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ORAL ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Polytypic B-Cells, B-Cell Lymphoproliferative Disorders/Lymphomas, and Neoplastic T-Cells Divergently Differentiate from *TET2-/ DNMT3A*-Mutated Clonal Hematopoiesis in Patients with Follicular Helper T-Cell Lymphomas/Lymphoproliferative Disorders

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Introduction:
Patients with follicular helper T-cell lymphomas/lymphoproliferative disorders (TFH-LPDs) commonly develop B-cell lymphoproliferative disorders and lymphomas (B-LPDs), but the pathophysiology is incompletely understood. TFH-LPDs often arise from *TET2-/ DNMT3A*-mutated clonal hematopoiesis (CH). Here we show *TET2/ DNMT3A* mutations are commonly shared by polytypic B-cells (PBCs), B-LPDs, and TFH-LPDs, with the latter two often carrying additional unique mutations.
Methods:
Pathology database search at Memorial Sloan Kettering identified patients with TFH-LPDs and PBCs or B-LPDs available for genotyping. If available, myeloid cells were also genotyped. PBCs lacked aberrancies by morphology and flow cytometry (FC) immunophenotyping (including polytypic light chain expression). TFH-LPDs and B-LPDs were defined using International Consensus Classification criteria. Genotyping assays included targeted next-generation sequencing (NGS) with (n=13) or without (n=8; cases 1, 4, 9, 10, 15, 16, 17, 22) a matched germline control and droplet digital PCR (n=4; cases 2, 3, 5, 6). Genotyping was performed on bulk samples or FC-sorted cells, including T-, B-, and myeloid as available. In bulk samples, mutations with allele frequencies (VAFs) >2x the percentage of neoplastic T- and myeloid cells combined in B-LPD samples and of neoplastic T- and total B-cells in bulk blood (PB)/bone marrow (BM) samples were considered present in B-LPD or myeloid compartments, respectively. A >2% VAF cutoff was utilized. EBV status was assessed using EBER in situ hybridization on tissues, serum EBV DNA by quantitative PCR, and/or evaluation of off target EBV reads by NGS. Statistical analyses utilized Mann-Whitney U tests.
Results:
In total, 25 patients (10 female, 15 male; median age 70 [range 38-82] years) with TFH-LPDs (19 TFH lymphoma, angioimmunoblastic type, 4 TFH lymphoma, NOS, 2 T-LPD with TFH phenotype [defined by morphologically and/or immunophenotypically atypical T-cells with both TFH-like phenotypes and genomic alterations that did not fulfill morphologic criteria for diagnosis of lymphoma]) were identified. The TFH-LPDs harbored *TET2* (25/25, 100%), *DNMT3A* (12/25, 48%), *RHOA* p.G17 (15/25, 60%), and *IDH2* p.R172 (9/25, 36%) mutations (Figure 1A).
PBCs from 11 patients were evaluated (7 EBV+, 3 EBV-, 1 EBV unknown; 5 from lymph node, 4 PB, 2 BM). PBCs from 7/11 (64%) shared identical *TET2* (n=6; median VAF 0.11 [range 0.02 - 0.27]) and/or *DNMT3A* (n=3; median VAF 0.05 [range 0.03-0.49]) mutations with corresponding TFH-LPDs. PBCs in 1 patient harbored a unique mutation (*TET2*). Four of 8 (50%) patients in which myeloid cells were assessed harbored identical *TET2* and/or *DNMT3A* mutations in the myeloid, PBC, and TFH-LPD compartments.
B-LPDs were evaluated from 14 patients (5 diffuse large B-cell lymphoma, 5 polymorphic B-LPD, 2 follicular lymphoma, 1 B-LPD, NOS, 1 plasma cell myeloma; 11 EBV+, 3 EBV-; 9 from tissue, 4 PB, 1 BM). Polymorphic B-LPDs showed atypical polymorphic morphology and an abnormal B-cell immunophenotype by FC and/or a clonal IgH gene rearrangement. The B-LPD, NOS showed an abnormal CD5-/CD10- immunophenotype with light chain restriction by FC without available tissue

for morphologic evaluation. Nine of 14 (64%) B-LPDs shared identical mutations with corresponding TFH-LPDs (*TET2* [n=9; median VAF 0.42 (range 0.10- 0.56)], *DNMT3A* [n=5; median VAF 0.27 (range 0.05-0.50)], *TET3* [n=1; VAF 0.32]). Myeloid compartments in 9/12 (75%) patients shared identical *TET2* and/or *DNMT3A* mutations with B- and/or T-LPDs. B-LPDs more commonly harbored additional mutations absent in corresponding TFH-LPDs than PBCs (12/14 [86%] vs 1/8 [13%] evaluated by NGS; p=0.001). Unique mutations in B-LPDs involved epigenetic/transcriptional regulation (n=14, e.g. *TET2*, *KMT2D*, *SETD5*), signaling pathways (n=22, e.g. *DTX1*, *KRAS*, *EPHA5*), and DNA damage response (n=3, e.g. *ATM*, *CHEK2*, *BRCA2*). Incidences of shared and unique mutations did not significantly differ among EBV+ and EBV- cases.

Conclusions:

Both PBCs and B-LPDs in TFH-LPD patients are commonly EBV+ and share *TET2/ DNMT3A* mutations with TFH-LPDs, consistent with common origin from CH. B-LPDs more often harbor additional unique mutations than PBCs. Thus, CH mutations and EBV activation in B-cells may predispose TFH-LPD patients to B-LPDs, which may develop with additional private genomic aberrations aiding transformation (Figure 1B).

Disclosures Lewis: *United States Drug Testing Laboratories:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Roshal:** *Physicians' Education Resource:* Other: Provision of services; *Celgene:* Other: Provision of services; *Auron Therapeutics:* Other: Ownership/Equity interests; Provision of services; *NGM:* Other: Funding; *Roche:* Other: Funding; *Beat AML:* Other: Funding. **Baik:** *Pauling.AI:* Current Employment. **Moskowitz:** *Merck:* Honoraria, Research Funding; *ADC Therapeutics:* Research Funding; *Bristol-Myers Squibb:* Research Funding; *Beigene:* Research Funding; *Incyte:* Research Funding; *Seattle Genetics:* Honoraria, Research Funding. **Horwitz:** *Takeda:* Consultancy, Research Funding; *Tubulis:* Consultancy; *Crispr Therapeutics:* Research Funding; *Millenium:* Research Funding; *Seattle Genetics:* Research Funding; *Verastem/SecuraBio:* Research Funding; *Trillium Therapeutics:* Consultancy, Research Funding; *Affimed:* Research Funding; *Celgene:* Research Funding; *Daiichi Sankyo:* Consultancy, Research Funding; *Kyowa Hakko Kirin:* Consultancy, Research Funding; *ONO Pharmaceuticals:* Consultancy; *SecuraBio:* Consultancy; *Shoreline Biosciences, Inc.:* Consultancy; *ADC Therapeutics:* Research Funding; *Yingli Pharma Limited:* Consultancy; *Cimieo Therapeutics:* Consultancy; *Abcuro Inc.:* Consultancy; *Auxilius Pharma:* Consultancy. **Dogan:** *Incyte:* Consultancy; *Peer View:* Honoraria; *Loxo:* Consultancy; *EUSA Pharma:* Consultancy; *Physicians' Education Resource:* Consultancy, Honoraria; *Seattle Genetics:* Consultancy; *Takeda:* Other: Research Funding; *Roche:* Other: Research Funding.

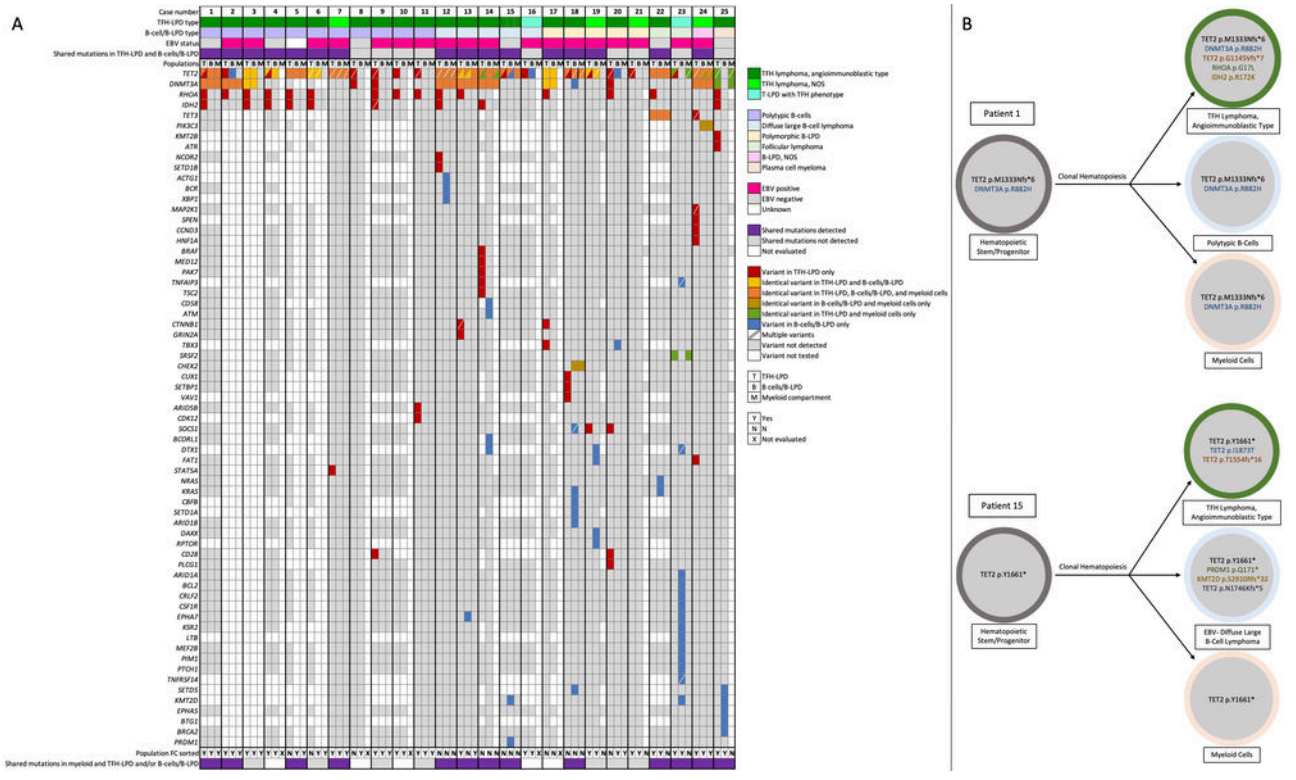

Figure 1

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