DOI: 10.55522/jmpas.V13I5.6714 **ISSN NO. 2320 – 7418**

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

Diffuse large B-cell lymphoma: causes, pathology, and emerging treatments

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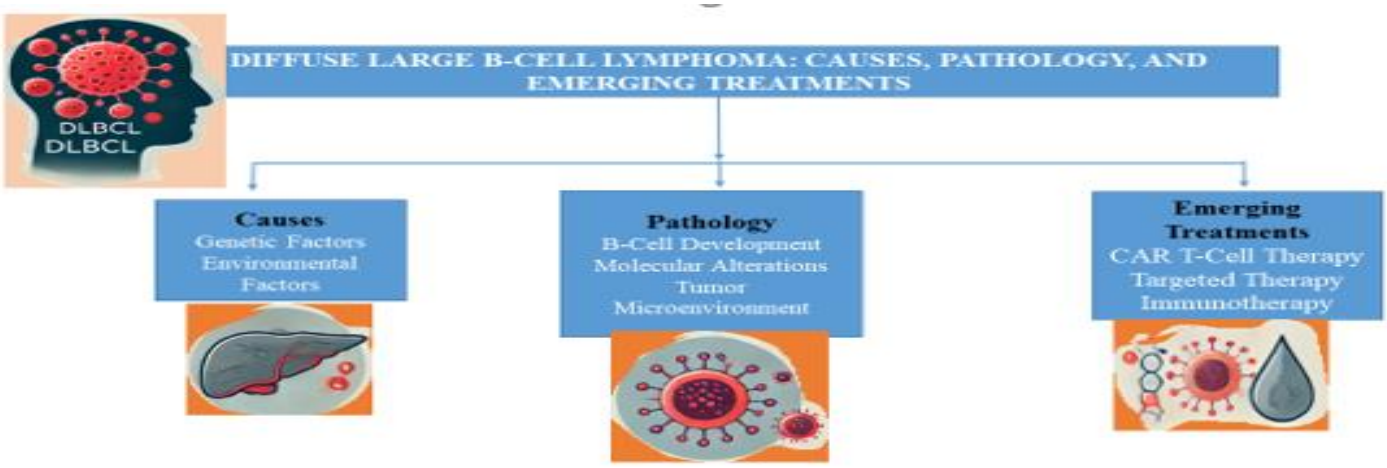
Received - 03-10-2024**, Revised** - 07-10-2024, **Accepted** - 12-10-2024 **(DD-MM-YYYY)**

Refer This Article

Ashok Kumar BS, 2024. Diffuse large B-cell lymphoma: causes, pathology, and emerging treatments. Journal of medical pharmaceutical and allied sciences, V 13 - I 5, Pages - 6791 – 6794. Doi: https://doi.org/10.55522/jmpas.V13I5.6714.

ABSTRACT

Diffuse Large B-Cell Lymphoma (DLBCL) is the most prevalent subtype of non-Hodgkin lymphoma, characterized by aggressive behavior and significant heterogeneity. Understanding the causes, pathology, and emerging treatments for DLBCL is essential for improving patient outcomes. This review synthesizes current research on the causes, molecular pathology, and novel treatment strategies for DLBCL, drawing on data from recent clinical trials, genetic studies, and advancements in therapeutic approaches. Genetic mutations such as translocations involving BCL-2, BCL-6, and MYC genes, along with chronic infections and immune deficiencies, are key risk factors for DLBCL. Pathologically, DLBCL can be classified into germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes, with differing prognoses. Emerging treatments include targeted therapies like BTK inhibitors (ibrutinib) and BCL-2 inhibitors (venetoclax), immunotherapies such as CAR T-cell therapy, and epigenetic modulators like HDAC inhibitors. Next-generation sequencing (NGS) is revolutionizing personalized medicine in diffuse large B-cell lymphoma (DLBCL) by enabling the identification of specific genetic mutations. Coupled with advancements in molecular pathology, NGS is driving the development of targeted therapies, immunotherapies, and epigenetic modulators. These innovations are collectively transforming the treatment landscape for DLBCL, offering more precise and effective therapeutic options tailored to individual genetic profiles. Continued research and clinical trials are essential for further refining these therapies and enhancing their effectiveness.



Keywords: Diffuse Large B-Cell Lymphoma, Non-Hodgkin Lymphoma, Activated B-cell-like, Targeted Therapy, Immunotherapy.

INTRODUCTION

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), constituting about 30-40% of all NHL cases [1]. It is a fast-growing, aggressive form of lymphoma that originates from mature B-cells and typically presents with rapidly enlarging lymph nodes, extranodal masses, or systemic symptoms such as fever, night sweats, and weight loss [2].

The etiology of DLBCL is multifactorial and involves a combination of genetic, environmental, and immunological factors. Genetic mutations, including translocations of the BCL-2, BCL-6, and MYC genes, play a significant role in the pathogenesis of DLBCL [3, 4]. These mutations can lead to dysregulation of cell growth and apoptosis, contributing to the aggressive nature of the disease. Additionally, chronic infections such as Epstein-Barr virus (EBV) and Helicobacter pylori have been implicated in the development of specific DLBCL subtypes [5, 6]. Immunodeficiency states, including HIV infection and post-transplant immunosuppression, are also known risk factors for DLBCL [7, 8].

Pathologically, DLBCL is characterized by large, atypical B-cells with a high proliferation rate and diverse morphological features. The disease can be classified into molecular subtypes based on gene expression profiling, notably the germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes [3]. These subtypes have distinct biological behaviors and clinical outcomes, with the GCB subtype generally associated with a better prognosis than the ABC subtype [9]. Immunohistochemistry and molecular techniques are crucial for accurate diagnosis and subclassification of DLBCL, which in turn guide therapeutic decisions [10].

Recent advancements in the understanding of DLBCL's molecular and genetic landscape have led to the development of novel therapeutic strategies. Targeted therapies, such as Bruton's tyrosine kinase (BTK) inhibitors and BCL-2 inhibitors, have shown promise in clinical trials, particularly for patients with refractory or relapsed DLBCL [11, 12]. Immunotherapy, including chimeric antigen receptor (CAR) T-cell therapy, represents a significant breakthrough, offering high response rates in patients with otherwise limited treatment options [13,14].

Moreover, epigenetic therapies and the application of next-generation sequencing (NGS) are paving the way for more personalized and precise treatment approaches. These advancements highlight the importance of continued research and innovation in the field of DLBCL to improve patient outcomes and address the challenges posed by this heterogeneous and aggressive disease.

Causes for Diffuse Large B-Cell Lymphoma

The precise etiology of Diffuse Large B-Cell Lymphoma (DLBCL) remains elusive, but a combination of genetic, environmental, and immunological factor contributes to its development. Genetic mutations are a hallmark of DLBCL, with chromosomal translocations involving the BCL-2, BCL-6, and MYC genes being frequently observed. These genetic alterations can disrupt normal cellular functions, leading to uncontrolled cell growth and survival, which are critical features of lymphoma pathogenesis [3,4].

Genetic Mutations: The translocation of the BCL-2 gene, often found in conjunction with the immunoglobulin heavy chain locus, results in the overexpression of the BCL-2 protein, which inhibits apoptosis and promotes cell survival. Similarly, translocations involving the BCL-6 gene, a key regulator of germinal center B-cell differentiation, can lead to deregulated growth of B-cells. MYC gene translocations result in the overexpression of the MYC protein, driving cell proliferation and contributing to the aggressive nature of DLBCL [4].

Chronic Infections: Persistent infections with certain viruses and bacteria have been implicated in the development of DLBCL. Epstein-Barr virus (EBV) infection is notably associated with DLBCL in immunocompromised individuals, such as those with HIV/AIDS or organ transplant recipients on immunosuppressive therapy. EBV-positive DLBCL is characterized by the expression of viral oncoproteins that can drive B-cell proliferation and survival [5]. Additionally, Helicobacter pylori infection has been linked to mucosa-associated lymphoid tissue (MALT) lymphoma, a precursor to DLBCL [6].

Immune Deficiencies: Immunodeficiency states, whether congenital or acquired, significantly increase the risk of developing DLBCL. Individuals with HIV/AIDS have a markedly higher incidence of DLBCL due to chronic immune activation and dysregulation. Post-transplant lymph proliferative disorders (PTLD), including DLBCL, arise in the context of prolonged immunosuppressive therapy, which impairs the immune system's ability to control oncogenic viruses and malignant cells [8].

Environmental Factors: Exposure to certain chemicals, such as pesticides and herbicides, has been associated with an increased risk of developing non-Hodgkin lymphoma, including DLBCL. Occupational exposure to organic solvents and benzene, commonly found in industries like agriculture and manufacturing, has also been linked to lymphoma development. Additionally, previous exposure to ionizing radiation, either through medical treatments or environmental sources, can increase the risk of lymphoid malignancies [1].

Epigenetic Modifications: Emerging research highlights the role of epigenetic changes in the pathogenesis of DLBCL. Aberrant DNA methylation and histone modifications can lead to the silencing of tumor suppressor genes and activation of oncogenes. These epigenetic alterations can cooperate with genetic mutations to drive lymphoma progression and influence the response to therapy [15].

Understanding the multifactorial causes of DLBCL is crucial for developing targeted therapies and preventive strategies. The interplay between genetic mutations, chronic infections, immune status, and environmental exposures underscores the complexity of DLBCL pathogenesis and highlights the need for a comprehensive approach to treatment and management.

Pathology of Diffuse Large B-Cell Lymphoma:

Diffuse Large B-Cell Lymphoma (DLBCL) is pathologically characterized by the presence of large, atypical B-cells with a high rate of proliferation. These malignant B-cells are typically larger than normal lymphocytes and possess prominent nucleoli, irregular nuclear contours, and abundant cytoplasm. The histopathological examination of DLBCL reveals considerable heterogeneity in both cellular morphology and tissue architecture.

Histological Subtypes

DLBCL can be classified into molecular subtypes based on gene expression profiles, namely germinal center B-cell-like (GCB) and activated B-cell-like (ABC) (3). The GCB subtype originates from germinal center B-cells and is generally associated with a better prognosis compared to the ABC subtype, which derives from post-germinal center B-cells and is often more resistant to standard therapies [9].

GCB Subtype

The GCB subtype is characterized by the expression of genes associated with normal germinal center B-cells, such as CD10, BCL-6, and LMO2. Histologically, these tumors often display a cohesive growth pattern with large, centroblastic cells that have round nuclei and prominent nucleoli. The presence of follicular dendritic cell networks is also a common feature of the GCB subtype [3].

ABC Subtype

The ABC subtype is identified by the expression of genes linked to activate B-cells, such as MUM1/IRF4, FOXP1, and BLIMP1. This subtype typically shows a diffuse infiltration of malignant cells with an immunoblastic or plasmablastic morphology. The cells are often larger and more pleomorphic compared to those in the GCB subtype, with more irregular nuclear contours and prominent nucleoli [9].

Histological Variability

The histological appearance of DLBCL can vary significantly. Some tumors may exhibit a cohesive growth pattern, resembling follicular structures, while others display a more diffuse infiltration of malignant cells throughout the lymph node or extranodal tissues. This variability in tissue architecture is reflective of the underlying biological diversity of the disease [1].

Immunophenotyping

Immunohistochemistry (IHC) is crucial for the diagnosis and sub classification of DLBCL. Commonly used markers include CD20, PAX5, CD79a (B-cell markers), and markers specific to GCB (CD10, BCL-6) and ABC (MUM1/IRF4, FOXP1) subtypes. The expression of these markers helps in distinguishing between different subtypes and can guide treatment decisions [10].

The image above shows a histological section of DLBCL with hematoxylin and eosin (H&E) staining. The large, atypical B-cells can be seen with prominent nucleoli and abundant cytoplasm, indicative of the high proliferation rate characteristic of DLBCL. The variability in cellular morphology and tissue architecture underscores the complexity of this disease.

Emerging Treatments for Diffuse Large B-Cell Lymphoma

The landscape of Diffuse Large B-Cell Lymphoma (DLBCL) treatment is rapidly evolving, with several innovative therapies showing promise in improving patient outcomes. These emerging treatments focus on targeted therapies, immunotherapies, epigenetic modulators, and the application of next-generation sequencing (NGS) for personalized medicine.

Targeted Therapies

The introduction of targeted therapies has revolutionized the treatment of DLBCL by focusing on specific molecular pathways critical for lymphoma cell survival and proliferation.

Bruton's Tyrosine Kinase (BTK) Inhibitors: Ibrutinib, a BTK inhibitor, has shown significant efficacy in treating the activated B-cell-like (ABC) subtype of DLBCL, which is often resistant to standard chemotherapy. By inhibiting BTK, ibrutinib disrupts B-cell receptor signaling, leading to apoptosis of malignant cells [11].

BCL-2 Inhibitors: Venetoclax targets the BCL-2 protein, which is overexpressed in many DLBCL cases, contributing to the resistance to apoptosis. Venetoclax has demonstrated promising results, especially when used in combination with other agents like rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), enhancing overall treatment efficacy [12].

Immunotherapy

Immunotherapeutic approaches have shown remarkable success, particularly in cases of relapsed or refractory DLBCL.

Chimeric Antigen Receptor (CAR) T-Cell Therapy: CAR T-cell therapies, such as axicabtagene ciloleucel and tisagenlecleucel, target the CD19 antigen on B-cells. These therapies involve modifying a patient's T-cells to express CARs that recognize and eliminate CD19-positive lymphoma cells. Clinical trials have reported high response rates and durable remissions in patients treated with CAR T-cell therapy [13, 14].

Epigenetic Modulators

Epigenetic modifications, such as DNA methylation and histone acetylation, play a crucial role in the pathogenesis of DLBCL.

Histone Deacetylase (HDAC) Inhibitors: Vorinostat and romidepsin are HDAC inhibitors that have shown potential in preclinical and clinical studies. These drugs work by altering the acetylation status of histones, thereby modifying the expression of

genes involved in cell growth, differentiation, and apoptosis. This approach can inhibit tumor progression and enhance the effects of other therapies [15].

Next-Generation Sequencing (NGS): The advent of NGS has revolutionized the understanding of the genetic landscape of DLBCL.

Personalized Medicine

NGS technologies have enabled the identification of novel genetic mutations and pathways involved in DLBCL. This information has paved the way for personalized medicine approaches, where treatments are tailored based on the genetic profile of the tumor. Personalized therapies aim to target specific genetic abnormalities, enhancing treatment efficacy and minimizing toxicity [16].

These emerging treatments represent significant advancements in the management of DLBCL, offering hope for better patient outcomes and personalized therapeutic strategies. The integration of targeted therapies, immunotherapy, epigenetic modulators, and personalized medicine holds promise for transforming the standard of care in DLBCL and improving long-term survival rates.

CONCLUSION

Diffuse Large B-Cell Lymphoma (DLBCL) is a heterogeneous and aggressive form of lymphoma with a multifaceted etiology. Significant advancements in understanding its molecular pathology have facilitated the development of innovative and effective therapeutic strategies. Targeted therapies, immunotherapy, epigenetic modulators, and next-generation sequencing (NGS) are among the promising approaches that are enhancing patient outcomes. Ongoing research and clinical trials are crucial for further refining these treatments and maximizing their efficacy.

ACKNOWLEDGEMENTS

The authors want to thank all individuals who helped to write this review.

Conflict of interests

The authors declared no conflicts of interest.

Funding

None

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