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603.LYMPHOID ONCOGENESIS: BASIC

Unraveling the Evolutionary Paths in Relapsed Early-Stage Follicular Lymphoma Showing Complete Remission

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Background: Follicular lymphoma (FL) develops through a stepwise acquisition of cooperative genetic changes with t(14;18)(q32;q21)/ *IGH*:: *BCL2* occurring early at the pre-B stage of B-cell development. Patients with FL typically show an indolent clinical course, remitting and relapsing, and eventually developing resistance to treatments. Interestingly, the majority of transformed FL do not progress directly from the preceding FL but originate from their clonally related lymphoma precursor cells (CLP). In light of this finding, we wanted to address whether such divergent tumor evolution also occurs in the setting of relapses in early-stage FL in patients who achieved complete remission following initial treatment.
Methods: We identified 13 cases of FL with an early clinical stage (stage I = 9; stage II = 4) at the initial diagnosis, who showed complete remission (mean: 5 years; range: 1-11.5 years) following local radiotherapy but subsequently relapsed (≥ 2 in 5). Paired formalin-fixed paraffin-embedded diagnostic and relapsed lymphoma biopsies were obtained in each case. BCL2 translocation status was investigated using interphase fluorescence in-situ hybridization (FISH). Genomic DNA was extracted from the tumor-rich areas in each tissue specimen and targeted next-generation sequencing was performed with a customized gene panel comprising 191 genes/ regions that are implicated in FL, diffuse large B-cell lymphoma (DLBCL), and B-cell biology using the TWIST target enrichment kits and Illumina NextSeq platform. Clonality analysis of *IG* gene rearrangements was performed by combining the BIOMED-2 PCR assays and Illumina MiSeq sequencing. Sequencing data analyses, variant calling, and filtering were performed using a well-established data analysis pipeline from a previous study (Cucco *et al.*, 2018).
Results: Interphase FISH showed *BCL2* translocation in 6 cases, *BCL2* amplification (up to 8 copies) in 1 case, and *BCL2* copy number gain (3-4 copies) in 3 cases. Pathogenic variants were identified in each of the lymphoma biopsies and were typical of those frequently seen in FL and DLBCL. There was no significant difference in the mutational burden between the paired diagnostic (mean: 7.8/sample; range: 1-13) and relapsed FL (7.9/sample; range: 2-13), excluding tFL. Both the diagnostic and relapsed lesions showed similar, frequent mutations in *BCL2* (33.3% vs 41.67%), *CREBBP* (58.3% vs 58.3%), *EP300* (41.7% vs 41.7%), *KMT2D* (50% vs 58.3%), *TNFRSF14* (66.7% vs 58.3%), and *STAT6* (50% vs 50%). The clonal relationship between the diagnostic FL and relapses was confirmed in 11 cases. In 6 cases, common and distinct variants were seen between the paired diagnostic and relapsed lymphomas, indicating their divergent evolution from a CLP. In 2 cases, distinct B-cell clones were involved in the diagnostic and the relapsed lymphomas, including 1 case involving 2 different *BCL2* translocations, indicating independent evolution of the new lymphomas. In the remaining 5 cases, the relapsed lymphomas developed via a linear progression from the preceding FL (n = 5).
Conclusion: Both divergent evolution, either from clonally related or unrelated precursors, and linear evolution processes are involved in the development of relapses in patients with an early-stage FL following complete remission, with the former being more frequent. The above findings, together with the evidence of divergent evolution of tFL in the majority of cases, challenge the current therapeutic strategy of early-stage FL, which does not target the premalignant cell population that underpins lymphoma recurrence in the majority of cases. Additionally, the routine diagnostic workup, which includes *IG* gene clonality and *BCL2* translocation analyses, cannot address the evolutionary path in clonally related lymphomas. Our results indicate the significance of mutational profiling at diagnosis as well as at relapse, and the need to comprehensively characterize and target the evasive CLP population to prevent recurrence.

Disclosures No relevant conflicts of interest to declare.

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