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Concept of Composite Lymphoma

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The term composite lymphoma (CL) was first proposed to denote the occurrence of more than one lymphoma type in a single patient; however, the present term is now restricted to the rare occurrence of 2 or more morphologically and immunophenotypically distinct lymphoma clones in a single anatomical site i.e. within a single organ or tissue Both distinct clone processes co-exist persistently and equally, i.e. a biclonal or oligoclonal origin. Rarely, a single original clone could deviate to form 2 distinct diseases**.** The term collision tumor is used to delineate the multidirectional pathways of malignant lymphomas**.** However, as morphologic cross-over among the B-cell NHL, T-cell NHL and HL is wide, confirmed immunohistochemical and/or molecular methods must be fulfilled for proof documentation of the concurrent composite disease entities [(1)].

CL may be confused with other lymphoma conditions, from which it must be differentiated:

1. Transformation and progression:

Lymphomas tend to evolve over time from small-cell to large-cell and from follicular to diffuse forms. Also the transformation of HL nodular lymphocytic predominance (NLP) into diffuse large B-cell lymphoma has been documented. Transformation of lymphoma over time is considered disease progression rather than composite lymphoma. In these situations, given the time, all malignant cells will eventually transform to the more aggressive disease as part of their natural history [(2)].

2. Discordant lymphoma:

Other rare conditions present different types of malignant lymphomas occurring in different sites of the body, e.g. nodal Hodgkin's lymphoma and intestinal MALT lymphoma. The two conditions may present clinically as concurrent or sequential disease [(2)].

3. Differentiation:

Occasionally, peripheral differentiation occurs in low grade lymphomas e.g. follicular lymphoma with marginal differentiation [(3)].

No single definite mechanism has been proposed to explain the pathogenesis of the different types of CL as the etiology is variable, complex and differs according to the types of lymphomas involved. Generally, the immunological status of patients is a crucial element that may predispose to CL. It may arise during the course of atypical lymphoproliferative lesions namely, Castleman disease states of immunosuppression, chemotherapy, or multiple viral infestations [(4)].

However, suggested theories for different combinations include the following:

i. Composite B-cell lymphoma could be due to:

A. Clonal selection:

A clone of malignant B cells within a tumor may be exposed to additional mutational accumulation and change into a more aggressive neoplasm, co-existing with the original clone. An example is Richter's syndrome of B-cell small lymphocytic lymphoma changing to diffuse large B-cell lymphoma with the persistent co-existence of both clones in the same tissue [(5)].

B. Genomic instability and congenital predisposition:

A state of immunoglobulin gene instability, that might be inherited, may predispose to multiple types of B-cell NHLs. This explains the positive family history in some cases of CL [(6)].

C. Common precursor cell:

Immature precursor cell may have a multi-deviant pathway which results in more than one type of B-cell lymphoma [(1)].

ii. B-cell NHL and HL:

The Reed-Sternberg cell in most cases of HL is a type of B lymphocyte. So, similarly, the co-existence of both diseases would be conceivable through a common precursor cell origin theory [(1)].

iii. T-cell lymphoma with HL or B-cell lymphoma:

Since there is difference in cell lineage, the development of T-cell lymphoma in the setting of B-cell NHL or HL raises the possibility of some cooperative process between T lymphocytes and B-lymphocytes that favored neoplasia. The presence of an infective agent, mostly a virus, could explain the theory of multiline age cooperative and reactive process [(6)]. Although Epstein Barr Virus (EBV) preferentially infects B cells, it may also infect T cells through the CD21 receptor, which is present on developing but not mature T cells. Although half of T-cell lymphomas show EBV-infected cells, EBER-positive cells are mostly B, null, with few T cells. Down regulation of surface markers could possibly be related to the viral infection process. EBV positive CL strongly expresses p53 protein, possibly with a background state of immunosuppression [(1)].

For documentation of CL, all morphologically consistent cases must be verified by the objective confirmation of the co-existence of 2 or more types of lymphomas, using one or more laboratory tests. Diagnostic tests could be applied on tissue sections, cell suspensions, or DNA extract. Results of tests done on DNA extracts are more accurate using the laser capture microdissection method [(3)].

Diagnostic tests include: (1) immunohistochemistry and protein expression profile; (2) flow cytometry; (3) immunoglobulin and T cell receptor gene rearrangement by PCR; (4) cytocytogenetics and FISH techniques for chromosomal translocations; (5) in-situ hybridization for detection of viral DNA; (6) DNA sequencing for clonality studies; and (7) cDNA microarray for gene expression profile .[(7)]

Synchronous occurrence of 2 or more types of NHLs is more common than the occurrence of NHL with HL. Moreover, composite B-cell NHL is more common than composite T-cell NHL. About 30-40% of cases with Richter's syndrome had a second B-cell lymphoma of a different origin. The combination could be restricted to lymphomas of germinal center origin (follicular and diffuse large B-cell NHL), non-germinal center cell origin (SLL, mantle, marginal NHL), post germinal center origin (LPL, plasmacytoma, immunoblastic NHL), or a mix of different compartmental origin [(1)].

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