(PF1246) SECONDARY PERIPHERAL T-CELL LYMPHOMA IN A PATIENT OF DLBCL HARBORING CANCER SUSCEPTIBILITY GENE MUTATION FOLLOWING CD19/CD22 BISPECIFIC CAR-T CELL THERAPY

Topic: 26. Gene therapy, cellular immunotherapy and vaccination - Clinical

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Background

Chimeric antigen receptor (CAR)-T cell therapy has revolutionized treatment for relapsed/refractory B-cell malignancies, but rare secondary T-cell malignancies have emerged as a serious safety concern.

Aims

We report a case of secondary peripheral T-cell lymphoma (PTCL) definitively proven to originate from infused CD19/CD22 bispecific CAR-T cells, with comprehensive molecular characterization of oncogenic mechanisms.

Methods

A 66-year-old woman with diffuse large B-cell lymphoma (DLBCL) and history of breast and cervical cancers received autologous CD19/CD22 CAR-T cells in November 2024 following CNS relapse. Nine months post-infusion, she developed a lower lip mass diagnosed as PTCL, not otherwise specified (PTCL-NOS). Comparative genomic analysis of the CAR-T product and PTCL tissue was performed. Whole genome sequencing (WGS), T-cell receptor (TCR) clonality assessment, single-cell RNA sequencing (scRNA-seq), and targeted mutation analysis were conducted on pre-infusion CAR-T product, peripheral blood mononuclear cells (PBMCs), and PTCL tissue.

Results

TCR sequencing identified identical clonal rearrangements (*TRBD1*01/*TRBJ2*701 and TRGV801/TRGJ101) in both CAR-T product and PTCL, confirming clonal origin. WGS revealed pathogenic somatic mutations in TET2 (p.R1261H, p.E1755*) with higher variant allele frequencies in PTCL versus CAR-T product, indicating pre-existing mutations with subsequent clonal expansion. The patient harbored a germline *BLM* p.L107Ffs*36 mutation, contributing to genomic instability. Additional oncogenic events included del(11)(q23.2q25) involving *KMT2A* and *ATM*, loss of chromosome X, and clonal CAR vector integrations within tumor suppressor genes (*NF1*, *CBX5*, *RNF213*). scRNA-seq and flow cytometry of the CAR-T product showed no malignant population at infusion, excluding pre-existing malignancy.

Summary/Conclusion

This case provides unequivocal molecular evidence of CAR-T cell malignant transformation driven by three convergent factors: (1) pre-existing *TET2* driver mutations representing clonal hematopoiesis, (2) germline *BLM* deficiency exacerbating genomic instability, and (3) insertional mutagenesis from CAR vector integration. These findings underscore the critical importance of pre-infusion genomic screening of CAR-T products for CHIP-related mutations, cancer susceptibility gene testing in patients with prior malignancies, and lifelong surveillance for secondary malignancies in CAR-T recipients.