E1. **DISCORDANT, COMPOSITE AND TRANSFORMED LYMPHOMAS.**

Ljubomir Petrov
Oncological Institute "Ion Chiricuţă" Cluj-Napoca, Romania

Discordant lymphomas

Discordant lymphomas (DL) are rare entities characterised by the simultaneous presence of two distinct types of lymphomas in different anatomic sites.
This peculiar presentation has to be differentiated from the so called "composite lymphoma" wich is occurrence of two or more morphologically and immuno-phenotyically distinct lymphoma clones in a single anatomic site, that is within a single organ or tissue.

Discordant morphology has been documented in 14 to 38% of patients undergoing multiple biopsies. Most frecvently, however, discordance is documented as a bone marrow (BM) infiltrate predominantly composed of small cells, compatible with infiltration by low-grade NHL in patients with large-cell lymphoma in an extramedullary site.

The reasons for BM discordance are unclear, but proposed mechanisms include tumor evolution, transformation of a low grade NHL microenvironement or the presence of two unrelated neoplasms.

There may be an increased risk for late relapse in patients who have apparently achieved CR after therapy. Although both tumor components are clonally related in majority of cases and the DLBCL might be regarded as transformation of a clinically innaparent low-grade NHL, there is evidence of a distinct clonal B-cell proliferation in a significant minority of cases.
Rare cases of DL consisting of splenic mantle cell lymphoma and marginal zone lymphoma involving the bone marrow and peripheral blood, and DL consisting of MALT lymphoma of parotid gland and follicular lymphoma of the small intestine was described.

Another examples includes MALT lymphoma of intestine and follicular lymphoma of the bone marrow.
Therapy of DL is directed against the more aggressive component.

Composite lymphoma

Composite lymphoma (CL) is a rare occurrence of 2 or more morphologically and immunophenotypically distinct lymphoma clones in a single anatomic site.
Many combinations of CL have been reported including multiple B cell lymphomas, B cell and T cell lymphomas, non Hodgkin's Lymphoma (NHL) and Hodgkin Lymphoma (HL) and complex B cell, T cell and HL cases.

The morphologic criteria must be confirmed by one or more tests, including immunohistochemical analysis, flow cytometria, immunophenotyping, conventional cytogenetic tests, FISH and/or molecular biology studies. Results are more accurate using the laser capture microdisection method.

It must be carefully diagnosed because the multiple disease entities may have entirely different natural histories, prognosis and treatment modalities.
Careful study of CL may clarify the possible pathogenetic mechanisms of the interrelationship of clonal evolution in lymphoma.

Several theories were proposed including clonal selection with additional mutational accumulation, genomic instability with genetic predisposition, a common precursor cell and the aid of viral factor, mostly EBV.

The incidence has been reported to vary between 1% and 4.7%.

Composite lymphomas have the similar prognosis that of more aggressive component.
Therapy in the rare situations of so called "composite" lymphomas has traditionally been directed against the more aggressive subtype.

In case of association HL with low-grade B cell lymphoma the treatment of choice is chemotherapy (for HL) in association with rituximab (for low-grade NHL).
In fact the treatment of composite lymphomas must be individulizated according the components of CL.

Transformed lymphomas

Evolution of an indolent non Hodgkin lymphoma (NHL) to an aggressive histology is know as histologic transformation (HT). HT is a frequent occurrence for all subtypes of indolent B cell lymphoproliferative disorders.

This complication presents with a rapid change in the clinical behavior of disease with evidence of a highly proliferative malignancy having a propensity to involve extranodal sites.

The frequency of HT is dependent on the definition of HT, length of follow up and whether biopsies or autopsies were performed to document HT.
The risk of HT is approximately 3% per year for patients with indolent lymphoma.

The clinician should suspect HT in case of: rapid growth or discordant growth between various disease sites, sudden rise in LDH, unusual extranodal involvement new and persistent onset of B symptoms, new hypercalcemia, high SUV (standard uptake value) at PET imaging. Biopsies should be directed to the site of greatest FDG activity.

Acquisition and accumulation of additional genetic abnormalities appear to be responsible for HT. The overwhelming majority of cases of transformed lymphomas are clonally related to initial indolent lymphomas.

No single cytogenetic abnormality appears to be associated with HT. Specific genetic lesions have been identified. These include alterations in genes regulating proliferation, control of cell cycle and apoptosis: C-MYC and C-mYC regulated genes CDKN2a, CDKN2b, TP53, BCL2.

Patients with HT generally have a poor prognosis, with a median OS of aproxymately one year.

The good prognostic factors included: prior complete response of indolent lymphoma, CR following HT, normal LDH activity, absence of marrow involvement and of systemic B symptoms, limited stage disease, treatment with CHOP-like regimen.

The most commonly employed treatment regimens for patients with HT include conventional therapy (CHOP or its variants) radioimmunotherapy and high-dose therapy followed by hematologic stem cell transplantation.