Uncovering Clinically Relevant Phenotypic Variations in Malignancies

CD23 in Mantle Cell Lymphoma

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An important consequence of the robust, multiparameter approach to the definition of lymphoma subtypes introduced in the Revised European and American Lymphoma classification in 1994, continued in the 2001 World Health Organization classification, has been that some established disease entities are now appreciated to have much broader phenotypic (morphologic, immunophenotypic, and clinical) variability than was previously appreciated. A case in point is mantle cell lymphoma (MCL). Since Banks et al initially proposed this term in 1992 to encompass lymphomas previously designated as intermediately differentiated lymphocytic lymphoma, centrocytic lymphoma, and mantle zone lymphoma, our concept of what this lymphoma can look like, stain like, and behave like has steadily expanded. Even the t(11;14), resulting in overexpression of cyclin D1, the absolutely necessary genetic lesion in MCL, is no longer necessary; as with other types of non-Hodgkin lymphoma, there appear to be multiple molecular pathways that produce the same disease. Fortunately, robust multiparameter disease definitions can accommodate such variability.

Immunophenotypically, MCL is CD5+/CD10−/FMC7+/CD23−/CD20(bright)/CD79b+ and surface immunoglobulin(bright). The problem, of course, is that it often is not.6,7 Being able to recognize the exceptions to the rules is one of the fundamental challenges of diagnostic pathology. Once we recognize these variations, though, the next logical step is to ask, “What do they mean?” The goal is to be able to predict how a particular tumor is going to behave and, ultimately, individualize therapy to achieve maximum clinical benefit.

One such immunophenotypic variation in MCL is the expression of CD23. In the current issue of the Journal, Kelemen et al report detection of this antigen at diagnosis in about one quarter of patients. These authors then ask, in a carefully performed, retrospective clinical study, “What does CD23 expression mean in MCL?” Since CD23 expression in conjunction with CD5 is a diagnostic hallmark of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), in the past it meant a diagnostic pitfall; it is likely that many CD23+ MCLs were previously diagnosed as CLL/SLL. In these authors’ hands, the answer is that while CD23− and CD23+ MCLs are similar in most ways, they differ in that CD23+ MCLs more often manifest with disease in extranodal sites (exclusive of gastrointestinal tract and bone marrow) and less often manifest bulky disease. Most important, CD23 expression is associated with superior event-free and overall survival in a univariate analysis.

These results are compelling, but enthusiasm must be tempered by the fairly small number in the CD23+ cohort, precluding robust multivariate analysis, the retrospective nature of the study, and the lack of uniform treatment across the study patients. Assuming for a moment that the results hold up with additional study—and experience teaches us that things are rarely as clear as they seem at first—several practical questions arise with respect to deploying CD23 expression as a clinical test. First is the problematic issue of discordant expression of CD23 in MCL detailed by Kelemen et al, at different time points and at different sites at the same time point, which they postulate to be related to the effect of the microenvironment on the expression of this antigen. Moreover, the cases with CD23 expression at any site or time point appeared to behave similarly to those that were CD23+ at all testing instances. The conclusion, strangely, is that merely the intrinsic potential to express...
CD23 would appear to be a favorable prognostic feature. While fascinating if true, it is also a frustrating finding from the clinical standpoint. Does this mean that one should biopsy multiple sites at multiple time points in all patients to find this potential CD23 expression?

Another issue obliquely alluded to by Kelemen et al is the technical issue of assessing positivity and negativity for CD23. As they indicate in their review of rates of CD23 expression in MCL reported in the literature, there is wide variability across studies, indicating that this is unlikely to be a trivial issue. Previous authors have reported that CD23 expression detected by flow cytometry is usually dim, in other words, not an all-or-none phenomenon. Kelemen et al also indicate that they distinguished “positive” from “dim positive” expression but do not provide additional data regarding this distinction. This prevalence of dim expression suggests that we can extrapolate from the experience with CD38 and ZAP-70 as prognostic markers in CLL/SLL. Specifically, even if an optimal cutoff can be established in any particular laboratory with specific reagents and instrument settings, it is unlikely that this can be generalized to other laboratories. Simply changing the voltages on the photomultiplier tubes of flow cytometry instruments can dramatically affect the assessment of expression of dimly or partially expressed antigens. Consequently, standardization is likely to be quite problematic. While an arbitrary cutoff point may be adequate for the purposes of clinical research, if a test is to be applied to clinical decision making, it must be reproducible across laboratories. It also appears that immunohistochemical analysis is much less sensitive than flow cytometry in detecting CD23 expression, indicating that this method will likely not be useful in this context.

It is tempting to speculate that expression of CD23 somehow makes MCL more like its CD5+ cousin, CLL/SLL, but the data do not appear to bear this out. For one thing, there was no difference in the rate of peripheral blood involvement between CD23+ and CD23– cases. In addition, the high prevalence of splenomegaly in the CD23+ group would be hard to reconcile with a more CLL/SLL-like disease phenotype. Based on data from CLL/SLL indicating that signaling through CD23 suppresses proliferation in CLL/SLL, Kelemen et al postulate that a similar effect could be operable in CD23+ MCL. However, proliferation data were available in too few cases for meaningful analysis. It is noteworthy that a monoclonal antibody against CD23 is highly variable across studies, indicating that this is unlikely to be a trivial issue. Previous authors have reported that CD23 expression detected by flow cytometry is usually dim, in other words, not an all-or-none phenomenon. Kelemen et al also indicate that they distinguished “positive” from “dim positive” expression but do not provide additional data regarding this distinction. This prevalence of dim expression suggests that we can extrapolate from the experience with CD38 and ZAP-70 as prognostic markers in CLL/SLL. Specifically, even if an optimal cutoff can be established in any particular laboratory with specific reagents and instrument settings, it is unlikely that this can be generalized to other laboratories. Simply changing the voltages on the photomultiplier tubes of flow cytometry instruments can dramatically affect the assessment of expression of dimly or partially expressed antigens. Consequently, standardization is likely to be quite problematic. While an arbitrary cutoff point may be adequate for the purposes of clinical research, if a test is to be applied to clinical decision making, it must be reproducible across laboratories. It also appears that immunohistochemical analysis is much less sensitive than flow cytometry in detecting CD23 expression, indicating that this method will likely not be useful in this context.

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In the end, it is unlikely that expression of a single antigen captures much of the complexity of the biologic puzzle that each lymphoma represents. Until we understand how CD23 interacts with other mediators of disease phenotype in MCL, we are like the blind man feeling only one small part of the elephant. Data regarding genotype and gene expression in MCL are accumulating, and hopefully we will one day understand the molecular bases of this disease sufficiently to allow us to construct the complex genotypic-phenotypic matrix that describes it. Until then, we will continue to use the tools we have readily at our disposal to decipher the clinical relevance of variations in disease phenotype in a piecemeal manner.

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References


