Conquering Blood Diseases – From Research to Patient Care

Peripheral T-Cell Lymphomas: An Historical Perspective

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Peripheral T-cell lymphomas (PTCL) remain largely unexplored due to disease rarity and biological heterogeneity as well as relatively recent recognition in modern classification systems. Before 1970, classifications of non-Hodgkin's lymphomas (NHL) were based on morphology. The discovery of distinct T-, B- and natural killer (NK)–cell lineages led to two immunologically based classification systems proposed in 1974: the European Kiel and the North American Lukes-Collins. In 1982, the Working Formulation (WF), based on clinical and morphologic criteria, was developed in the United States. The updated Kiel classification separated B- and T-cell lymphomas but still failed to address some disease types.

The addition of molecular genetic features/criteria and increasing immunophenotypic subclassification allowed for more diagnostic standardization and reproducibility. The International Lymphoma Study Group (ILSG) integrated morphologic, phenotypic, molecular and clinical information in the 1994 REAL (Revised European American Lymphoma) classification. The T-cell lymphomas were grouped into "precursor" neoplasms versus "peripheral" or post-thymic T-cell and NK neoplasms, the so-called "PTCLs." The World Health Organization (WHO) subsequently made the following modifications: PTCLs were subdivided into predominantly leukemic, extranodal and nodal types; cutaneous and systemic anaplastic large cell lymphomas (ALCL) were separated; terminology was updated for some diseases; and subcutaneous panniculitis-type and hepatosplenic $\gamma\delta$ T-cell lymphomas were recognized as distinct entities.

Almost a decade later, the recently published fourth edition of the WHO classification has refined the classification further, including defining ALK-negative ALCL as a provisional entity, confining subcutaneous panniculitis-like T-cell lymphoma to cases with an $\alpha\beta$ phenotype and combining the $\gamma\delta$ cases with primary cutaneous $\gamma\delta$ PTCL. Two other provisional categories have been established under the category of primary cutaneous peripheral T-cell lymphomas: primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma and CD8-positive cytotoxic T-cell lymphoma.

Several important advances in the pathobiology of PTCL have been made. Unlike mature B-cell lymphomas, there are virtually no recurrent translocations characterizing the PTCLs. The one exception is a proportion of ALCL cases in which a non-random t(2;5)(p23;q35) translocation produces a novel fusion protein composed of the nucleophosmin (NPM) and anaplastic lymphoma (ALK) coding regions. The use of more detailed cytogenetic analysis with comparative genomic hybridization and gene expression profiling now provide evidence for recurrent genetic changes in other PTCL subtypes.

Several PTCL subtypes have viral associations that may be involved in disease pathogenesis. In 1982, HTLV1 was found to be the etiologic agent of adult T-cell leukemia and lymphoma. In 1988, T-cell lymphomas were described in patients with chronic Epstein-Barr virus (EBV) infections, and EBV was subsequently found to be associated with extranodal NK/T-cell lymphoma, nasal type and angioimmunoblastic T-cell lymphoma.

With the development of molecular techniques in the 1990s, the importance of the $\gamma\delta$ T-cell receptor rearrangement and impact on prognosis is apparent. For example, in the updated WHO classification primary cutaneous $\gamma\delta$ T-cell lymphoma is recognized by an aggressive course and considered a new provisional entity.

Although significant progress has been made in defining specific disease categories within the diverse group of PTCLs and establishing the prognostic significance, advances in therapy have been much slower. In the last several years, attention has turned to testing new chemotherapy combinations, targeted agents and high-dose chemotherapy approaches specifically in PTCL. The hope for the future is that treatment can be tailored better for PTCL and outcomes will more approximate what is observed in aggressive B-cell NHL.

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