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Hodgkin's lymphoma and *Grey-zone* lymphomas

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The considerable progress made during the last years in molecular morphology and genotyping of hematopoietic tumors has defined more precise criteria for the diagnosis and classification of Hodgkin (HL) and Non-Hodgkin Lymphomas (NHL). However, a diagnostic *grey zone* still exists at the interface between HL and NHL, and in some of the cases lack of clear-cut diagnostic criteria represents a problem for both the pathologist and the clinician. These *grey-zone* lymphomas (GZL) can be defined as distinct lymphomas with marked morphological overlap but no established biological relationship (*morphological GZL*), or as lymphomas biologically related and with variable, sometimes marked, morphological similarities (*biological GZL*).

The challenging diagnosis due to the morphological overlap existing between classical HL(cHL), peripheral T-cell NHL expressing CD30 or anaplastic large cell lymphomas (ALCL) are now easily solved in the majority of the cases with selected and specific immunohistochemical markers or gene rearrangement analysis. cHL diagnosis is based on the expression of the B-cell transcription factor Pax5; CD15 is tipically, although not uniquely found in cHL, especially when the highly sensitive anti-CD15 MMA antibody is used; the lack of ALK1 protein definitely distinguishes cHL from ALK1+ ALCL; the ALK1- ALCL cases and peripheral T-cell NHL can be distinguished from cHL by the lack of Pax5, together with the expression of CD45RB, T-cell markers (including LAT/linker for activation of T-cells and ZAP70), as well as cytotoxic molecules (TIA1 and/or Granzyme B). A potential diagnostic pitfal is represented by the expresssion of T-cell markers found in less than 5% of cHL; in the majority of these cases, however, this positivity is limited to a single T-cell antigen (usually CD2), it is associated with other *classical* cHL markers (such as Pax5), and, due to the lack of T-cell receptor rearrangement, it is considered to represent an aberrant antigen expression, rather than to indicate a T-cell origin of the tumor. It should be noted, however, that cases of cHL of *true* T-cell origin do exist, although extremely uncommon; they might be included in the spectrum of biological GZL with T cell neoplasms.

Nodular lymphocyte-predominant HL (nlpHL) shows nodular or nodular and diffuse proliferation of large neoplastic B cells of centroblastic origin (the L&tH cells), within a meshwork of follicular dendritic cells filled by small mantle B-lymphocytes. Tumor cells of nlpHL strongly express CD20 and several B-cell transcription factors (Pax5, Oct2, BOB1, PU.1), while they are negative for CD15 and CD30; on the basis of this antigenic profile, nlpHL is easily distinguished from lymphocyte-rich cHL, that shows and identical small B-cell rich nodular growth pattern, but contains $CD15^{\pm}$, $CD30^{+}$ atypical cells, lacking coordinate expression of Oct2, BOB1 and PU.1.

T-cell/histiocyte-rich B-cell lymphoma (T/HRBCL) is a variant of diffuse large B-cell lymphoma, in which neoplastic CD20+ B-cells, accounting for less than 10% of the infiltrate, are scattered among the majority of non-neoplastic T cells with or without histiocytes. A grey zone between nlpHL and T/HRLBCL is represented by cases of nlpHL with a cell composition identical to T/HRLBCL, either within nodules or diffuse areas. These GZL cases suggests a biologic continuum between nlpHL and T/HLBCL. Interestingly, many of the nlpHL cases with T/HLBCL nodules present at a high stage and B symptoms similarly to T/HRLBCL, but have an excellent survival, as nlpHL. Nevertheless, nlpHL and T/HRLBCL should be distinguished, as treatment and prognosis are definitely different in the majority of the cases.

Since malignant cells in classical Hodgkin lymphoma (cHL) have been demonstrated to represent in nearly all cases altered B-cells, it is therefore not surprising that overlap exists between cHL and subsets of diffuse large B-cell lymphomas (DLBCL), particularly those with anaplastic cytological features associated with CD30 expression,

the T/HRLBCL with Reed-Sternberg-like cells expressing CD30 and EBV, and the DLBCL primitive of the mediastinum (MDLBCL).

cHL-nodular sclerosis (cHL-NS) and MDLBCL have several features in common. They both arise predominantly in young females, who present a mediastinal mass associated with enlarged supraclavicular lymph nodes. Both cHL-NS and MDLBCL lack Ig expression and functional HLA class I antigens. Both share amplification of the *REL* lucus on chromosome 2p and of the *JAK2* locus on 9p. Moreover, gene profiling analysis demonstrated common patterns of gene expression in MDLBCL and tumoral cells in cHL. These data have indicated the possibility that distinct genetic hits on a common precursor result in either MDLBCL or cHL-NS. This hypothesis has been supported by the occurrence of cases combining in the same biopsy areas of cHL-NS and MDLBCL, or developing at different times either tumors with identical JH rearrangement.

More recently, the missing link between cHL-NS and MDLBCL has been identified in lymphoid tumors, predominantly occurring in the mediastinum of males, that share morphological and phenotypical features with cHL-NS and MDLBCL. These neoplasms have been defined as to *Mediastinal GZL*. Some cases show a morphology reminiscent of cHL-NS, but the classic $CD15^+CD30^+$ cHL phenotype is associated with strong and diffuse CD20 expression. Other cases present a morphology of MDLBCL, but they contain $CD15^+$ $CD30^+$ Hodgkin/Reed-Sternberg and lacunar cells, that do not express or weakly express CD20. B-cell transcription factor expression in all these mediastinal GZL cases more closely resemble MDLBCL than cHL, with positivity for Pax5, Oct2, and BOB.1.

Thiese tumors can be extremely difficult to classify and are even more problematic since they can be alternatively assigned to entities that behave differently and require distinct treatments.

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