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MODERN TECHNOLOGIES FOR DIFFERENTIAL DIAGNOSIS OF LARGE B-CELL LYMPHOMAS

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Annotation: Large B-cell lymphomas (LBCLs) are a heterogeneous group of non-Hodgkin lymphomas that originate from B-lymphocytes and exhibit diverse clinical, morphological, and molecular characteristics. Accurate differential diagnosis of LBCL subtypes often exceeds the capabilities of conventional histopathological methods alone. Therefore, modern diagnostic technologies — including immunohistochemistry, flow cytometry, molecular and genetic profiling, advanced imaging techniques (such as PET/CT), and artificial intelligence-based algorithms are increasingly being utilized in clinical practice. This article reviews the role, applications, and advantages of these contemporary approaches in improving the precision of differential diagnosis in large B-cell lymphomas, supported by the latest scientific literature.

Key words: Diffuse large B-cell lymphoma (DLBCL); Immunohistochemistry (IHC); Molecular profiling; Flow cytometry; PET/CT

imaging; Artificial intelligence; Differential diagnosis; WHO classification; Biomarkers; Precision oncology.

Introduction. Large B-cell lymphomas (LBCLs) are a group of malignant lymphoproliferative disorders originating from B-lymphocytes, with diffuse large B-cell lymphoma (DLBCL) being the most common subtype. These lymphomas often present with aggressive clinical behavior, requiring prompt diagnosis and timely therapeutic intervention. However, the morphological and immunophenotypic similarities among various LBCL subtypes frequently pose diagnostic challenges.

In recent years, the rapid advancement of medical technologies has significantly enhanced the diagnostic capabilities in hematopathology. Beyond conventional histopathological methods, modern techniques such as immunohistochemistry, flow cytometry, molecular and genetic profiling, PET/CT imaging, and artificial intelligence-based algorithms have emerged as pivotal tools in achieving precise differential diagnosis [1].

This article aims to explore the significance of modern diagnostic technologies in differentiating various subtypes of LBCL, highlighting their practical applications, diagnostic value, and potential in improving patient outcomes.

Objective: To evaluate and analyze the role of advanced diagnostic tools in the differential diagnosis of large B-cell lymphomas.

Overview of Large B-Cell Lymphomas. Large B-cell lymphomas (LBCLs) represent a heterogeneous group of mature B-cell neoplasms characterized by the proliferation of large atypical lymphoid cells. Among these, Diffuse Large B-Cell Lymphoma (DLBCL) accounts for approximately 30–40% of all non-Hodgkin lymphomas (NHL) worldwide, making it the most prevalent and clinically significant subtype [3].

According to the 2022 WHO Classification of Haematolymphoid Tumours, LBCLs encompass multiple entities, including:

- DLBCL, not otherwise specified (NOS)
- High-grade B-cell lymphomas (HGBCLs) with MYC and BCL2 and/or BCL6 rearrangements (also known as double/triple-hit lymphomas)
- Primary mediastinal large B-cell lymphoma (PMBCL)
- T-cell/histiocyte-rich large B-cell lymphoma
- Intravascular large B-cell lymphoma
- EBV-positive DLBCL and others

Each subtype exhibits distinct clinical, morphological, immunophenotypic, and genetic features, which are crucial for accurate classification and treatment planning.

DLBCL, for instance, can be further subdivided based on gene expression profiling (GEP) into:

- Germinal Center B-cell–like (GCB)
- Activated B-cell–like (ABC)
- Unclassified subtypes

These molecular subgroups differ not only in pathogenesis but also in response to therapy and prognosis, emphasizing the need for precise subclassification during diagnostic workup [4].

Moreover, with the integration of next-generation sequencing (NGS) and digital pathology, it is now possible to identify recurrent mutations (e.g., MYD88, BCL2, TP53), chromosomal translocations, and epigenetic alterations that further refine diagnosis and guide personalized therapy.

Modern Diagnostic Technologies in the Differential Diagnosis of LBCLs.

The complexity and heterogeneity of large B-cell lymphomas (LBCLs) necessitate the use of advanced diagnostic technologies that go beyond traditional histology. These modern tools not only improve diagnostic precision but also aid in molecular subtyping, prognostication, and personalized treatment planning. The key technologies currently used in clinical and research settings include:

1. Immunohistochemistry (IHC). IHC remains a cornerstone in the initial evaluation of LBCLs. It is essential for identifying B-cell lineage (e.g., CD20, CD79a, PAX5), proliferation index (Ki-67), and for subclassification using algorithms such as Hans classifier, which differentiates between GCB and non-GCB (ABC) subtypes. [3].

2. Flow Cytometry. This technique enables rapid and quantitative analysis of surface and intracellular markers in fresh or frozen tissue samples. It is particularly useful in differentiating LBCLs from other lymphoproliferative disorders like Burkitt lymphoma or follicular lymphoma. [5].

3. Molecular and Genetic Profiling. Techniques such as fluorescence in situ hybridization (FISH), PCR, and next-generation sequencing (NGS) allow for the detection of chromosomal rearrangements (e.g., MYC, BCL2, BCL6), gene mutations (e.g., MYD88, EZH2), and clonality. Identification of “double-hit” or “triple-hit” lymphomas using these methods significantly affects prognosis and treatment strategy. [4].

4. PET/CT Imaging. 18F-FDG PET/CT is the imaging modality of choice for staging, response assessment, and identifying extranodal involvement. Dissemination features on PET, such as total metabolic tumor volume (TMTV), are now recognized as strong predictors of treatment outcome. [2].

5. Artificial Intelligence (AI) and Digital Pathology. AI-driven algorithms and digital image analysis are increasingly used to automate morphological assessment, predict molecular subtypes from H&E slides, and integrate multi-omics data. These technologies promise higher accuracy and reproducibility, especially in resource-limited settings. [3].

Discussion. The differential diagnosis of large B-cell lymphomas (LBCLs) remains a clinical challenge due to their heterogeneity in morphological, immunophenotypic, and genetic features. The integration of modern diagnostic technologies has significantly improved the precision and depth of lymphoma diagnostics, allowing clinicians to move beyond basic histological interpretation.

The use of immunohistochemistry (IHC) provides the foundation for initial diagnosis and is indispensable in resource-limited settings. However, IHC alone is

often insufficient to distinguish between LBCL subtypes with overlapping features. Incorporation of molecular classification (e.g., GCB vs. ABC) has significant prognostic implications and influences treatment decisions, such as the use of targeted agents like BTK inhibitors in ABC subtypes. [3].

Molecular profiling, particularly next-generation sequencing (NGS), allows for the identification of mutations such as MYD88, EZH2, and TP53, which have diagnostic, prognostic, and therapeutic implications. The detection of double- or triple-hit rearrangements using FISH or PCR is crucial for identifying high-grade B-cell lymphomas that require more intensive chemotherapy regimens.

Advanced PET/CT imaging not only aids in initial staging but also plays a pivotal role in response assessment. Recent research demonstrates that imaging features like total metabolic tumor volume (TMTV) and dissemination scores can independently predict patient outcomes, further guiding risk-adapted therapy. [2].

While AI and digital pathology are still emerging tools, their integration is accelerating, particularly in academic centers. AI-based classification systems have shown promising results in predicting molecular subtypes from histological slides with high accuracy. These tools also hold potential in reducing inter-observer variability and enhancing reproducibility of diagnoses.

Despite these advancements, several challenges remain. Molecular diagnostics and AI technologies often require expensive infrastructure, trained personnel, and standardized protocols — limiting their widespread use in low-resource settings. Additionally, variability in interpretation, lack of universally accepted diagnostic algorithms, and the complexity of integrating multimodal data still pose barriers to routine clinical implementation.

Nevertheless, the continued evolution of diagnostic platforms and collaborative research will likely overcome many of these limitations, paving the way for more personalized and effective management of LBCLs.

Conclusion. The diagnostic landscape of large B-cell lymphomas (LBCLs) has transformed remarkably with the advent of modern technologies. While

traditional histopathology and immunohistochemistry remain essential, they are now complemented by molecular profiling, advanced imaging, and artificial intelligence tools that enable more accurate and individualized diagnoses. These advancements have significantly improved our ability to differentiate between LBCL subtypes, predict prognosis, and guide targeted therapeutic strategies.

The incorporation of next-generation sequencing, PET/CT imaging, and AI-assisted digital pathology offers a comprehensive diagnostic approach that aligns with the principles of precision medicine. However, successful implementation of these technologies in routine clinical practice requires addressing challenges such as accessibility, cost, and standardization.

Overall, embracing a multidisciplinary diagnostic framework that integrates both conventional and cutting-edge tools is critical for optimizing patient outcomes in LBCLs. Continued research, technological development, and global collaboration will further enhance the accuracy and equity of lymphoma diagnosis in the future.

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