Burkitt's lymphoma (BL)
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Abstract
Review on Burkitt's lymphoma, with data on clinics, and the genes involved.

Keywords
Burkitt's lymphoma; MYC; IGH; IGK; IGL

Identity
Other names: Burkitt's tumor; Malignant lymphoma Burkitt's type

Clinics and pathology

Phenotype/cell stem origin
Pan-B antigens positive (CD19, CD20, CD21, CD22 and CD79a); co-expression of CD10 and Bcl-6. TdT-, CD5-, CD23-, Bcl-2- and CD138-; slgM+. The cell of origin is a peripheral IgM+ memory B-cell (presence of somatic hypermutation of the Ig gene). Ki67 expression is close to 100% of neoplastic cells.

Etiology
Burkitt lymphoma (BL) originates from germinal or post-germinal center B cells. The three clinical subtypes are: endemic, sporadic and immunodeficiency-related. All of these likely arise from B cells at different stages of development. The development of BL is dependent upon the constitutive expression of the MYC proto-oncogene located at chromosome 8q24. The transcription of MYC protein modulates the expression of target genes that regulate many cell processes including cell growth, division, metabolism and apoptosis. Chronic Epstein-Barr virus (EVB) infection appears to play a role in all cases of endemic BL and minority of sporadic and immunodeficiency-associated BL (Klapproth and Wirth, 2010).

Epidemiology
Most common in children (1/3 of lymphomas). Endemic BL is mainly confined to equatorial Africa where it accounts for 30-50% of all childhood cancers diagnosed each year (3-6 cases per 100.000 children). Sporadic variant is mostly seen in the US and Western Europe. 30% of pediatric lymphomas and 3 distinct peaks at around age 10, 40 and in the elderly. In all groups, most patients are male with a 3:1 or 4:1 male to female ratio (Magrath, 2012).

Clinics
African endemic variant usually develops in children with a jaw or facial bone tumor; initial involvement of the abdomen is less common. The primary tumor can spread to mesentery, ovary, testis, kidney, breast, and meninges, spreading to lymph nodes, mediastinum, and spleen less frequently. The non-endemic variant may be associated with immunodeficiency states and usually presents with abdominal involvement (distal ileum, cecum, mesentery). Presenting symptoms can be related to bowel obstruction or gastrointestinal bleeding,
mimicking acute appendicitis or intussusception. Lymphadenopathy is generally localized. The disease is very aggressive and requires prompt treatment with appropriate regimens.

**Cytology**

The blast cells in the peripheral blood and bone marrow display a basophilic cytoplasm with characteristic vacuolization, a picture indistinguishable from acute lymphoblastic leukemia (ALL) L3 of the FAB classification, which represents the leukemic counterpart of BL. WHO recognize three different types of Burkitt Lymphoma:

- **Classic Burkitt lymphoma:** Characterized for the monomorphic medium-size blast proliferation, with lax chromatin, multiple nucleoli and intense basophilic cytoplasm.
- **Plasmablastic Burkitt Lymphoma and Atypical Burkitt lymphoma:** Cells with nuclear pleomorphism and nucleoli of big size but in inferior number to the observed in the classic form. The three variants, blastic cells can be associated with plenty mitotic images.

**Pathology**

The tumor mass demonstrate complete effacement of the normal architecture by sheets of atypical lymphoid cells.

At low power, the tumor has a 'mouth-eaten' appearance, often with interspersed areas of coagulative necrosis or hemorrhage. High rate of proliferation and high rate of apoptotic cell death is observed. A classic 'starry-sky' pattern is usually present, imparted by numerous benign macrophages that have ingested apoptotic tumor cells. The benign histiocytes are large with abundant, clear cytoplasm and are dispersed throughout of basophilic tumor cells. At high power, classically are monomorphic, medium-size cells with round nuclei, multiple dark nucleoli, and basophilic cytoplasm.

The related form 'Burkitt-like' lymphoma shows intermediate features between diffuse large cell lymphoma and BL and probably includes different disease entities. It was suggested by the WHO panel that only those cases with MYC rearrangement and/or a >99% proliferation fraction as demonstrated by Ki-67 positivity should be classified as Burkitt-like lymphoma.

**Treatment**

Aggressive regimens specifically designed for this lymphoma must be used. Multiple intensive regimens demonstrate excellent activity in BL and are composed of doxorubicin, alkylators, vincristine, and etoposide combined with therapy directed at the eradication and/or prevention of central nervous system disease. In patients younger than 60 years of age, including those with well-controlled HIV, and those up to 70 years of age with good baseline functional status, CODOX-M is recommended. Patients with extensive disease and elevated LDH, 2 cycles each of R-CODOX-M and R-IVAC can be used.

For patients with low-risk disease (a single site of disease and normal LDH) 3 cycles of R-CODOX-M. For patients with preexisting organ dysfunction, or significant comorbidities and patients older than 60 years of age with low-risk disease, DA-REPOCH could be considering a great option associated with IT therapy or systemic methotrexate upon the completion of cycle 6.

The addition of rituximab to hyper-CVAD may improve outcome in adult BL or B-ALL, particularly in elderly patients (Castillo et al., 2013; Jacobson and LaCasce, 2014; Dozzo et al., 2016).

**Evolution**

Apart from the occasional refractory case, a few responsive BL patients will relapse soon after treatment completion and generally within the first 6 months of follow-up. Results in refractory/relapsed BL are extremely poor, and new options are urgently needed. Relapse and progression frequency varies according to first-line treatment used. In chemoresistant disease cases, experimental therapies, due to the globally poor results of traditional salvage programs, should be considered in all refractory or relapsed cases.

**Prognosis**

If treated promptly with appropriate regimens the majority of patients can be cured.

**Cytogenetics**

**Cytogenetics morphological**

The molecular hallmark of BL is the translocation of the MYC proto-oncogene to the Ig heavy or 1 light chain genes, leading to constitutive MYC activation. In classic BL, either endemic type or sporadic type, 90-95% of Ig loci are involved, 85% for t(8:14)/IgH-MYC, 10% for t(8;22)(q24;q11) /lg-lambda /MYC and approximately 5% for t(2;8)(p12;q24) /lg-kappa/MYC.

In the Burkitt-like form there are at least 3 cytogenetic categories: one with an 8q24/MYC translocation, one with an 8q24 and 18q21/ BCL2 translocation and another with "miscellaneous" rearrangements, frequently including an 18q21 break (Bellan et al., 2005).
Additional anomalies

Recurrent chromosome aberrations associated with the 8q24 translocations include 1q21-25 duplications, deletions of 6q11-14, 17p deletions and trisomy 12, +7, +8 and +18.

Genes involved and proteins

**MYC**

**Location** 8q24.21

**Protein**

MYC functions as a transcriptional regulator. MYC binds to MAX that is an obligate heterodimeric partner for MYC in mediating its functions. The MYC-MAX complex is a potent activator of transcription. Thousands of MYC target genes have been identified. Genes targeted by MYC include mediators of metabolism, biosynthesis, and cell cycle progression (Mohamed 2017).

**IGH**

**Location** 14q32.33

**Note**

Alternatively: IGK, located in 2p11.2 or IGL, located in 22q11.22

Result of the chromosomal anomaly

**Fusion protein**

**Oncogenesis**

Constitutive expression of MYC is crucial for the pathogenesis of BL, this protein being a key transcriptional regulator, controlling cell proliferation, differentiation and death. The deregulated expression of MYC, caused by the 8q24 translocations, is achieved through multiple mechanisms: a) juxtaposition to regulatory elements of the Ig loci, b) mutations in the MYC 5’ regulatory region and c) aminoacid substitutions occurring in exon 2, making the MYC transactivation domain less susceptible to modulation (Hecht and Aster, 2000).

Additional gene alterations include the following: truncating mutations of ARID1A and amplification of MCL1; point mutations of LRP6; truncating alterations of LRP1B, PTPRD, PTEN, NOTCH1, and ATM; amplifications of RAF1, MDM4, MDM2, KRAS, IKBKE, and CDK6; deletion of CDKN2A; overexpression of MIR17HG; activating mutations of TCF3 and/or inactivating mutations of its negative regulator ID3; and CCND3 activating mutations (Havelange et al., 2016).

References


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