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LEUKEMIC PHASE OF B-LINEAGE NHL

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B-cell non-Hodgkin lymphomas (NHL) mostly present as disseminated diseases involving lymph nodes, spleen and liver and often the bone marrow (BM). Tumor cells can also be found in the blood (leukemic disease), especially in the indolent lymphomas. High white blood cell counts and a differential demonstrating a lymphocytosis in the blood require immunophenotyping for characterization of the leukemic cells. Molecular/cytogenetic analyses may also have a role in the diagnostic classification of the disease. Besides the specific diagnosis, the clinical evaluation of the patient and prognostic markers are of most importance for selecting the best type of therapy.

Follicular lymphoma (FL) is the indolent lymphoma with the highest incidence. Most patients present with advanced stage disease with BM involvement in 40–70% of the cases, and few are leukemic at the time of diagnosis. By high-resolution analysis circulating FL cells may be detected in more patients. Leukemic patients mostly have concomitant lymph node involvement and high tumor burden. A pure FL-cell leukemia with $CD20^+CD10^+CD5^-$ clonal cells has also been described, mostly associated with an indolent clinical outcome. FL carry a t(14;18)(q32;q21) translocation in more than 90% of cases, juxtaposing the immunoglobulin heavy chain (IGH) 3' Regulatory Regions (IgH-3'RR) to the *BCL2* gene, resulting in overexpression of the Bcl2 anti-apoptotic protein. FL cells are also dependent on signals from the microenvironment to survive and proliferate. Several groups, including ours, have reported that immune cells in the lymphoma microenvironment and in blood influence prognosis. In patients treated before the introduction of rituximab, we have found that a high number of PD-1^+, $FOXP3^+$ and $CD8^+$ T-cell subsets in the tumor microenvironment predict superior outcome, while $CD4^+$ follicular helper T cells and $CD68^+$ macrophages are associated with an inferior outcome. The introduction of the anti-CD20 antibody rituximab has improved the prognosis for FL patients. The efficacy of this drug is excellent also as monotherapy especially in patients with high numbers of $CD8^+$ T-cells in the lymph nodes as well as in the blood.

***Mantle cell lymphoma (MCL)*:** MCL cells carries the t(11:14) translocation resulting in enhanced cyclin D1 expression and cyclin D1-dependent kinase activity, promoting cell cycle progression. Immunological markers show a typical phenotype ($CD20^+CD5^+CD23^-$), but also atypical phenotypes ($CD20^+CD5^-CD23^-$ or $CD20^+CD5^+CD23^+$) in some cases. Most MCL patients have an unfavorable prognosis and intensive treatment strategies are required. However, in around 10% of the patients the disease shows an indolent clinical course with often a non-nodal, leukemic disease. In one study the clinicopathologic features, gene expression and genomic profiles were compared in patients with indolent (iMCL) and in those with conventional disease (cMCL). iMCL and cMCL shared a common gene expression profile that differed from other leukemic lymphoid neoplasms and a signature of 13 genes was underexpressed in iMCL, among these *SOX11*. The *SOX11*-negative tumors exhibited more frequent non-nodal presentation and better survival compared with *SOX11*-positive MCL. Recently, our group found that *SOX11*-negative MCL had a higher frequency of lymphocytosis, but also elevated LDH and p53 positivity. Moreover, *SOX11*- negative cases had a shorter overall survival than *SOX11*-positive cases. Due to the conflicting results, the conclusion is that *SOX11* cannot be used for predicting an indolent disease course. In another study, deletions at 17p13 *(TP53)* and 13q14 were frequent in leukemic MCL and involved the majority of the leukemic clone. Cases with *TP53* deletion were more likely to have splenomegaly and marked leucocytosis ($> 30 \times 10^9$/L), and were less likely to have lymphadenopathy than those without the deletion. Other distinctive biological features in non-nodal leukemic MCL are mutated IGHV and a transcriptional profile lacking tumor invasion properties, which might contribute to the absence of nodal involvement. In conclusion, MCL patients with leukemic disease but without clinical symptoms might be managed conservatively with a "wait and watch" policy, while blastoid morphology, high proliferation and *TP53* aberrations are markers of aggressive disease, which will require intensive immunochemotherapy.

Marginal zone lymphoma (MZL): There are three clinicopathological entities of MZL, including extranodal, mucosa-associated lymphoid tissue (MALT) lymphoma, nodal (NMZL), and splenic (SMZL) type. Leukemic presentation is more common in SMZL. The leukemic

lymphocytes are usually small or morphologically "villous", and the leukemic manifestation of SMZL is named splenic lymphoma with villous lymphocytes (SLVL). The typical immunophenotype is $CD19^+CD20^+CD22^+CD45^+$ and the clone is often also $CD\ 103^+$ and $CD38^+$. Moreover, CD11c is highly associated with SMZL. The genetics and pathogenesis of SMZL are poorly understood and specific prognostic features are lacking. Aberrant karyotypes are seen as gains of 3/3q and 12q, deletions of 7q and 6q and translocations involving 8q/1q/l4q. Trisomy 3 and deletions of chromosome 7q22-34 are most common and found in approximately 25 and 45% of cases, respectively. A strong association has been described between usage of the IGVH1-2 and deletion 7q and 14q alterations. Clinical and epidemiological data suggest that chronic hepatitis C virus (HCV) infection may have an etiological role in a subset of cases. MicroRNA (miR)-26b, a miRNA known to have tumor suppressive properties, has been shown to be downregulated in HCV positive cases. Recent data suggest that certain SMZL subtypes could derive from progenitor populations adapted to particular antigenic challenges through selection of VH domain specificities, in particular the IGHV 1-2(*)04 allele.

The anti-CD20 antibody rituximab is mostly effective in MZL patients as monotherapy, but for many patients with symptomatic splenomegaly, splenectomy is still a therapeutic option.

In summary, the presence of lymphocytosis in the blood in patients with a suspicion of lymphoma requires careful evaluation for the presence of neoplastic lymphocytes, especially in the absence of easily accessible enlarged lymph nodes. The differential diagnosis between the WHO defined mature B-cell malignancies has improved by using multiple-color flow cytometry of phenotypic data of the lymphoma cells. This method is also of value for characterization of the immune cells in the microenvironment and blood. Molecular/cytogenetic analyses have a role in classification of the disease and for understanding of pathogenesis. Therapeutic decisions are always dependant on the specific diagnosis, prognostic factors and a careful clinical evaluation of the patient.

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PRIMARY GASTROINTESTINAL LYMPHOMAS

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Epidemiology and classification

Primary gastrointestinal lymphomas comprise less than 5% of all lymphomas diagnosed in the western world, with a variable geographical and ethnic incidence. The biology and management vary with the main diagnostic (WHO) subtypes which include Gastric MALT lymphomas, Enteropathy associated T-cell lymphoma (EATCL). Other lymphomas which frequently involve the gastrointestinal tract include diffuse large B-cell lymphoma, mantle cell lymphoma and Burkitts lymphoma; but are not considered primary gut lymphomas and will not be covered in this lecture. The pathogenesis of MALT and EATCL lymphomas is linked to abnormal antigen drive (gluten/*Helicobacter* infection) resulting in chronic inflammation and lymphoma development. The lymphomas are otherwise radically different; MALT lymphomas are indolent B-NHL, which respond to antigen-drive withdrawal and minimal therapy with an overall survival (OS) > 80% at 5 years, whereas EATCL is an aggressive T-cell lymphomas associated with a poor outcome.

Gastric MALT lymphoma

***Clinical features*:** Gastric MALT lymphomas incidence in the Western World is approximately 6 per