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BURKITT LYMPHOMA: UNPACKING THE COMPLEXITIES OF DIAGNOSIS AND MANAGEMENT

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ABSTRACT This comprehensive review explores the pathogenesis, clinical features, pathology, and diagnosis of Burkitt Lymphoma (BL). BL arises from B-cells within the germinal center and is driven by the constitutive expression of the MYC proto-oncogene on chromosome 8q24, leading to deregulation of cellular processes like cell growth, division, and apoptosis. The characteristic chromosomal translocation involving MYC is a result of errors during immunoglobulin gene diversification in B-cells. Additional mutations complement MYC deregulation. EBV infection is implicated in African BL cases and some sporadic and immunodeficiency-associated cases. Clinically, BL presents with rapid tumor growth and spontaneous tumor lysis, resulting in elevated LDH and uric acid levels. The three clinical forms are endemic, sporadic, and immunodeficiency-associated, each with distinct characteristics. Accurate diagnosis relies on anatomopathological evaluation and identification of MYC translocations. Treatment involves intensive chemotherapy with CNS prophylaxis, and rituximab has been shown to improve outcomes. This review emphasizes the need for precise diagnosis and tailored management to combat this aggressive malignancy effectively.

KEYWORDS : Burkitt Lymphoma, B-cell Lymphoma, Non-Hodgkin Lymphoma, Epstein-Barr Virus Infections.

INTRODUCTION

Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma characterized by the translocation and deregulation of the MYC gene on chromosome 8. There are three distinct clinical forms of BL: endemic (African), sporadic (non-endemic), and immunodeficiency-associated. Although they are histologically identical and exhibit similar clinical behavior, there are differences in epidemiology, clinical presentation, and genetic features among the three forms, as described above (1).

The 2016 World Health Organization (WHO) classification considers BL and Burkitt leukemia as distinct manifestations of the same disease. Additionally, the WHO proposes three aggressive B-cell lymphoma entities resembling BL. This article provides a concise review of BL's epidemiology, clinical features, pathology, and diagnosis. The pathobiology and treatment of BL, as well as a general approach to the diagnosis, staging, and prognosis of non-Hodgkin lymphomas, will also be explored in this comprehensive overview (2).

Methods

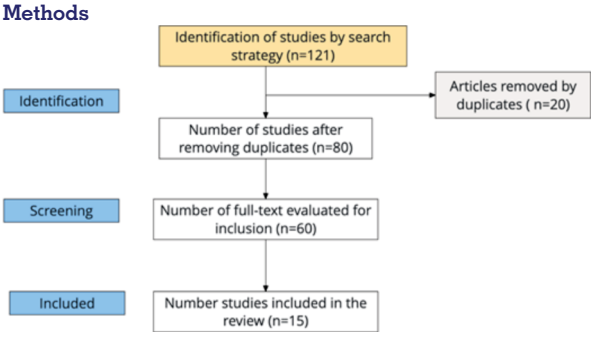

Figure 1. PRISMA.

In this narrative review, a systematic search is conducted in the Medline and Scopus databases to explore the topic of Burkitt Lymphoma comprehensively. The search strategy incorporates relevant Mesh and Decs terms in English, such as "Burkitt Lymphoma," "BL," "pathogenesis," "clinical features," "diagnosis," and "treatment." The review focuses on peer-reviewed articles, clinical trials, and reviews published within the last five years. Only English language publications are included. The review's scope encompasses epidemiological aspects, the molecular basis, diagnostic criteria, treatment modalities, and management approaches for Burkitt Lymphoma. Studies that do not meet the inclusion criteria are excluded, and any duplicates are removed. After an initial screening based on titles and abstracts, selected full-text articles are further assessed for final inclusion in the narrative review.

Pathogenesis

Burkitt lymphoma (BL) arises from B-cells within the germinal center. Its development depends on constitutive expression of the proto-oncogene MYC located on chromosome 8q24, encoding the transcription factor MYC protein. This factor regulates the expression of target genes that control various cellular processes, including cell growth, division, immortalization, Warburg metabolism, and apoptosis. The characteristic chromosomal translocation involving MYC in BL originates from errors during immunoglobulin gene segment diversification in B-cells. Chromosomal translocations result from non-homologous DNA end joining at different genomic locations simultaneously (3).

Studies indicate that DNA breaks near MYC are a consequence of activation-induced cytidine deaminase (AID) recruitment to enhancer sites adjacent to the MYC gene. The spatial proximity of DNA breaks at MYC and Ig loci within the cell nucleus is a prerequisite for their fusion into MYC translocations. Additional oncogene and tumor suppressor mutations, the basis of which remains largely unknown, complement MYC deregulation in BL. Chronic Epstein-Barr virus (EBV) infection appears to play a role in almost all endemic (African) BL cases and a minority of sporadic and immunodeficiency-associated BL cases. Mouse models suggest that malaria selectively induces B-cell lymphomas with MYC-involved chromosomal translocations by causing prolonged AID expression in germinal center B-cells (4).

Clinical Features

Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma with distinctive clinical features. Patients with BL present with rapidly growing tumor masses and often experience spontaneous tumor lysis, resulting in significantly elevated levels of lactate dehydrogenase (LDH) and uric acid. The tumor doubling time is remarkably short, approximately 25 hours (5).

BL is recognized in three distinct clinical forms: endemic (African), sporadic, and immunodeficiency-associated. The endemic form commonly presents as a tumor in the jaw or facial bones, whereas the sporadic form often involves the

abdomen, with massive disease and ascites. The immunodeficiency-associated form is often accompanied by signs related to the underlying immune deficiency. The 2016 WHO classification of malignant hematological neoplasms has led to recategorization of some BL cases. The leukemic presentation, previously distinguished as acute lymphoblastic leukemia, L3 type, is no longer differentiated. Additionally, aggressive lymphomas with features intermediate between BL and diffuse large B-cell lymphoma are now termed "high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement" and "high-grade B-cell lymphoma, not otherwise specified."(5).

Understanding the distinct clinical characteristics of BL aids in accurate diagnosis and tailored management of this aggressive malignancy, leading to improved patient outcomes. Early recognition and appropriate treatment are vital in combating this challenging disease.

Pathology

Burkitt lymphoma (BL) is an exceptionally aggressive tumor characterized by rapidly growing masses with a "moth-eaten" appearance and a distinctive "starry sky" pattern due to macrophages ingesting apoptotic cells. BL presents in three clinical forms: endemic, sporadic, and immunodeficiency-related. The disease is closely associated with translocations involving the MYC oncogene and immunoglobulin (Ig) genes. The tumor cells express several B-cell markers, including IgM, CD19, CD20, CD22, CD79a, CD10, BCL6, HLA-DR, and CD43, while lacking others like CD5, BCL2, and TdT. EBV involvement varies across the forms (6).

Genetically, MYC translocations are almost universally present, with occasional double/triple hits. Furthermore, mutations involving BCL6 and ID3 have been observed. Gene expression profiling is being explored as a potential tool for diagnosis. A better understanding of the pathological features and molecular basis of BL is crucial for developing more effective treatment strategies and improving patient outcomes. Early diagnosis and targeted therapies are essential to combat this aggressive malignancy (7).

Diagnosis

The diagnosis of Burkitt lymphoma (BL) relies on anatomopathological evaluation of affected tissue, usually an abdominal mass or another extranodal site (e.g., a mandibular mass in endemic regions) (algorithm 1). Less commonly, typical extranodal sites are not affected, and diagnosis is made through pathological evaluation of other tissues (e.g., lymph node, lung, kidney, testicle). Histology reveals monomorphic medium-sized cells with basophilic cytoplasm and a high proliferation fraction, with Ki-67+ fraction approaching 100%. Cytogenetic analysis demonstrates a translocation involving the MYC gene on chromosome 8, which can be detected by routine cytogenetics or fluorescence in situ hybridization (FISH). Although MYC rearrangement is a hallmark, some tumors with BL-like characteristics lack MYC translocations, prompting the reclassification of these cases as "Burkitt-like lymphoma with 11q aberration." (8)

The differential diagnosis of BL includes other aggressive B-cell lymphomas and tumors presenting as abdominal or facial masses. Other entities in the differential diagnosis depend on the patient population and site of the tumor. For intraabdominal tumors in children, Wilms tumor and neuroblastoma are common differential considerations. Tumors with facial involvement may be sarcomas, carcinomas, salivary gland tumors, or benign entities like paragangliomas. Accurate diagnosis is crucial, as the optimal therapy varies depending on the specific type of lymphoma (9).

Distinguishing BL from diffuse large B-cell lymphoma (DLBCL) can be challenging in some cases due to overlapping histological features. However, accurate differentiation is essential to select the most appropriate treatment. The 2016 update of the World Health Organization classification proposed specific criteria for diagnosing BL, DLBCL, and BL-like lymphomas. Lymphoblastic lymphoma is another aggressive lymphoma with histological resemblance to BL. Immunophenotyping can differentiate these two entities with high certainty, as lymphoblastic lymphoma typically expresses TdT and is often of T-cell phenotype, while BL does not (10).

Overall, a precise diagnosis of BL is crucial for guiding the appropriate management and achieving optimal outcomes in patients with this aggressive lymphoma.

Pre-treatment Evaluation

Pre-treatment assessment determines the disease extent and provides information on individual comorbidities that may impact treatment choices. Alongside medical history and physical exams, our practice involves these pre-treatment studies for BL patients (10):

- Laboratory studies: complete blood count, liver and renal function tests, electrolytes, LDH, hepatitis B, HIV, and uric acid.
- Unilateral bone marrow biopsy for all patients.
- Lumbar puncture, especially if intrathecal chemotherapy is used.
- Diagnostic PET/CT scans when possible.
- Cardiac ejection fraction study for anthracycline patients.
- Fertility counseling for reproductive-age patients.

Treatment tailored to risk is vital for effective BL management. Adding rituximab to chemotherapy improves outcomes. Prevent tumor lysis syndrome with hydration and rasburicasa. Radiation and surgery are not standard. Our approach prioritizes cooperative research trials for eligible patients (11).

Initial Treatment

The standard of care for BL is still undefined, and our preferred treatment approach is enrolling patients in well-controlled cooperative research trials. However, for patients ineligible or opting out of trials, we use aggressive combination chemotherapy with central nervous system (CNS) prophylaxis. Minimizing dose reductions, treatment initiation is prompt, aiming to start therapy within 48 hours of suspicion. Given BL's rapid chemo-sensitivity and diffuse nature, radiation plays no role, even for localized disease. Surgery is no longer employed. Most BL patients can be treated with the following method. Special consideration is needed for HIV-related lymphoma, cardiac disease, CNS involvement at presentation, and elderly patients. Their treatment is discussed separately (12).

Choice of chemotherapy: LB patients require intensive, multi-drug therapy with appropriate CNS prophylaxis. Less intensive regimens (e.g., CHOP) used for other NHL subtypes are inadequate, leading to frequent relapses. Approximately 30-50% of patients will relapse in the CNS without CNS prophylaxis. With CNS prophylaxis, CNS relapse rates have reduced to around 6-11%. Chemotherapy regimens for adults with BL are adapted from those used in children. No randomized trials allow direct comparisons due to differing diagnostic criteria, staging, and age inclusion (13).

Three main treatment approaches have been used in adults with BL. While initial studies didn't include rituximab, it is now routinely added to the treatment (starting from cycle 2), potentially improving outcomes. Intensive short-duration combination chemotherapy (e.g., R-CODOX-M/IVAC, CALGB 9251, GMALL-B-ALL/NHL2002). ALL-like therapy with stepwise induction, consolidation, and maintenance for at

least two years from diagnosis (e.g., CALGB 8811, R-HyperCVAD) (14).

Among these approaches, for most adults with LB, we suggest intensive short-duration combination chemotherapy instead of an ALL-like therapy, mainly due to its speed, simplicity, and our clinical experience. Dose-adjusted EPOCH infusion chemotherapy plus rituximab is an acceptable alternative for patients who may not tolerate more aggressive regimens (e.g., older or less fit patients). Details on using these regimens are presented below. Larger studies are needed to better evaluate this approach for this population before routine incorporation into the treatment of sporadic BL. It may be an acceptable option for patients not tolerating more aggressive regimens (e.g., older or less fit patients). The dose-adjusted EPOCH regimen does not penetrate the CNS, but it includes intrathecal methotrexate (14,15).

Incorporating rituximab: For most LB patients, we recommend adding rituximab to combination chemotherapy. Although practices vary, we generally wait until the second chemotherapy cycle to add rituximab to minimize tumor lysis. Several prospective uncontrolled trials and a randomized trial suggest that adding rituximab improves event-free survival and overall survival without increasing toxicity; two-year overall survival rates ranged from 77% to 100%. Our treatment approach: For most LB patients, we suggest intensive short-duration combination chemotherapy with CNS prophylaxis. Our preferred regimen is R-CODOX-M/IVAC. For older or less fit patients who may not tolerate more aggressive regimens, we suggest dose-adjusted EPOCH infusion chemotherapy plus rituximab (15).

All intensive short-duration chemotherapy regimens for BL are toxic, mainly to the hematopoietic system and mucosal surfaces, and most patients require prolonged hospitalization with antibiotic therapy and blood product support. As direct comparisons between different regimens are lacking, physician experience with administration is crucial when choosing among these regimens.

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