EDITORIAL

bcl-1, t(11;14), and Mantle Cell-Derived Lymphomas

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THE t(11;14)(q13;q32) translocation and its molecular counterpart, bcl-1 rearrangement, were originally reported as recurring cytogenetic and molecular genetic abnormalities in the lymphoproliferative diseases in 1979 and 1984, respectively. Although sporadic reports of these abnormalities continued to appear in the literature, particularly in the lymphocytic lymphomas and leukemias, no consistent association with any particular lymphoproliferative disease was observed. However, recently several reports have appeared linking these abnormalities to a distinct histologic subtype of low to intermediate grade lymphoma, which has been called lymphocytic lymphoma of intermediate differentiation (IDL or ILL) in the American literature and centrocytic lymphoma (CC) in the European literature. The article by Williams et al in this issue of Blood further strengthens the association of the molecular lesion with this lymphoma subtype. Nonetheless, several questions remain regarding the specificity of the t(11;14) translocation/bcl-1 rearrangement for IDL/CC and its reported occurrence in other lymphoproliferative diseases. Before we address these questions, it is necessary to review our current understanding of centrocytic lymphoma and IDL.

CENTROCYTIC LYMPHOMA AND INTERMEDIATE LYMPHOCYTIC LYMPHOMA: IDENTICAL NEOPLASMS DERIVED FROM FOLLICULAR MANTLE CELLS

Both centrocytic lymphoma and IDL are relatively rare lymphoproliferative disorders accounting for 5% to 10% of all non-Hodgkin's lymphomas. Although the conceptual origins of IDL and CC were quite different, over the last 10 years the morphologic definitions of these two lymphomas have converged, and they are now regarded by most hematopathologists as the same entity. IDL was originally recognized by its cytologic features. It was defined by Berard and Dorfman in 1974 as a diffuse or vaguely nodular low grade lymphoma composed of cells intermediate in form between the small, round, cytologically normal cells of "well-differentiated" lymphoma (WDL) or chronic lymphocytic leukemia (CLL) and the irregular, cleaved cells of "poorly differentiated" lymphocytic lymphoma (small cleaved cell lymphoma). Early on, Nanba et al recognized that IDL cells frequently surrounded residual germinal centers in a pattern reminiscent of an expanded follicular cuff or mantle. Based on shared phenotypic and enzyme histochemical properties with normal follicular mantle zone lymphocytes, an origin from these cells was postulated. Subsequently, mantle zone lymphoma was proposed as a term for those cases of IDL in which a nodular pattern of growth was especially prominent. Further refinements in the histologic and immunologic criteria over the subsequent years provided a more homogeneous group of tumors. Particularly important was the elimination of cases with growth centers that we now recognize to occur only in CLL/WDL. Ultimately, the concept that IDL was a distinct entity derived from follicular mantle zone cells became firmly implanted.

Centrocytic lymphoma, on the other hand, was originally defined by Lennert as a diffuse or, less commonly, vaguely nodular follicular center cell-derived lymphoma composed exclusively of small cleaved germinal center cells. Over the years, this strict morphologic definition has become somewhat broader with many groups accepting a somewhat wider spectrum of small lymphoid morphology. A further step toward the convergence of the two diagnoses was the recognition of a variant with a mantle zone growth pattern similar to that seen in IDL.

Immunologic studies showed that both lymphomas had a similar immunophenotype. Both possessed the pan-B-cell markers CD19, CD20, and CD22, and, unlike CLL/WDL, both displayed a relatively high density of surface Ig (usually of μ or μδ heavy chain type) with an unexplained preference for λ light chain expression. IDL and CC could be distinguished from follicular lymphomas by the expression of the pan-T-cell marker CD5 and the frequent absence of CD10. Although the expression of CD5 may appear anomalous for follicular mantle B cells, CD5 expression is known to occur in the primary follicles of the developing fetal lymph node before germinal center formation. In rare cells of the adult mantle zone, IDL and CC have also been shown to contain membrane-associated alkaline phosphatase, an enzyme normally found primarily within the follicular mantle cells. These features not only separated IDL/CC from small lymphocytic neoplasms (WDL/CLL) and follicular lymphomas, but also provided additional confirmation of their common origin from follicular mantle zone cells.

CLASSIFICATION OF IDL/CC IN THE WORKING FORMULATION

The classification of IDL/CC has been a source of confusion. The working formulation does not include IDL/CC as this classification scheme was developed before the general acceptance of IDL/CC as a separate entity. As a consequence, recognition of IDL/CC as a biologic entity has been hampered and classification of recognized cases can be problematic. Most cases of IDL/CC are placed within the diffuse small cleaved cell category. However, if the nuclear irregularities of the small cells are not prominent, they may occasionally be placed into the small lymphocytic category. Finally, the mantle zone pattern and the vague nodularity may be mistaken for a follicular lymphoma.

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IDL/CC may show variant morphologic forms that appear to be associated with a more aggressive course. These variants have been referred to as “blastic”22 or as the large-cell variant of CC. Although histologic transformation during the course of disease is extremely uncommon, rare cases of transformation to a large-cell or immunoblastic lymphoma have been reported.20

A significant minority of IDL/CC have leukemic involvement. The lymphocytosis is usually mild and counts above 30,000 are unusual. The cells are generally described as irregular and clefted, or “lymphosarcoma cell”-like. However, cases in which the cells are indistinguishable from CLL have been described21 and some investigators have reported peripheral blood involvement by atypical prolymphocyte-like cells.3 Furthermore, unusual cases of other lymphoid disorders appear to be associated with a more aggressive course. These unusual cases of lymphoproliferative disease that possess the (11;14) translocation and bcl-1 rearrangement may show variant morphologic forms that appear as “blastic” or as the large-cell variant of CC.22 Although histologic transformation during the course of disease is extremely uncommon, rare cases of transformation to a large-cell or immunoblastic lymphoma have been reported.20

The breakpoints on chromosome 11 showed tight clustering and this region was named bcl-1 (B-cell lymphoma/leukemia 1).28 The breakpoints on chromosome 14 were within the Ig heavy chain joining region. Structurally, this translocation was similar to the t(14;18) and t(8;14) translocations in which the bcl-2 gene on chromosome 18 and the c-myc gene on chromosome 8 are rearranged into the Ig heavy chain gene locus. This aberrant relocation of these two genes results in their transcriptional deregulation and this deregulation is believed to play an important role in lymphomagenesis. By analogy, it was believed that the t(11;14) translocation would affect the transcription of a putative growth related gene near the bcl-1 locus on chromosome 11. However, the predicted oncogene was not identified. Rare variant breakpoints located as far as 63 kb away from the original bcl-1 breakpoints were identified and cloned by other groups (three from cases of CLL with "prolymphocytic features"9,20 and one from a plasma cell leukemia cell line15), but none of these variant breakpoints was associated with a transcriptional unit. However, recently a gene designated parathyroid adenomatosis 1 (PRAD1) has been identified on chromosome 11q13 by virtue of its rearrangement with the parathyroid hormone locus on chromosome 11p15.25 PRAD1 has been shown to be deregulated by the rearrangement and to have homology with the cyclins, proteins that have been implicated as regulators of the cell cycle.25 Interestingly, this locus is approximately 200 kb from the bcl-1 locus and the investigators state that PRAD1 is overexpressed in lymphoproliferative disorders having the t(11;14) translocation. Thus, the long search for the bcl-1 gene may be over.

IDENTIFICATION OF T(11;14) TRANSLOCATIONS AND BCL-1 REARRANGEMENTS IN IDL/CC

Although the initial cloning of the bcl-1 breakpoint was a tribute to the power of molecular biologic analysis, it tended to refocus the search for bcl-1 involvement away from the adult lymphomas where the t(11;14) translocation was originally identified, and reoriented it toward the CLls. Only recently has it become clear that the t(11;14) translocation and bcl-1 rearrangement is the characteristic abnormality, not of CLL, but rather of IDL/CC.

Three sizable cytogenetic studies have been published that include cases of IDL/CC.24 In the earliest study of 12 IDLs, Weisenburger et al identified 5 of 10 cases with chromosomal abnormalities having structural abnormalities of chromosome 11. Three of these were t(11;14) translocations. More recently, Leroux et al identified t(11;14) translocations in 13 of 163 serially studied patients at their institution.4 All but one, a large cell lymphoma not further subcategorized, had been classified as IDL or centrocytic lymphoma. In a similarly designed study, Van-denberghe et al identified and reviewed nine lymphomas having the t(11;14) translocation.4 Although all were classified as diffuse small cleaved cell lymphomas in the working formulation, these investigators concluded that all nine were examples of IDL/CC. It is important to note that three of their nine cases had been diagnosed as CLL before lymph node biopsy, again pointing out the danger of diagnosing small lymphocytic neoplasms without a lymph node biopsy.

Five groups of investigators have examined a total of 77 cases of IDL/CC for rearrangements of bcl-1.5-8 Forty-nine percent of these cases (38 of 77) were positive for the rearrangement, including the 12 of 23 cases reported by Williams et al in this issue of Blood.8 This report is also notable for the identification of a second clustered breakpoint in four of their cases. Each of the five groups reported rearrangements in 30% to 55% of their cases of IDL/CC except for one group,4 which failed to identify bcl-1 rearrangements in any of five cases studied.

These recent series of cytogenetic and molecular studies identifying the t(11;14) translocation and/or bcl-1 rearrangement in a high percentage of both IDL and CC suggest that the t(11;14) translocation and its corresponding molecular abnormality, rearrangement of the bcl-1 locus, is related to the pathogenesis of IDL/CC. Furthermore, these studies provide additional genetic evidence that IDL and CC are identical neoplasms.

IDENTIFICATION OF T(11;14) TRANSLOCATIONS AND BCL-1 REARRANGEMENT IN LYMPHOPROLIFERATIVE DISORDERS OTHER THAN IDL/CC

Both the t(11;14) translocation and bcl-1 rearrangement have been reported in lymphoproliferative disorders other
than IDL/CC. Juliusson and Gahrton35 reviewed 427 cases of CLL in a combined European group study and found 11 cases (4%) with this translocation. Additional immunologic data or biopsy data regarding these cases was not provided and the possibility that some of these cases might be leukemic IDL/CC cannot be excluded. The t(11;14) translocation was reported in one of six CLLs studied by Nowell et al36 in 1979 (case 271). This case was notable because of its bright surface Ig fluorescence, a feature more characteristic of IDL/CC than CLL. This same case was one of three original cases cloned by Tsujimoto et al in their seminal series of papers identifying the bcl-1 breakpoint on chromosome 11.27,28 The other "CLL" cloned (case 1386) was a case provided by us that initially presented as a leukemic prolymphocytic variant of CLL.26 In addition, Pallesen et al described a case of PLL that showed a classic mantle zone pattern in a biopsied lymph node and in which the neoplastic cells in the nodules stained for membrane alkaline phosphatase.29 Thus, although there is no doubt that a modest percentage of cases (~20%) with the morphology of PLL have t(11;14) translocations, and bcl-1 rearrangements, it is still uncertain whether these cases have any relationship to IDL/CC.

It is quite clear that outside of IDL/CC the percentage of cases having the t(11;14) translocation and bcl-1 rearrangement is small. Careful scrutiny of cases reported positive in the diffuse and/or nodular adult lymphomas, and in CLL, suggests that some of these are probably unrecognized IDL/CC. It does appear that t(11;14) and bcl-1 rearrangement occur in a small percentage of PLL and multiple myeloma.

CONCLUSIONS

IDL and CC are identical neoplasms derived from follicular mantle cells and should be united under a common terminology. They have common morphologic features, common immunologic features, and have now been shown to have common cytogenetic and molecular genetic features. We propose the term mantle cell lymphoma, nodular or diffuse variant, which would take into account the apparent biologic origin of these lymphomas in the same way that the term follicular lymphoma takes into account the follicular center cell origin of these lymphomas.

Mantle cell lymphomas are characterized by a common and recurring cytogenetic and molecular abnormality, the t(11;14) translocation and its molecular counterpart bcl-1 rearrangement. The reported 50% incidence of bcl-1 rearrangement is likely to be an underestimate of the true incidence because most investigators analyzed only the major translocation cluster region. Other breakpoints known to exist were usually not studied.

The t(11;14) translocation and its molecular counterpart, bcl-1 rearrangement, is rare outside of the mantle cell lymphomas. Careful documentation of positive cases is crucial because of the ability of mantle cell lymphoma to simulate other low grade lymphoproliferative diseases. There is probably a subset of PLL and multiple myeloma that contains these abnormalities. The biologic relationship of these subsets to the mantle cell lymphomas is not clear.

Recurring molecular and cytogenetic abnormalities, such as the t(11;14) translocation and bcl-1 rearrangement, have proven extremely useful in helping us recognize the biologic
relationships among the various lymphoproliferative disorders. This, in turn, has aided our ability to comprehend meaningful classification schemes.

Finally, the dissection of these recurring cytogenetic and molecular abnormalities has provided us with many new insights into understanding the molecular mechanisms of normal and abnormal lymphoid cellular proliferation and promises to continue to do so for many years to come.

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