**AGGRESSIVE B-CELL LYMPHOMAS ASSOCIATED WITH IMMUNOSUPPRESSION**

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Immunosuppressed patients are at an increased risk for developing aggressive, primarily B-cell, lymphoproliferative disorders / lymphomas (LPDs). The WHO classification recognizes four clinical settings associated with development of LPDs: (1) primary immune disorders, (2) HIV infection, (3) iatrogenic immunosuppression following solid organ or allogenic bone marrow transplantation (PT-LPD) and (4) methotrexate therapy, usually for an autoimmune disorder. The majority of LPDs are Epstein Barr virus (EBV)-related. Thus, in situations where immunocompetence can be re-established these EBV-driven proliferations may regress. However, development of secondary genetic structural alterations results in transformation to a neoplastic process. The diagnosis of LPDs is often difficult. In some instances the lesions are clearly neoplastic, particularly in the HIV-positive population, however, other cases, particularly PT-LPDs, are difficult to classify due to their polymorphic appearance. Thus, the accurate diagnosis of these lesions often requires not only morphologic examination, but also the use of immunophenotypic and genotypic techniques.

**CLASSICAL BURKITT LYMPHOMA AND VARIANTS: STRATEGIES FOR ACCURATE DIAGNOSIS**

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The WHO classification recognizes several variants of Burkitt's lymphoma (BL), all of which share deregulation of the c-myc gene leading to the characteristic histological and clinical features of BL. This molecular lesion results in a high grade lymphoma which, in addition to a growth fraction of 100%, is associated with certain clinical features, such as a risk of central nervous involvement, that necessitate therapeutic strategies distinct from diffuse large B-cell lymphoma (DLBCL). The three clinical variants of BL are associated with different clinical settings: *endemic BL, sporadic BL, and AIDS-associated BL*. In addition, three morphological variants are defined: *classical BL, atypical BL, and BL with plasmacytoid differentiation*. The last variant is most often seen in association with HIV-infection, whereas the other two variants can be encountered in both endemic and sporadic clinical settings. The distinction of Burkitt's lymphoma (BL) from morphologically similar aggressive B-cell lymphomas has been problematic for pathologists and clinicians. The category of small non-cleaved cell lymphoma, non-Burkitt, in the working formulation was biologically and clinically heterogeneous. In addition, the c-myc translocation as a secondary event is not associated with identical clinical consequences. Current strategies use immunophenotypic and molecular methods to diagnose BL as a homogeneous biological and clinical entity.

**TRANSFORMATION OF LOW GRADE TO AGGRESSIVE B-CELL LYMPHOMAS**

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Many indolent lymphomas are characterized by a continuous pattern of relapse, and eventual transformation to aggressive lymphomas with poor treatment outcome. Specific patterns of lymphoma transformation, defined as clonal progression within any one neoplasm, will be described. Follicular lymphomas to take one example may transform from follicular lymphoma grade 1 to grades 2 or 3, to Diffuse Large B-cell lymphoma, to aggressive B-cell lymphoma with features of Burkitt lymphoma, and more rarely to lymphoblastoid lymphoma, Classical Hodgkin lymphoma, and sinusoidal CD30+ lymphoma with anaplastic cytologic features. Other transformation events include transformation of MALT and marginal zone lymphoma, blastoid transformation in mantle cell lymphoma, and transformation of small lymphocytic lymphoma. In addition to changes in morphology, lymphoma progression is associated with successive accumulation of recurrent chromosomal defects. These include known abnormalities in p53, myc, rel, bcl-2 and p16, but other transforming oncogenes remain largely uncharacterized. Different molecular pathways can lead to transformation of lymphomas in a multistep fashion. The discussion will highlight new techniques such as laser microdissection and gene chip arrays to examine cellular pathways and complex cytogenetic abnormalities associated with transformation.

**DIFFUSE LARGE B-CELL LYMPHOMA: MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL CORRELATIONS**

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Diffuse large B-cell lymphoma is the most common lymphoma worldwide (30-40%). It may involve lymph nodes or extra-nodal sites and typically presents as rapidly growing masses. This category includes de novo lymphomas, cases of histologic progression/transformation and cases associated with underlying immunodeficiencies. The WHO classification recognizes several morphological variants, namely centroblastic, immunoblastic, T-cell rich /histiocyte rich and anaplastic; however, their diagnostic reproducibility is poor and their clinical significance remains undetermined. Based on immunophenotypic data two variants have been identified: plasmablastic and diffuse large B-cell lymphoma with ALK expression. In addition, the WHO identifies three clinical subtypes: primary mediastinal B-cell lymphoma, intravascular large cell lymphoma and primary effusion lymphoma. Nonetheless, diffuse large B-cell lymphoma remains clinically and biologically a heterogeneous group. Immunophenotypic studies have shown that antigenic expression can have prognostic significance. For example, p53 and Bcl-2 protein expression both correlate with an adverse prognosis. Recent gene expression profiling has led to the identification of at least three prognostic groups, and immunophenotypic studies are underway to confirm and to better define more homogeneous categories.

**GENE EXPRESSION PROFILING IN DIFFUSE LARGE B-CELL LYMPHOMA: NEW INSIGHTS INTO MOLECULAR HETEROGENEITY AND RATIONAL TREATMENT TARGETS**

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Diffuse large B-cell lymphoma (DLBCL), the most common lymphoid malignancy in adults, is currently curable in only 40% of patients. Clinical prognostic factor models such as the International Prognostic Index identify patients who are unlikely to be cured with standard therapy. However, these clinical models do not provide additional insights regarding more effective treatment strategies. The clinical features used to identify "high-risk" DLBCL are likely to surrogate variables for intrinsic molecular heterogeneity in the disease. The recent development of DNA microarrays provides an opportunity to take a genome-wide approach to identifying molecular signatures of previously unrecognized DLBCL subsets and prognostic categories. Recent studies indicate that supervised learning classification techniques can be used to predict

outcome in DLBCL and identify rational targets for intervention. The rapidly evolving area of gene expression profiling in DLBCL will be reviewed with particular emphasis on newly identified disease subsets and novel treatment targets.

## MOLECULAR PATHOGENESIS OF DIFFUSE LARGE CELL LYMPHOMA

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B-cell derived diffuse large cell lymphoma (DLCL) derive from the germinal center (GC), the structure where naïve B-cells encounter the antigen, undergo Immunoglobulin (Ig) V region somatic hypermutation (SH) and class switch recombination (CSR), and are selected to become memory B-cells or plasma cells. SH and CSR mechanisms are involved in the generation of specific chromosomal translocations, which contribute to the pathogenesis of DLCL by deregulating the expression of oncogenes like BCL2 and BCL6. New findings indicate that: i) the somatic hypermutation mechanism is aberrantly activated in >50% of DLCL leading to the mutation of multiple proto-oncogenes and, possibly, to the generation of chromosomal translocations; ii) the BCL6 proto-oncogene, which is normally downregulated by CD40 signaling, becomes constitutively expressed in the majority DLCL cases; iii) the function of BCL6 is controlled by three distinct pathways that can be modulated for therapeutic purposes.