Composite Lymphoma and Related Disorders

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The Working Formulation of non-Hodgkin’s lymphomas (NHLs) for clinical usage defines the composite lymphomas (CLs) as those with “two distinctly demarcated types of non-Hodgkin’s lymphoma or the rare association of Hodgkin’s disease with a form of non-Hodgkin’s lymphoma within a single organ or tissue.” This definition is based entirely on morphologic features, and is essentially identical to that proposed by Kim and colleagues in 1977, when they broadened the original concept of Custer3 and of Rappaport and co-workers.4 Immunologic heterogeneity of lymphomas was already well-established at that time; nevertheless, the definition was suggested because the morphologic subclassification of lymphomas, and not the immunophenotype, was the major determinant for the prognosis and the treatment of patient. Since then, immunologic, molecular genetic,5 and cytogenetic6 studies have added considerably to the understanding of malignant lymphomas. Partly because of this progress, the publications in the last decade have reflected varying definitions of CL, and include those in which CL is defined as two lymphomas that differ as to their presumed cell of origin.7 This paper reviews recent publications on the subject of CL and related disorders.

DEFINITION

The knowledge accumulated in this field necessitates the incorporation of both morphology, because of its prognostic and therapeutic implications, and molecular genetic and/or immunologic data into the definition of CL.

The term CL then may be defined as two or more different morphologic types of NHL and/or Hodgkin’s disease (HD) that may or may not be clonally related, and that occur in a single organ or tissue. This definition does not change the morphologic definition of the Working Formulation,1 and specifically excludes lymphomas in which neoplastic cells of different origin are closely intermingled without clear morphologic delineation in tissue sections. The well-known phenomena of histologic conversion of lymphoma over time,8–11 and histologic discordance at different sites in the same patient12–17 are mentioned below only in relation to the genesis of CL, although they may have essentially identical clinical implications.

INCIDENCE

The true incidence of two different morphologic types of lymphoma occurring in a single organ or tissue is difficult to assess, especially because the term CL has not been applied uniformly by different authors. In the study of more than 1,000 cases for the Working Formulation of NHL, the incidence of CL varied between 1 and 4.7% depending on the pathologist and the classification system used.14 In the initial laparotomy series from Stanford, three CLs were discovered in 84 patients with NHL who were uniformly staged (3.5% incidence).15 The incidence of discordance, i.e., different histologic types of lymphoma at different sites, in patients with multiple sites of involvement by NHL is higher and ranges between 9.3%17 and 33%.13

COMPOSITE B-CELL LYMPHOMA

Composite B-cell lymphomas consist of two or more different morphologic types of B-cell lymphoma in a single organ or tissue. This category is probably the most frequent among all CLs. The component lymphomas comprising composite B-cell lymphomas may be bitemic,16–19 bicalonial,20–22 or monoclonal.20–21 In the series of Kim and colleagues,2 12 of 20 CLs comprised follicular lymphomas of small cleaved or mixed-cell type, and of diffuse or follicular lymphomas of a more aggressive histologic nature. The single most common combination was follicular lymphoma of the small cleaved cell type, and diffuse lymphoma of the “histiocytic” type (7/12,
58%). Although no immunologic studies were performed on these cases, current studies suggest that they represent an evolution of a single clone of cells even in those cases in which the constituent components are immunologically bitypic.20 Unusual in this category are CLs that have the novel, low-grade monocytoid B-cell lymphoma as one component. In the study of Ngan and co-workers,24 CLs were encountered in 7 of 36 monocytoid B-cell lymphoma. Among the seven cases, follicular center cell lymphoma (FCCL) was the second component in five. Another of the patients in that series had no composite pattern initially, but subsequently there was evolution to diffuse large-cell lymphoma (DLCL). Similar progression from monocytoid B-cell lymphoma to large-cell lymphoma was previously described by Sheibani and colleagues and Traweek and colleagues.25,26 These morphologic combinations or transitions suggest a histogenetic relationship between neoplastic cells of monocytoid B-cell lymphoma and follicular center cells. Such a linkage, however, awaits further studies, because a t(14;18) chromosomal translocation or bcl-2 overexpression was not evident in the study by Ngan and co-workers24.

Some authors7 question the validity of using the term CL when both components originate from B cells. We believe that this terminology is applicable, however, because their different histologic components may have an entirely different clinical behavior and natural history although they may be of the same clonal origin. Our position is that CLs should be diagnosed and their component specified in a manner that is similar to that of testicular germ cell tumors, which are classified according to the histologic components because they differ in their biologic behavior and therapeutic implications.

Some B-cell lymphomas have been shown to be bitypic or biclonal when two different specimens from the same patient were analyzed either sequentially or simultaneously. A meaningful discussion about determination of the clonality of a malignant lymphoma is beyond the scope of this review. Nevertheless, reports by Cleary and colleagues,20 Cossman and associates,7 de Jong and co-authors,21 and Zelenet and co-workers,11 among others, describe how and why most, if not all, of these bitypic or biclonal lymphomas, especially FCCL, may be monoclonal in origin. These studies also demonstrate that immunophenotyping, cytogenetics, and gene rearrangement analysis are all important elements in the process of deciding the clonality of different lymphomas, and that the results of these studies must be evaluated carefully to determine their meaning. This caveat is justified, especially because immunoglobulin gene rearrangement and idiotope expression are not necessarily pathognomonic of a lymphoid malignancy, and they may not be consistently accurate clonal markers.20

**COMPOSITE T-CELL LYMPHOMA**

Composite T-cell lymphomas consist of two or more different morphologic types of T-cell lymphoma in a single organ or tissue. We have not been able to find a case of a composite T-cell lymphoma thusly defined, with the possible exception of mycosis fungoides d’emblée, also known as the tumor stage of mycosis fungoides.27,28 The cells of mycosis fungoides may undergo progressive transformation, and may evolve into a pleomorphic large-cell lymphoma.28,29 The large-cell lymphoma then may coexist with the typical smaller and sometimes cerebriform neoplastic cells of mycosis fungoides. A recent study by Cerroni and co-workers29 showed the significance of the transformation of mycosis fungoides to large-cell lymphoma. Of their 36 patients with mycosis fungoides, 20 developed large-cell lymphoma. Compared with the 10-year survival rate of 46.6% for patients without transformation, those who developed large-cell lymphoma had a survival rate of 11.2% for the same period. In 17 of the 20 cases, the large-cell lymphoma proved to originate from T cells when investigated by immunohistochemistry.

**COMPOSITE B- AND T-CELL LYMPHOMA**

Composite B- and T-cell lymphomas consist of two or more morphologically different B-cell and T-cell lymphomas in a single organ or tissue. T-cell lymphomas developing in patients with previous FCCL30–33 or other B-cell lymphomas occasionally have been reported.34,35 Rarely have CLs been reported, however, in which one component is immunologically a B-cell lymphoma and the other a T-cell lymphoma.

York and colleagues7 reported three such patients who initially had small cleaved FCCL, and who subsequently developed CL consisting of small cleaved FCCL and DLCL. In each of the three patients, one component was predominantly composed of small cleaved follicular center cells, whereas the second component had histologic features associated with peripheral T-cell lymphomas. These authors showed the cells of the second component to be T cell in two patients when the cells failed to stain for cytoplasmic immunoglobulin. In the third patient, a T-cell nature was evidenced by the percentage of lymphocytes rosetting with sheep erythrocytes. Unfortunately, no other immunologic, cytogenetic, or gene rearrangement studies were performed on these patients. Hu and co-workers34 described another patient in whom NHL developed in which one component was made up predominantly of large B lymphocytes, whereas the sec-
Hodgkin’s disease may develop in patients with NHL, and conversely, NHL may occur in patients with HD, especially after treatment. Simultaneous occurrence of HD and NHL in one patient is rare, however, and their coexistence in a single organ or tissue is even more rare, especially for CLs including HD other than the NLPHD subtype.

**Nodular Variant of Lymphocyte-Predominant Hodgkin’s Disease and Diffuse Large-Cell Lymphoma**

In the series of Kim and co-workers, 8 of 20 patients with CL had a combination of HD and NHL. In 1 of the 8 patients, LPHD was shown to coexist with diffuse “histiocytic” lymphoma. At least seven different single case reports or series describe 27 patients who developed CL consisting of NLPHD and DLCL. The series of Sundeen and colleagues included 7 such patients. In the series of Hansmann and co-workers, the NLPHD either coexisted simultaneously (11 cases) or transformed into DLCL (3 cases) in 14 of 337 cases of NHL (2.6%). In both series, patients with CL that combined NLPHD and DLCL generally had more localized disease and a longer survival time than did patients with B-cell CL not associated with NLPHD. In all except one case in Hansmann’s series, the DLCL component proved to be B-cell in nature when studied by immunologic or molecular-genetic means. These authors considered this to be a histologic progression of a low-grade B-cell malignancy to a tumor of a higher grade, as in the evolution of low-grade FCCL to large noncleaved FCCL. Their studies also provide further evidence of a close relationship between NLPHD and the B-cell system.

**Hodgkin’s Disease Other than Lymphocyte-Predominance and Non-Hodgkin’s Lymphoma**

Composite lymphoma consisting of HD other than NLPHD and NHL also exists. Seven such patients are included in the series of Kim and co-workers. More recently, Gonzalez and colleagues reported on nine additional such patients. All NHL components in their series were proved by immunohistochemical studies to be of the B-cell type. The authors suggest that this raises the possibility of a close relationship between B lymphocytes and the malignant cells of HD, even when the HD is of other than the nodular lymphocyte-predominant type.

**Hodgkin’s Disease and Mycosis Fungoides**

In addition to the coexistence of HD and B-cell NHL, rare case reports describe the occurrence of nodal HD and cutaneous mycosis fungoides in the same pa-
tient.71-74 In most of these cases, HD followed the diagnosis of mycosis fungoides by 1 month to several years. Although HD and mycosis fungoides were diagnosed simultaneously in one patient in Chan’s series,71 no cases of CL have been reported in which HD and mycosis fungoides coexisted in one organ or tissue side by side.

Richter’s Syndrome and Related Disorders

Richter’s Syndrome

In 1928, Richter described the occurrence of “reticular cell sarcoma” in a patient with chronic lymphocytic leukemia (CLL).75 Since the original description, many such cases have been reported. The incidence in patients with CLL is estimated to be 3 to 10%.76-78

The term Richter’s syndrome is now used whenever large-cell lymphoma supervenes in patients with CLL and is considered to represent a terminal phase of the leukemia. Most of the earlier reports emphasize the clinical and morphologic aspects of this syndrome.76,78-80 Only recently has the clonal relationship between CLL and large-cell lymphoma become the focus of publications.77,81-87 Almost all cases of Richter’s syndrome have involved B-CLL, and it is generally considered that DLCL in patients with Richter’s syndrome in B-CLL is a manifestation of clonal evolution.77,81,84,86 Sometimes, however, neoplastic lymphocytes of CLL and those of large-cell lymphoma show different light-chain restrictions. In such biphenotypic cases of Richter’s syndrome, some investigators reached the conclusion that DLCL represents the growth of a separate clone.83,87,88 Most recent studies,77,84 however, suggest that DLCL in these patients is the result of a clonal evolution despite the difference in light-chain restriction. We view large-cell lymphoma coexisting with small lymphocytic lymphoma,80,85,89 or large-cell lymphoma that occurs in patients with Waldenstrom’s macroglobulinemia68,80,90 as phenomena that are essentially identical to Richter’s syndrome in patients with B-CLL.

Two case reports describe the T-cell variant of Richter’s syndrome.91,92 The rarity of the T-cell form of Richter’s syndrome may be a direct reflection of the relative rarity of T-cell CLL.

Hairy cell leukemia is a rare chronic B-cell disorder93 that also may evolve into DLCL94,95 as it does in Richter’s syndrome in patients with CLL.

Hodgkin’s Disease Variant of Richter’s Syndrome

The occurrence or coexistence of HD in patients with CLL has been controversial, partly because pleomorphic cells resembling Reed-Sternberg cells may be observed in CLL.96,97 especially in the terminal phase.98,99 Recent reports from different centers, however, convincingly demonstrate that HD may coexist with CLL.68,100,101 Because only small numbers of such cases have been recorded, no conclusions can be drawn about the relationship between HD and CLL. Brecher and Banks,100 however, emphasize that their patients with the HD variant of Richter’s syndrome had survival times of 2 to 4 months, which is much shorter than that for uncomplicated CLL. Hodgkin’s disease also may develop in patients with another chronic B-cell disorder, hairy cell leukemia.102

SUMMARY

Lymphomas evolve over time, usually from the small-cell to the large-cell category, and from follicular histologic characteristics to diffuse architecture. The histologic characteristics of lymphomas may be discordant in patients with multiple sites of involvement. When different types of lymphomas are encountered in a single organ or tissue, they are designated as CLs in the Working Formulation of NHL. The most common CLs consist of different subsets of follicular center cell lymphomas, usually one with low-grade follicular histologic characteristics and another with diffuse architecture and/or more aggressive cytologic features. These lymphomas now are considered to represent different phases of clonal evolution rather than representing a coincidental simultaneous occurrence of two unrelated lymphomas.

Whether B-cell large-cell lymphoma coexisting with another B-cell lymphoma, namely, the nodular variant of lymphocyte-predominant Hodgkin’s disease, also represents clonal evolution requires further study. Composite lymphomas consisting of a B-cell lymphoma and a T-cell lymphoma are extremely rare. The histogenetic implications for a clonal relationship between component subsets in these and other equally rare combinations remain uncertain. The CLs should continue to be recognized because (1) the component morphologic subsets may have entirely different natural histories, requiring different treatment modalities although they may be clonally related; and (2) the study of such cases may provide us with information regarding the complex interrelationship of the lymphoid system and its clonal evolution. The morphologic definition for CL of the Working Formulation should continue to be used whenever possible, with addition of appropriate immunologic and/or molecular-genetic data.

Addendum. Since the submission of this manuscript, additional studies have been published that are pertinent to the subject of this review article. Strickler and co-workers describe two patients in whom small B-cell lymphoma coexisted with T-cell lymphoma.103 Medeiros and Stetler-Stevenson discuss composite B-cell and T-cell lymphoma.104 A patient with a Hodgkin’s disease variant of Richter’s syndrome is de-
tailed in a case record of the Massachusetts General Hospital.109 Mo-
mose and coauthors suggest a possible role for Epstein-Barr virus in the
formation of Reed-Sternberg-like cells in patients with chronic lympho-
cytic leukemia.106 The entire November 1992 issue
is devoted to the interrelationship of Hodgkin’s
disease and non-Hodgkin’s lymphoma.107

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Composite Lymphoma


