Immunotyping malignant lymphomas
A boon to diagnosis

As the case report by Linden et al in this issue shows,[1] recent advances in immunotyping have given us much insight into the immunobiology of lymphomas. With the benefit of widely available monoclonal antibodies, it is now possible to identify the cell of origin of a lymphoid tumor precisely in the maturation sequence of B and T cells, from stem cell to mature cell. For example, Linden et al were able to take a tumor of uncertain histologic type and state with certainty that it was a B-cell large-cell lymphoma derived from late-secretory, preplasma cells.

Although most immunotyping studies have not yet yielded statistically significant results useful for prognoses, these studies are beginning to find broad clinical utility and practical application. What statisticians and group studies have so far failed to measure are the many cases in which immunology has influenced clinical decision making, thereby benefitting patients.

Among these cases are large-cell lymphomas with sclerosis, as Linden et al describe, and cases of sinusoidal, large-cell lymphoma,[2] which had frequently been called carcinomas because of malignant cell "nesting." Clearly, these patients benefit from improved diagnostic insight by receiving more appropriate therapy. Patients previously referred to as having "undifferentiated" malignancies also benefit. Whereas the diagnosis of undifferentiated malignancy was once common in hospital practice, it is now becoming rarer because of immunotyping.[3] We now commonly overcome the price previously paid for diagnostic uncertainty: vague messages to the patient and ill-defined treatment plans. Because of immunotyping, fewer non-Hodgkin's lymphomas are now confused with Hodgkin's lymphomas. In such instances, by detecting monoclonality (immunoglobulin restriction or the presence of a single T-cell subset), we give more appropriate therapy and may eliminate the need for laparotomy.[4] In another instance, we now recognize that peripheral T-cell lymphomas frequently show aberrant myelocytopoiesis, and we no longer confuse them with granulocytic sarcomas.[5,6] In patients with pseudolymphoma, immunotyping obviates overtreatment because detailed analysis reveals the nonmalignant nature of the lesion.[7] We now recognize the peripheral T-cell phenotype as an aggressive subtype of large-cell lymphoma prone to relapse. These peripheral T-cell lymphomas may require different treatment strategies.[8,9] Similarly, lymphoblastic lymphomas of remarkably different immunotypes have been detected, including some with pre-B or pre-pre-B phenotypes, suggesting that treatment of lymphoblastic phenotypes may need to vary, as with acute lymphocytic leukemia phenotypes.[10,11] Thus, complex phenotypes are now seen to delineate many subtypes of lymphoma.

On the other hand, the detailed immunotypes are also revealing the close immunologic relatedness of certain entities previously believed to be unrelated, for example, small lymphocytic lymphoma, mantle-zone lymphoma, and intermediate lymphoma, all of which frequently coexpress pan-B B_1 and pan-T leu 1.[12] Detailed immunotypes have also revealed the relationship of transformed malignant lymphomas to their more indolent predecessors.[13]

Preliminary data on the reproducibility of immunohistochemical results are emerging. A recent double-blind, interinstitutional comparative study (Grogan TM and Tubbs RR, unpublished) indicates that immunotyping greatly improves the capability to diagnose lymphoma subtypes,

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with 93% immunotypic agreement vs. 55% to 58% for histologic diagnoses.[14,15] Indeed, some subtypes readily delineated by immunotyping cannot be reproducibly diagnosed by histology, even by experts.[16,17] In one study on nodular mixed lymphoma, seven experts agreed on the diagnosis of nodular mixed lymphoma in only one of 39 cases.[17] Clearly, these limits on histologic reproducibility pose major restraints on group study. The long-term debate over whether nodular mixed lymphoma is curable cannot be resolved because experts cannot agree on the histologic diagnosis, thus casting doubt on the treatment results. Even the basic histologic exercise of distinguishing low-grade from high-grade lymphoma has a high diagnostic error rate.[18] Immunotyping promises to reduce it.[16]

We believe that immunophenotyping studies have not yet detected prognostic significance, largely because few cases have been studied with immunologic completeness. The most recent immunologically complete studies suggest immunotyping is useful. Most studies of peripheral T-cell lymphoma now suggest an aggressive course distinguishable from other large-cell lymphomas (LCLs) or diffuse, mixed lymphomas.[8,9] Lymphoblastic cases with pre-B and pre-pre-B phenotypes have a different clinical profile from other forms of lymphoblastic lymphoma.[10,11] CALLA expression in myeloma has been associated with poor prognosis.[18] Interestingly, the present case report by Linden et al shows mature plasma cell-like features to be prognostically relevant; plasma-cell malignancies with immature B-cell features also have proved to be prognostically relevant.[18] The poor prognosis in the case described by Linden et al may also relate to the expression of immunoglobulin (Ig). In two studies, SIg^+ LCLs have poor five-year survival (15%) relative to SIg^- LCLs (63%).[19,20] Clearly, surface markers are beginning to identify high-risk, poor-prognosis patients who may benefit from different treatment strategies. Improved treatment is only a prospect unless preceded by diagnostic insight.

We are learning that there is more to tumor immunology than the tumor's phenotype. Recent evidence suggests that the immunotype of the host response may be pivotal.[21] Future immunotyping, then, should include not only a tumor phenotype but also a host-response profile. Because of an interest in this level of information, we now use 45 monoclonals for all lymphoma and leukemia cases to fully characterize the tumor as well as the response to it.

We anticipate the day when a single biopsy can generate a histologic report, a tumor phenotype, a host response profile, a printout of this phenotype compared to others, and a statement of the usual clinical profile and past treatment history of patients with similar profiles. This prospect is momentarily beyond our reach, but technologically within our grasp. Furthermore, this revolution is not restricted to lymphoma; one day all tissue biopsies will benefit from this degree of "chemical proof." As prospective patients, we all welcome that day.

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