Commentary

Classification of lymphomas is an evolving process because various sophisticated diagnostic tests have helped us to understand the biology of these tumors. Diffuse large B-cell lymphoma (DLBCL) is clinically, morphologically and genetically a heterogeneous group of NHL.[1] Identification of these clinicopathological entities can help us refine our classification and treatment. Gene expression profiling studies have recently identified three molecularly distinct forms of systemic DLBCL as germinal center B-cell-like (GCB), the activated B-cell-like (ABC) and the so-called type 3, a subgroup that did not express genes characteristic of the GCB-like nor the ABC-like subgroup.[1] Various studies have showed that immunohistochemistry also helps to identify these subgroups. Generally CD10 and bcl-6 are used as GCB subgroup markers and MUM1/interferon regulatory factor 4 as an activated or non-GCB subgroup marker.[1] Tumor cells of DLBCL can co-express both MUM1 and bcl-6 unlike normal germinal-centre B cells.[2]

Most primary central nervous system lymphomas (PCNSL) are high-grade, CD20 positive DLBCLs. PCNS DLBCLs are biologically different from nodal DLBCLs and probably evolve through different molecular mechanisms. The clinical behavior and prognosis of PCNS DLBCL also differ significantly in comparison to nodal DLBCL. PCNS DLBCLs are more frequently classified into the non-GCB subgroup than nodal DLBCL.[3] The study on PCNSL published in this issue also proves that PCNSL has an activated B-cell immunophenotype with almost universal expression of MUM1 and frequent co-expression of MUM 1 and bcl-6.[4] The nodal DLBCL with a GCB phenotype has a longer survival compared to the ABC group.[3] However, studies have not demonstrated a statistically significant difference in terms of overall and disease free survival between these two subtypes in PCNS DLBCL, as discussed by Mahadevan *et al*.[4] The high prevalence of non-GCB phenotype with MUM1 positivity probably explains the uniformly poor prognosis of PCNSL.[4]

Another controversial issue is the role of Epstein-Barr virus (EBV) in lymphomagenesis. It is important to understand this association because of the possibility of EBV-targeted therapy.[5] Though EBV is present in the majority of AIDS-associated PCNSL, tumors in immunocompetent individuals are infrequently associated with EBV. Studies worldwide showed that only about 5-10% of PCNS DLBCLs are associated with EBV in immunocompetent patients. A Japanese study revealed a slightly higher incidence of 13.6% in immunocompetent individuals.[6] Interestingly Indian studies have not demonstrated any etiological role for EBV in immunocompetent patients. The study by Mahadevan, *et al*. also showed that all tumors were negative for EBV by *in situ* hybridization of EBV-encoded RNA (EBER) and immunohistochemistry for athe latent membrane protein-1(LMP-1) antigen.[4] EBER *in situ* hybridization is ideal for detecting and localising latent EBV in biopsy samples. Though detection of EBV-associated antigens such as LMP-1 by immunohistochemistry is rapid and economical, false positivity can result from various reasons like poor fixation and immunostaining of some brain tissue tumor cells.[5] The role of viruses in the pathogenesis of PCNSL is still not clear. The potential role of neurotropic viruses such as the JC virus is to be investigated.[7]

Mahadevan, *et al*. have to be congratulated for their extensive research on the immunophenotypic subtyping of PCNSL and its association with EBV. Further research is required in India to understand the pathogenesis of PCNSL.

Marie Moses Ambroise

Department of Pathology, Pondicherry Institute of Medical Sciences, Puducherry, India

Address for correspondence:
Dr. Marie Moses Ambroise,
Department of Pathology,
Pondicherry Institute of Medical Sciences,
Puducherry, India.
E-mail: drmosesa@yahoo.com

References

1. De Paepe P, De Wolf-Peeters C. Diffuse large B-cell lymphoma: A heterogeneous group of non-Hodgkin lymphomas comprising several distinct clinicopathological entities. Leukemia 2007;21:37-43.
2. Falini B, Fizzotti M, Pucciarini A, Bigerna B, Marafioti T, Gambacorta M, *et al*. A monoclonal antibody (MUM1p) detects expression of the MUM1/IRF4 protein in a subset of germinal center B cells, plasma cells, and activated T cells. Blood 2000;95:2084-92.
3. Lin CH, Kuo KT, Chuang SS, Kuo SH, Chang JH, Chang KC, *et al*. Comparison of the expression and prognostic significance of differentiation markers between diffuse large B-cell lymphoma of central nervous system origin and peripheral nodal origin. Clin Cancer Res 2006;12:1152-6.
4. Mahadevan A, Rama Rao C, Shanmugham M, Shankar SK. Primary central nervous system diffuse large B cell lymphoma in the immunocompetent: Immunophenotypic subtypes and EBV association. J Neurosci Rural Pract 2015;6:10-6.

5. Tandon A, Challa S, Shanmugam M, Gopalan S, Paul RT, Digumarthi R. Epstein-Barr virus as a possible etiologic agent in primary central nervous system lymphoma in immunocompetent individuals. Neurol India 2009;57:36-40.
6. Kitai R, Matsuda K, Adachi E, Saito Y, Nakajima T, Takeuchi H, *et al.* Epstein-Barr virus-associated primary central nervous system lymphoma in the Japanese population. Neurol Med Chir (Tokyo) 2010;50:114-8.
7. Del Valle L, Enam S, Lara C, Miklossy J, Khalili K, Gordon J. Primary central nervous system lymphoma expressing the human neurotropic polyomavirus, JC virus, genome. J Virol 2004;78:3462-9.

Access this article online

Quick Response Code:

Website: www.ruralneuropractice.com