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Genomic Landscape and Immune Escape Mechanisms in Intravascular Large B-Cell Lymphoma

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Abstract

Intravascular Large B-Cell Lymphoma (IVLBCL) is a rare, extranodal, non-Hodgkin lymphoma characterized by selective growth within vessels. Recent phenotypic and genetic studies have shed insight into disease pathogenesis and potential therapeutic targets. Frequently mutated genes detected include MYD88 L265P, CD79B and PIM1. This molecular profile shows similarities to diffuse large B-cell lymphomas with MCD/Cluster 5 genetic signature, a finding also shared with primary central nervous system lymphoma and primary diffuse large B-cell lymphoma of the testis. A subset of IVLBCL cases also express programmed cell death protein 1 (PD-1) ligands, PD-L1 and/or PD-L2 and harbor underlying PD-L1/PD-L2 genetic alterations. Emerging reports suggest other immune evasion mechanisms may also be exploited, including alterations in Major Histocompatibility Complex (MHC). Although data is still limited, in part due to the rarity of IVLBCL, recent studies have expanded our understanding into the disease biology and provide rationale for potential targeted therapies.

Keywords: Intravascular lymphoma; Extranodal lymphoma; Genomics; NF-kB, PD-L1; Immune escape

Description

Intravascular Large B-Cell Lymphoma (IVLBCL) is a rare, aggressive, extranodal non-Hodgkin lymphoma characterized by selective growth within vessels. The clinical manifestations can be non-specific and highly variable. The two most recognized variants include classic and Hem Phagocytic Syndrome (HPS) associated forms. The classic variant typically presents with cutaneous and neurological symptoms. Hemo Phagocytic Syndrome (HPS) associated variant presents with multi organ failure, hepatosplenomegaly and pancytopenia [1]. An isolated cutaneous variant has also been described, which tends to have a more indolent course [2]. Rituximab based therapy has improved clinical outcomes in IVLBCL [3]. However, the frequency of Central Nervous System (CNS) involvement and relapse is relatively high [4]. Clinicopathologic data regarding IVLBCL has been limited in part due to the rarity of disease. However, recent phenotypic and genetic characterization has greatly evolved our understanding into the disease pathogenesis. Here we summarize the history of IVLBCL and provide an update on studies that have defined genetic alterations and pathways that are relevant to the biology of this uncommon lymphoma.

Historical perspective

IVLBCL was first described in literature as “angioendotheliomatosis proliferans systemisata” and thought to be derived from endothelial cells [5]. The disease was later defined through immunophenotyping as an intravascular lymphoma [6]. Clonal rearrangement of the immunoglobulin gene was subsequently demonstrated through polymerase chain reaction [7]. Though cytogenetic data is limited, complex karyotype with abnormalities involving chromosomes 1, 6, 8, 9, 14, 18 and/or 19 have been described [8,9]. The exact pathogenetic mechanism of IVLBCL is not currently fully understood. In one study, somatic mutations were detected in the variable region of the immunoglobulin heavy chain gene and the authors suggested that the neoplastic cells may originate from a post germinal centre origin [10]. Based on Hans Algorithm Using Immunohistochemistry (IHC) to predict cell of origin most IVLBCL cases express a Non-Germinal Center B-Cell (nGCB) like immunophenotype [11,12]. RNA gene expression analysis in one IVLBCL case showed greater molecular similarity to nGCB Diffuse Large B-Cell Lymphoma (DLBCL) than to GCB DLBCL [13].

Genetic investigations and insights

Relatively larger case studies have recently provided further insight into the genetic landscape of IVLBCL and how it compares to other large B-cell lymphomas. Evaluation using targeted next generation sequencing and/or whole exome sequencing have shown a high prevalence of mutations in MYD88 L265P and/or mutations in CD79B, as well as PIM1

[14-18]. Mutations in these genes are involved in activating the NF-kB signaling pathway associated with B-cell lymphomagenesis. This molecular profile shows similarities to the recently described MCD/Cluster 5 genetic DLBCL subgroup. This subgroup is enriched with DLBCLs with Activated B-Cell (ABC) phenotype and propensity for involving extranodal sites, particularly the CNS and testis [19-21]. Additional mutations detected in IVLBCL include, but are not limited to other genes related to the B-cell receptor/NF-kB signaling pathway such as IRF4, KLHL14 and RAC2 [16-18].

Genetic alterations in PD-L1/PD-L2 and overexpression of programmed cell death protein 1 (PD-1) ligands, PD-L1 and PD-L2 have also been recently described in IVLBCL. PD-L1 expression in 4 of 9 (44%) evaluable IVLBCL cases [22]. Similar results were subsequently reported (36%, 4/11) and (35%, 12/34) [17,23]. In our study cohort, we previously described 39% (n=12/31) of IVLBCL cases which expressed PD-L1 and/ or PD-L2 by IHC [24]. Underlying genetic alterations are at least one potential mechanism leading to PD-L1 and/or PD-L2 overexpression. PD-L1/PD-L2 structural variants or copy-number gains in 10 of 21 cases (48%) [16]. Copy number gains and amplification in 3 of 9 (33%) cases [17]. We found 7 of 29 cases (24%) in our study cohort with chromosomal alterations involving gains, amplification and rearrangements [24]. Other mechanisms of immune escape may also be implicated in IVLBCL, including alterations in Major Histocompatibility Complex (MHC). Missense mutations in B2M have been described in IVLBCL cases in one study [17]. Deletions and frameshift indels in genes associated with HLA-A/B/C and HLA class II were detected in another [16]. By IHC, we found loss of MHC class I and/or II expression in 27% of our study cohort [24].

Recent genetic studies have provided a way to sub classify the heterogeneous category of DLBCL into distinct molecular subgroups. IVLBCL appears to show similarities with DLBCLs corresponding to the recently described MCD/cluster 5 genetic signatures. These features are shared with certain other extranodal large B-cell lymphomas such as primary CNS lymphoma and primary DLBCL of the testis [25,26].

Conclusion

IVLBCL is an uncommon aggressive B-cell lymphoma with characteristic but non-specific clinical features and distinct pathologic feature of atypical cells confined to intravascular spaces. Genetic abnormalities leading to the activation of the NF-kB pathway and supporting immune evasion are relatively common. Currently, the 5th edition World Health Organization (WHO) and 2022 International Consensus Conference (ICC) categorize intravascular lymphoma as a distinct entity. However, both the 5th edition WHO and ICC classifications acknowledge that future data may support grouping IVLBCL under an umbrella category with other primary extra nodal large B-cell lymphomas with similar genetic signature. Further insight into the immune escape strategies exploited by IVLBCL could also provide rationale to investigate new therapeutic strategies in this aggressive disease.

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