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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Refining Diagnostic Subtypes of Peripheral T-Cell Lymphoma Using a Multiparameter Approach

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Peripheral T-cell lymphoma (PTCL) encompasses a diverse group of post-thymic lymphomas, with ~40% of cases not further classifiable and designated as PTCL-not otherwise specified (PTCL-NOS). Two molecular prognostic subtypes of PTCL-NOS, PTCL-TBX21 and PTCL-GATA3, were identified through gene expression profiling (GEP). A subset of PTCL-NOS with T-follicular helper (TFH) differentiation was subsequently categorized as nodal PTCL with TFH phenotype (PTCL-TFH), also known in current classifications as nodal PTCL-TFH, NOS, or TFH lymphoma, NOS. However, the boundary between PTCL-NOS and PTCL-TFH remains poorly defined. To refine these subtypes, 101 PTCL-NOS with centralized pathology review and extensive immunophenotyping by immunohistochemistry (IHC) using 22 antibodies, digital GEP (nCounter, NanoString Inc) (n= 70), and RNA sequencing (n= 73) were included in this study. IHC was used to identify PTCL-TFH cases (those with strong expression of more than two TFH markers); the remaining patients were classified as PTCL-GATA3 and PTCL-TBX21 using pre-defined GEP signatures.

Cases were reclassified into PTCL-NOS (n= 63) and PTCL-TFH (n= 38), with PTCL-NOS subclassified into PTCL-GATA3 (n= 22; 34%) and PTCL-TBX21 (n= 41; 66%) and showing significant differences in OS ($p<0.001$). PTCL-GATA3 was characterized by medium to large transformed cells (average= 90%, 70-100%) and had minimal tumor microenvironment (TME) (TME-poor: 100%). In contrast, PTCL-TBX21 was more heterogeneous, associated with pleomorphic cells in a polymorphous background (TME-rich: 78%), including Lennert lymphoma-like cases (22%). mRNA and CIBERSORT analysis substantiated the findings and identified a subset enriched in cytotoxic features in the PTCL-TBX21 subtype.

IHC indicated that PTCL-GATA3 cases were CD4+/CD8- (83%) or CD4-/CD8- (17%) and lacked expression of CD8 or cytotoxic markers compared to PTCL-TBX21 ($p<0.01$). PTCL-GATA3 showed significantly higher expression of LEF1 (average= 80%), Ki67 (80%), and MYC (25%) than PTCL-TBX21 (25%, 30%, <5%, respectively, $p<0.01$). mRNA and protein expression of these biomarkers showed a significant positive correlation ($r=0.5$, $p<0.001$), and expectedly higher mRNA expression of LEF1 and

MYC was observed in the PTCL-GATA3 versus PTCL-TBX21 ($p<0.05$). Strong expression of CD30 (>50% of cells) was only seen in PTCL-GATA3 cases. EBER positivity, found only in rare background cells, was not significantly different (18% of PTCL-GATA3 vs. 12% of PTCL-TBX21).
Within PTCL-TBX21, we identified cytotoxic and non-cytotoxic subsets with divergent morphological, phenotypic, and clinical findings. The cytotoxic PTCL-TBX21 exhibited an activated cytotoxic phenotype (23/25, 96%), denoted by TIA1 and granzyme-B and/or perforin expression. Extranodal involvement and single-cell apoptosis were observed in 17% and 45% of the cytotoxic cases, respectively, but absent in non-cytotoxic PTCL-TBX21 cases. A trend towards higher Ki67 expression (average= 40% vs. 20%, p= 0.08) was seen in the cytotoxic subgroup. In contrast, the non-cytotoxic PTCL-TBX21 was associated with a CD4+/CD8- phenotype and higher ICOS expression (average= 30%) and CCR4 (60%) compared to the cytotoxic PTCL-TBX21 (p= 0.001).
PTCL-TFH cases showed a CD4+/CD8- phenotype (90%) and rarely a CD4-/CD8- phenotype (10%). While a subset of PTCL-TFH cases had AITL-like features such as numerous clear cells and/or prominent vasculature (31% of cases), which were not seen in the other subgroups, the remaining cases exhibited morphology that was indistinguishable from other PTLC-NOS cases including sheets of transformed cells or pleomorphic cells in a polymorphous background. Morphologically, PTCL-TFH cases, like PTCL-TBX21 were associated with a rich TME (TME-rich: 75%). CIBERSORT analysis showed enrichment of plasma cells ($p<0.01$) in PTCL-TFH, compared to PTCL-TBX21, and validated by morphology (30% of cases vs. 5%). Expression of one TFH marker was frequent in some PTCL-NOS cases (PTCL-GATA3= 41% of cases, PTCL-TBX21-non cytotoxic= 47%, PTCL-TBX21-cytotoxic= 5%).
Conclusion: Our comprehensive evaluation underscores the importance of integrating morphology, immunophenotyping, and GEP in achieving an accurate diagnosis, potentially leading to more tailored treatment strategies for PTCL. Correlation with pending whole-exome sequencing studies will be provided at the time of presentation.

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