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Atypical immunoproliferative disorders: when of age?

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The past two decades have witnessed explosive progress in the identification and thorough description of lymphoid disorders. Precise histological criteria have been provided for the diagnosis of a variety of benign and malignant entities and have been correlated with immunophenotypic, genotypic and cytogenetic characteristics: such information has been essential for our advances in the management of lymphoid disorders.

For a long time, however, pathologists have recognized the existence of lymphadenopathies which do not fit the histological criteria for known benign or malignant entities completely, the best example perhaps being the lesions that develop in patients treated with anticonvulsants. The term "atypical" lymphoproliferative disorder (ALPD) or "pseudolymphoma" is often used in these cases (Schroer and Franssila 1979; Lopez-Berestein et al. 1983; Krueger et al. 1987; Whitten et al. 1990), obviously implying not only unusual histological characteristics, but also a suspected propensity to evolve into a lymphoma. Older studies of these lesions have attempted a histological grading correlated with the clinical evolution: this was based on generic features of suspicion for malignancy (such as capsular infiltration, cytological atypia, etc.) (Kreyberg and Iversen 1959) or simply on the inability to classify a lesion as either benign or malignant ("probably benign," "probably malignant") (Schroer and Franssila 1979). A more specific description of these cases was defeated by their extreme histological heterogeneity.

Angioimmunoblastic lymphadenopathy (AIL) was the first entity to be recognized as a "hyperimmune" reaction with a potential for developing into a lymphoma, and to be clearly defined in histopathological and clinical terms (Frizzera et al. 1974). A variety of similar patterns was identified at the same time, such as three types of immunoblastic lymphadenopathy (quoted in Dorfman and Warnke 1974; Lukes and Tindle 1975), and as many as five types of lymphogranulomatosis X (Knecht et al. 1985). Other ALPDs were later recognized on the basis of characteristic histological features: the polymorphic B-cell hyperplasias and lymphomas that develop in transplant recipients (Frizzera et al. 1981) and multicentric angio-follicular lymphoid hyperplasia, or Castleman's disease (Frizzera et al. 1983; Weisenburger et al. 1985). A large body of information (immunophenotypic, molecular genetic, and cytogenetic, as well as clinical – reviewed in Frizzera 1992) has accumulated on these three types of disorders and has led to a general theory of the pathogenesis of ALPDs. They may be seen as unstable lymphoproliferative states originating in reaction to unknown antigens, but not properly downregulated by a defective immune system. In this situation chromosomal errors are bound to occur, with the emergence of one or more clones, some of which may develop into bona fide clinical malignancies (Frizzera et al. 1981; Lipford et al. 1987; Cleary et al. 1988). This theory accounts for the pathological heterogeneity within each of the categories of ALPDs better than the view that clonality equals malignancy, often espoused in the case of AIL (Namikawa et al. 1987; Nakamura and Suchi 1991; Anagnostopoulos et al. 1992).

Little progress has been made beyond these three prototype entities. From a histological viewpoint, some other patterns that may fit in the general category of ALPDs have been reported. Only one, described under the term "systemic polyclonal immunoblastic proliferations" (Peterson et al. 1988; Poje et al. 1992) is, in my view, a clearly definable clinico-pathological entity, distinct from both AIL and multicentric Castleman's disease (Frizzera and Seo, in press). Others, such as the "hyperimmune reactions" (Knecht et al. 1985), the "autoimmune disease-associated lymphadenopathies" (Koo et al. 1984), and the "hyperimmune B lymphocyte disorder" in children (Nezelof and Virelizier 1983), are less well characterized and appear to be defined largely by not being quite similar to AIL. Even more importantly, from a clinical viewpoint, the general pathogenetic interpretation of ALPDs outlined above has not yet translated into a consistent philosophy of management. With the exception of occasional innovative attempts to modify the biological response of the host (Starzl et al. 1984; Shapiro et al. 1988; Schwarzmeier et al.

1991), the most widely used treatment continues to be aggressive chemotherapy, as for lymphomas (Siegert et al. 1992).

There are several reasons for the slowness of our progress in the area of ALPDs. First of all, these are uncommon disorders and only a few are bound to be observed at a single institution. Second, their recognition and collection is hampered by the lack of a generally accepted definition of this nosological category. Third, their study is usually based on retrospective series, in which clinical information is incomplete and non-uniform, and the evaluation of disease course and efficacy of treatment is uncertain. Finally, the study of ALPDs is made difficult by their extraordinary histopathological heterogeneity. Indeed, our insight into the genomic events occurring in these processes has overrun or by-passed our knowledge of their morphological and immunophenotypic variety. It would be unfortunate, however, if the similarity of genomic events led to a simplistic combining of all these processes, so obscuring possible differences in etiology and pathogenesis, reflected in different morphologies.

Besides AIL, multicentric Castleman's disease, post-transplant LPDs and systemic polyclonal immunoblastic proliferations, we continue to observe unusual patterns of nodal reaction, the etiology and biological significance of which are obscure. Histopathologically, these lesions run the gamut from partial to diffuse obliteration of the architecture, and feature involvement of the germinal centers (GCs) and the paracortical areas in variable proportions, a large variety of GC changes and of cell composition in the interfollicular areas, and sometimes vasculitic lesions of various types. In the same patient different histopathologies can be observed in multiple biopsies (Poppema et al. 1985; Winberg et al. 1986). Immunophenotypically, in addition to the already mentioned variable cell composition, unusual reactivities are frequently noted: in different cases, the immunoblasts may or may not express strongly the Ki-1 antigen (Pallesen 1990), may lose the expression of leukocyte common antigen, as observed in Reed-Sternberg cells, or manifest discordant reactions to L-26 and MB2; the GCs may show breaking down of the dendritic reticulum cell network, excess of T- cells or of Leu7-positive cells; on a polyclonal background, excess of light chain restricted plasma cells may be seen in the interfollicular areas or within the GCs. The clinical presentation may vary from indolent, localized lymphadenopathy to aggressive, severely symptomatic disease.

Obviously, such a variety of morpho/immunophenotypic and clinical expressions points to a multiplicity of disorders and pathogenetic mechanisms that require better characterization. It is perhaps time that ALPDs be looked at formally and categorized – like the Hodgkin's and non-Hodgkin's lymphoma have been – with the advantage of all the experience that has been acquired in, and the techniques that are applied to, the study of lymphoid malignancies.

The field of inquiry should first be delimited vis-à-vis other situations that may qualify as "atypical', such as the odd lesion that "I don't know what it is" and the bona fide lymphoma disguised and made difficult to recognize by an usual histopathology (Williams et al. 1991). The best general definition of ALPDs is a pathogenetic one, i.e., one of many forms of abnormal immune response, in which a dysfunction of immunoregulatory mechanisms allows the reaction to progress unchecked. Second, positive histopathological criteria – rather than negative ones ("difficult to classify as clearly reactive or malignant") – are required for the identification of ALPDs: those that we have recently offered (Frizzera 1992) may be a starting point. On this or similar basis, a histological categorization might then be attempted.

The histopathological patterns can be expressed as changes in the immuno-architecture of the lymph node, by utilizing B- and T-cell reagents, as well as markers for dendritic reticulum cells (identifying GCs), high endothelial venules (identifying the paracortex), or endothelial cells of the sinuses. To the identification of the cell lineage one can add the study of functional characteristics of the cells, as expressed by activation markers, adhesion molecules, and production of growth factors and cytokines. This may lead to the elucidation of the functional relationships among the multiple cell components of these disorders, which are a puzzle today (O'Connor et al. 1986). Immunohistochemical and DNA hybridization techniques are available for the detection of possible viral etiologies and the same techniques and cytogenetics can provide information as to possible molecular mechanisms of pathogenesis (translocations, oncogenes, tumor suppressor genes). Finally, correlations of all this information with clinical findings are needed: these will become possible as ALPDs will be identified as a distinct category of disorders and studied prospectively, and resources from different institutions will be pooled for cooperative efforts.

The final goal is to unravel the mechanisms that lie behind these abnormal immune responses. The focus today seems to be on the development of clonal populations within them, and this may result in concentrating all our efforts on the elimination of such clones by cytoreductive approaches. If a lesson needs to be learned from the post-transplantation LPDs (Starzl et al. 1984), as well as from innumerable other clinical situations in which clonal growths have been detected, it is that clonal evolution does not necessarily indicate biological and clinical malignancy (Fishleder et al. 1987; Radaszkiewicz et al. 1989; van der Harst et al. 1990). Focusing instead on the different mechanisms underlying ALPDs will help direct therapeutic efforts to the correction of the specific immunoregulatory defect(s) involved. Only then will the step be made from the empirical approach used today to a rational management of these disorders.

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