

Review Article

Composite Lymphoma

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ABSTRACT

Background: Composite lymphoma (CL) is a rare disease that has been identified in recent literature. The term composite lymphoma was first proposed to denote the occurrence of more than one lymphoma in a single patient; however, the present accepted definition is the occurrence of 2 or more distinct lymphoma types in a single anatomic site. The condition could be concurrent or sequential. Unlike disease progression or transformation in lymphoma, CL should include two distinct clones proven by morphological and laboratory tests.

Pathogenesis: No single definite mechanism has been suggested to explain the pathogenesis of the different types of CL. The etiology is variable, complex and differs according to the types of lymphomas involved. Several theories were proposed including clonal selection with additional mutational accumulation, genomic instability with genetic predisposition, common precursor cell and the aid of a viral factor, mostly EBV.

Diagnosis: The morphologic criteria must be confirmed by one or more tests including immunohistochemistry, flow cytometry, gene rearrangement by PCR, cytogenetics, FISH, in-situ hybridization, DNA sequencing and cDNA microarray. Results are more accurate using the laser capture microdissection method. Many combinations of CL are reported, including: Multiple B-cell lymphomas; B-cell and T-cell lymphomas; NHL and HL; or complex B-cell, T-cell and HL cases.

Conclusion: Due to the great advancement in molecular characterization of lymphoma, CL is being increasingly identified. It must be carefully diagnosed, because the multiple disease entities may have entirely different natural histories, prognosis and treatment modalities. Also, careful study of such cases may clarify the possible pathogenic mechanisms of the interrelationship of clonal evolution in lymphoma.

Key Words: Composite lymphoma – EBV.

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INTRODUCTION

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 [1]. 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 [2]. The term collision tumor is used to delineate the multidirectional pathways of malignant lymphomas [3].

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.

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 [4]. 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- *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 [4].
- 3- *Differentiation*: Occasionally, peripheral differentiation occurs in low grade lymphomas e.g. follicular lymphoma with marginal differentiation [5].

Incidence

CL is a rare condition documented in the literature mostly as case reports or small rather than large study series [1-4]. However, these cases could well be under-estimated, as they need rather advanced techniques for proving them. Such tests may not be available in many parts of the world.

Pathogenesis

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 [6], states of immunosuppression, chemotherapy, or multiple viral infestations [7]. However, suggested theories for different combinations include the following:

- 1- *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 [1-3].
- 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 [8].

C- *Common precursor cell*: Immature precursor cell may have a multi-deviant pathway which results in more than one type of B-cell lymphoma.

2- *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 [2].

3- *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 multilineage cooperative and reactive process [7,8]. 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 [1]. Although half of T-cell lymphomas show EBV-infected cells, EBV-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 [7], possibly with a background state of immunosuppression.

The logistic approach of B-cell and T-cell lymphomas could be one of the following:

- A- EBV infection in B-cells or R-S cells could cause reactive T-cell proliferation. Then due to the capability of B cells to alter T-cell growth through the production of cytokines and expression of T-cell directed growth stimulatory molecules, T-cells may ultimately undergo malignant transformation.
- B- An alternate explanation would be the presence of T-cell neoplasm first that provokes a B-cell response with a pathogenic role for EBV. Such B cells infected with EBV may later transform to R-S cells of Hodgkin's lymphoma.
- C- A state of immunosuppression associated with some cases of T-cell lymphoma may lead to a prominent EBV-associated B-cell

lymphoproliferation and to EBV+ B-cell neoplasms. This is due to clonal expansion of an immortalized EBV-infected B cell clone. Such a mechanism is similar to the pathogenesis of Burkitt-like lymphoma associated with HIV infection, as well as other states of multiple malignancies, disease-related and therapy-induced immunosuppression.

- D- The etiology could be an origin from a common EBV-infected progenitor cell, or an origin from the same clonal IgH gene rearrangement.
- E- Another theory to explain T-cell lymphoma and HL is a totally coincidental existence of 2 independent de novo neoplastic growth with 2 separate histogenic processes.

Clinical Presentation

Cases are more common in elderly people, but with wide age range (26-88 years) and male predominance (2.5:1). Positive family history of NHL is also documented in occasional reports with moderate penetrance [9].

Clinically, CL presents either as concurrent or sequential (metachronous) disease in the same organ. In case of sequential disease, the second malignancy may be identified with recurrence of the primary type. The topography could be nodal, splenic or extranodal. Common extranodal sites include G.I.T., respiratory system, salivary glands, bone, skin and orbit [3,10-15]. Bone marrow or liver involvement could demonstrate a single component only, mostly the more aggressive type, but rarely both types could be represented.

DISCUSSION

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 [5].

Diagnostic tests include: (1) immunohistochemistry and protein expression profile; (2) flow cytometry; (3) immunoglobulin and T cell receptor gene rearrangement by PCR; (4) cyto-

genetics 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 [9-13].

Classification:

The different combinations of lymphomas documented in the literature are as follows:

1- *Non-Hodgkin's lymphoma and another non-Hodgkin's lymphoma:*

- A- Follicular lymphoma and small lymphocytic lymphoma/leukemia (SLL/CLL) [5].
- B- Small lymphocytic lymphoma or LPL and diffuse large B-cell lymphoma (Richter's syndrome) [14].
- C- Mantle cell lymphoma and plasmacytoma [3].
- D- Mantle cell lymphoma and nodal marginal zone lymphoma [12].

2- *B-cell lymphoma and T-cell lymphoma:*

- A- Marginal zone lymphoma and enteropathy T-cell lymphoma [10].
- B- Diffuse large B-cell lymphoma and peripheral T-cell lymphoma [18].
- C- Small lymphocytic B-cell lymphoma and peripheral T-cell lymphoma [9].
- D- Mycosis fungoides and CLL or skin marginal zone lymphoma [14].
- E- Bone large B-cell and T-cell lymphoma [15].

3- *Non-Hodgkin's lymphoma and Hodgkin's lymphoma:*

- A- B-cell lymphoma and HL:
 - i- Classic Hodgkin's lymphoma: It is associated with (i) splenic marginal zone lymphoma [13]; (ii) mantle cell lymphoma [19]; (iii) diffuse large B-cell lymphoma [20]; and (4) MALT lymphoma [21].
 - ii- Nodular lymphocyte predominance Hodgkin's lymphoma: It is associated with (i) follicular lymphoma [22]; and (ii) diffuse large B-cell lymphoma [23].

B- T-cell lymphoma and HL:

- i- Classic HL with peripheral T-cell lymphoma [1].
- ii- HL NLP with T-cell lymphoma (NOS) [24].

4- Complex B-cell, T-cell and HL [25]:

One rare combination included three distinct diseases: Primary cutaneous marginal zone B cell lymphoma (MZBL), nodal Epstein-Barr virus (EBV)-associated classic Hodgkin's lymphoma (cHL) of the B cell type and peripheral T cell lymphoma, coexisting in the skin and cervical lymph nodes. Such complex disease is usually aided by a virus, EBV. However, EBV negative clonal inter-relation was also documented in a complex CL of B-CLL, anaplastic T-cell lymphoma, and HL, where the CLL and HL components showed a common IgH gene rearrangement [2].

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.

T-cell lymphoma associated with B-cell lymphoma usually shows diffuse large cell types of both counterparts and EBV latency type 2. The combination of B-cell NHL, T-cell NHL, and HL concurrently in the same organ or tissue is very rare, mostly with a background of leukemia (CLL). Cases of HL that present as CL could be of the classic HL lymphocyte-rich, nodular sclerosis and mixed cellularity subtypes [1,13,19-21], or nodular lymphocyte predominance subtype [22-24].

Therapy:

A combination of chemotherapy and subsequent immunotherapy might be considered as a promising therapeutic option for cases of CL, while radiotherapy has a limited role. The addition of targeted therapy using anti CD20,

Rituximab, produces CR in lymphomas with B-cell component [13].

Conclusion:

CL is a rare entity [26] that is being identified and reported in recent literature. Several combinations are possible with alternate pathogenesis and strict diagnostic criteria. The disease must be carefully proven by immunophenotyping and/or molecular tests. CL must continue to be recognized because the disease subsets may have variable natural histories, prognosis and different treatment modalities. Also, the study of such cases may provide us with the etiology and inter-relationship of clonal evolution in lymphoma.

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Composite lymphomas are rare and defined as hematopoietic neoplasms with more than 1 malignant lymphomatous clone showing different phenotypic features. Of all possible combinations between non-Hodgkin lymphomas, B cell or T cell, and Hodgkin lymphoma, the least frequent are the ones combining T-cell non-Hodgkin lymphoma and classic Hodgkin lymphoma. We report a case of a 55-year-old woman with cervical and mediastinal lymphadenopathy, fever, weight loss, and night sweats.