for the representation.

● ● ● RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Lin et al, page 891

C3dg-CR3 interaction in erythrophagocytosis

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In this issue of *Blood*, Lin et al elegantly demonstrate that the erythrocytes from patients with paroxysmal nocturnal hemoglobinuria (PNH) undergoing eculizumab treatment, which are opsonized with the complement C3dg, can interact with complement receptor 3 (CR3) on activated monocytes, thus leading to erythrophagocytosis.[1]

The central complement system component C3 undergoes a complex cascade of activation steps, generating multiple activation fragments (C3a, C3b, iC3b, C3dg, C3d, etc), each of which interacts with different receptors and has distinct functions.[2,3] After the discovery of the complement receptors ~35 years ago, CR3 was considered essential for phagocytosis of iC3b opsonized immune complexes and pathogens, without interacting with C3dg.[4] Nevertheless, recent studies have demonstrated that CR3 interacts with C3dg.[5] Lin et al provide evidence for the pathophysiologic relevance of this interaction in the context of the PNH. In this disease, the red blood cells of patients lack 2 membrane-expressed complement regulators, CD55 and CD59, and hence are susceptible to complement-mediated lysis, leading to a life-threatening intravascular hemolysis. The approval for clinical use of the complement C5-blocking antibody eculizumab revolutionized the treatment of these patients, because it prevents complement-mediated intravascular hemolysis.[6] It is noteworthy that eculizumab blocks only the late stages of the complement cascade, thus leading to an accumulation of C3d(g)-opsonized erythrocytes in the circulation of patients with PNH.

Lin et al investigate the role of C3dg opsonization for the phagocytosis of these cells. They confirm that C3dg can interact with the phagocytic receptor CR3 using purified proteins. Further, they demonstrate that this interaction can occur at the phagocytic synapse between patients' erythrocytes and activated monocytes (see figure). The level of erythrophagocytosis was linearly correlated with the level of C3d opsonization of patients' purified erythrocytes. These results provide a hint to explain the residual hemolysis that occurs despite treatment with eculizumab in some PNH patients. Further studies are needed, however, to identify the proportion of cells that are lysed by the proposed mechanism in vivo. A recent study correlated the level of hemolysis in PNH patients with the level of free eculizumab present in the circulation.[7] They found that the low levels of circulating eculizumab (measured at the moment before the next injection of the drug) correlated with a detectable complement activity, the presence of hemolysis, and a need for blood transfusion. Moreover, in this study, the level of C3d(g) on patients' erythrocytes did not correlate with increased hemolysis or a need for blood transfusion. Analysis in 2 additional cohorts (where the level of free eculizumab was not measured) suggested that the opsonization of PNH erythrocytes by C3d(g) leads to extravascular clearance of these cells, and that this type of clearance may contribute to the low level of hemolysis and residual transfusion requirement observed in some patients on

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