

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.^{1,2} 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 reports³⁻¹⁰ 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)¹¹⁻¹³ in the American literature and centrocytic lymphoma (CC)^{14,15} in the European literature. The article by Williams et al⁸ 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, clefted cells of "poorly differentiated" lymphocytic lymphoma (small cleaved cell lymphoma).¹¹ 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.¹⁶ Based on shared phenotypic and enzyme histochemical properties with normal follicular mantle zone lymphocytes, an origin from these cells was postulated.^{12,17} Subsequently, mantle zone lymphoma was proposed as a term for those cases of IDL in which a nodular pattern of growth was especially prominent.¹⁸ 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.¹⁵ 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.^{19,20}

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 $\mu\delta$ heavy chain type) with an unexplained preference for λ light chain expression.²⁰⁻²² 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,^{23,24} and in rare cells of the adult mantle zone.²⁵ IDL and CC have also been shown to contain membrane-associated alkaline phosphatase, an enzyme normally found primarily within the follicular mantle cells.¹⁷ 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.¹⁹ 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.^{19,20}

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 described³ and some investigators have reported peripheral blood involvement by atypical prolymphocyte-like cells.³ Furthermore, unusual cases of otherwise classic CLL have been reported with a high percentage of cleaved cells.²⁶ Thus, a diagnosis of IDL/CC can neither be rendered nor excluded on the basis of a peripheral blood study only. As we shall see, these difficulties in diagnosis are likely to have led, at least in some cases, to erroneous conclusions regarding the frequency and even the spectrum of lymphoproliferative disease that possesses the t(11;14) translocation and bcl-1 rearrangement.

THE t(11;14)(q13;q32) TRANSLOCATION AND bcl-1

The t(11;14)(q13;q32) translocation was first identified as a recurring cytogenetic abnormality in the lymphoproliferative diseases by van den Berghe in 1979.¹ The breakpoints were cloned in 1984 by Tsujimoto et al from two cases reported to be CLL and one large cell lymphoma cell line.^{2,27} 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"^{29,30} and one from a plasma cell leukemia cell line³¹), 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 11p15.³² 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.³³ Interestingly, this locus is approximately 200 kb from the bcl-1 locus and the investiga-

tors 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.³⁻⁵ In the earliest study of 12 IDLs, Weisenburger et al³ 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, Vandenbergh et al identified and reviewed nine lymphomas having the t(11;14) translocation.⁵ 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.^{6-10,34} 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,³⁴ 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) TRANSLOCATION 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.^{2,27,28} The other "CLL" cloned (case 1386) was a case provided by us that initially presented as a leukemic process interpreted as CLL, but on subsequent lymph node biopsy showed an unmistakable IDL pattern. Thus, it appears that at least one and possibly both of the original cases from which the bcl-1 breakpoint was cloned were IDL/CCs rather than CLLs. bcl-1 rearrangements have been reported in 14 of 203 cases (6%) of either CLL or small lymphocytic lymphoma (SL).^{8-10,27,34,37-39} At least one of these cases was reported to be a small lymphocytic lymphoma "of mantle zone variant,"³⁹ again suggesting that some cases previously classified as CLL or SL may in fact be IDL/CC.

The cytogenetic translocation or molecular rearrangement has also been reported in 25 of 391 (6%) adult B-cell lymphomas.^{1,4,8-10,27,34,37,39-42} Included in this figure are the original four t(11;14) cases reported by van den Berghe.¹ Two of these cases were classified as "diffuse and nodular lymphomas," one was classified as a "nodular lymphosarcoma," and the fourth was called a "lymphocytic lymphoma composed of poorly differentiated lymphocytes." Because true follicular lymphomas have not been shown to have the t(11;14) translocation, the use of the term nodular in three of the four cases might suggest the vague nodularity or mantle zone pattern of IDL/CC. Seven other t(11;14)-translocated or bcl-1-rearranged cases were classified as diffuse small cleaved cell lymphomas, the most common working formulation category for IDL/CC. The remaining 14 cases included four follicular lymphomas, four large cell lymphomas, three diffuse mixed lymphomas, and two small non-cleaved cell lymphomas.

There have been sporadic reports of multiple myeloma possessing the t(11;14) translocation. In the three largest cytogenetic series, 4 of 136 cases (3%) were positive.⁴²⁻⁴⁴ Two cell lines derived from patients with multiple myeloma or plasma cell leukemia have been reported to have this translocation.^{45,46} One of these cases has a rearranged bcl-1 allele that has been sequenced. bcl-1 rearrangements have also been reported in abstract form by one group in 5 of 120 cases of multiple myeloma.⁴⁷ However, these data have not been confirmed and two other groups with a combined total of 37 patients have not identified bcl-1 rearrangement in their cases.^{8,48} Thus, the incidence of bcl-1 rearrangement in multiple myeloma appears to be quite low.

Brito-Babapulle et al have reported 4 of 22 cases (18%) of prolymphocytic leukemia (PLL) having the t(11;14)

translocation.⁴⁹ In addition, three of the variant bcl-1 region breakpoints were cloned from cases reported as PLL or prolymphocytic variants of CLL.^{26,27} (Again, it should be noted that none of these cases had accompanying lymph node biopsies.) Although the cells of PLL are not usually considered similar to the cells of IDL/CC, several investigators have described prolymphocyte-like cells in IDL/CC. "Atypical prolymphocytes" were identified in five of Weisenburger et al's cases of IDL, including two with documented t(11;14) translocations,³ and Swerdlow et al reported prolymphocytes in 1 of his 18 cases published in 1982.²⁰ 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.⁵⁰ 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 unified 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 those 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 provide 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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