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The expanding spectrum of CAR-T related T-cell lymphomas

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Editorial

In this issue of *Haematologica*, Terakawa and colleagues[1] report a clinically important case illustrating the complex interplay between immune effector cell (IEC) therapies, immune dysregulation, and clonal T-cell evolution. The authors describe a patient with relapsed diffuse large B-cell lymphoma (DLBCL) who developed severe hemophagocytic lymphohistiocytosis (HLH) concurrently with a secondary peripheral T-cell lymphoma during treatment with the CD3×CD20 bispecific antibody epcoritamab, following prior CAR-T therapy with tisagenlecleucel. Through molecular analyses, they demonstrate that the malignant T-cell population originated from a pre-existing T-cell clone detectable in the leukapheresis material used for CAR-T manufacturing, which harbored alterations affecting the *TET2* locus and subsequently acquired a pathogenic *TP53* mutation during the clinical course.

Importantly, rare CAR-T–associated T-cell lymphomas have emerged as severe and increasingly recognized complications as CAR-T cell therapies gain broader regulatory approval and become more widely accessible.[2] Initially, most reported cases involved T-cell lymphomas derived from CAR-transduced T cells with detectable CAR transgene integration.[2] However, an expanding body of literature now describes secondary T-cell lymphomas arising after CAR-T therapy in which the malignant cells lack detectable CAR expression. To date, a limited but growing number of such cases have been reported (**Table 1**), highlighting that CAR expression is not a prerequisite for malignant T-cell evolution in this setting.

Clinically, these CAR-negative secondary T-cell lymphomas share several features with CAR-positive counterparts, including frequent predisposition for extranodal manifestations. Virtually all CAR-negative T-cell lymphomas presented a mature, often cytotoxic immunophenotype, frequently characterized by loss of the pan–T-cell antigen CD5,[1,3–5] a feature well recognized in cytotoxic T-cell neoplasms including T-large granular lymphocytic leukemia (T-LGLL).[6] Moreover, many of these cases are classified as peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS),[1,3,5,7] underscoring that their biology and clinical presentation do not consistently align with established pathogenic categories of specified mature T-cell lymphomas.

Surveying the genomic landscape of reported CAR-T–associated T-cell lymphomas, loss-of-function alterations affecting *TET2* emerge as a recurrent theme.[1,7,8] This pattern, previously recognized in CAR-positive T-cell lymphomas,[2] suggests shared pathogenic mechanisms centered on therapy-driven clonal selection. The case reported by Terakawa *et al.*[1] is particularly instructive in this regard, as it demonstrates that such selective pressure may not

be exerted by CAR-T therapy alone but can be compounded by subsequent T-cell–engaging immunotherapies, such as bispecific antibodies. TET2 appears to play a central role in this process. Experimental data have identified TET2 as a critical regulator of CAR-T cell proliferation, acting as a safeguard against uncontrolled expansion.[9] In murine models, biallelic loss of TET2 enables antigen-independent CAR-T cell proliferation, driven by sustained expression of the AP-1 transcription factor BATF3 and activation of an MYC-dependent proliferative program. Importantly, *TET2* is also among the most frequently mutated genes in clonal hematopoiesis of indeterminate potential (CHIP), a condition characterized by age-related expansion of hematopoietic clones harboring mutations in epigenetic regulators.[10] This observation provides a conceptual framework in which pre-existing *TET2*-altered T-cell clones may persist silently for years, only to undergo malignant transformation upon exposure to strong immune and inflammatory selective pressures (**Figure 1**). Secondary genetic events, distinct across individual patients, may then drive overt lymphomagenesis. In the case presented by Terakawa *et al.*, this evolutionary step is compellingly illustrated by the acquisition of a *TP53* nonsense mutation, effectively abrogating a critical tumor suppressor pathway.

An additional layer of complexity is introduced by the frequent overlap between HLH and the detection of aberrant clonal T-cell populations in this setting. Such overlap is evident not only in the present case but also in prior reports, including the CAR-positive T-cell lymphoma described by Kobbe and colleagues.[11] HLH is a well-recognized complication of T-cell lymphomas,[12] yet its coexistence with clonal CAR-T or CAR-negative T-cell expansions underscores that the boundary between IEC-associated hyperinflammation and overt T-cell malignancy may be fluid rather than discrete. Indeed, spontaneous regression of clonal CAR-T populations has been reported, as in the case described by Maurer *et al.*,[8] and transient clonal expansions resolving after short-course corticosteroid therapy have been observed in other patients, including the case reported by Mehr *et al*.[4] These observations highlight the critical importance of integrating clinical phenotype, temporal dynamics, and molecular findings in the diagnostic evaluation of suspected CAR-T–associated T-cell lymphomas. Current diagnostic criteria for T-cell lymphomas, largely developed in the context of immunocompetent or conventionally treated patients, may be insufficient in the era of immune effector cell therapies. In selected cases with ambiguous findings, close clinical and molecular follow-up may guide the diagnosis.

Collectively, the case presented by Terakawa and colleagues[1] expands the spectrum of CAR-T–associated T-cell lymphomas and underscores the role of immune-mediated selective pressure in driving clonal T-cell evolution. As immune-based therapies continue to reshape hematologic oncology, refined diagnostic frameworks and heightened clinical

vigilance will be essential to distinguish transient immune dysregulation from emerging T-cell malignancy.

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Table

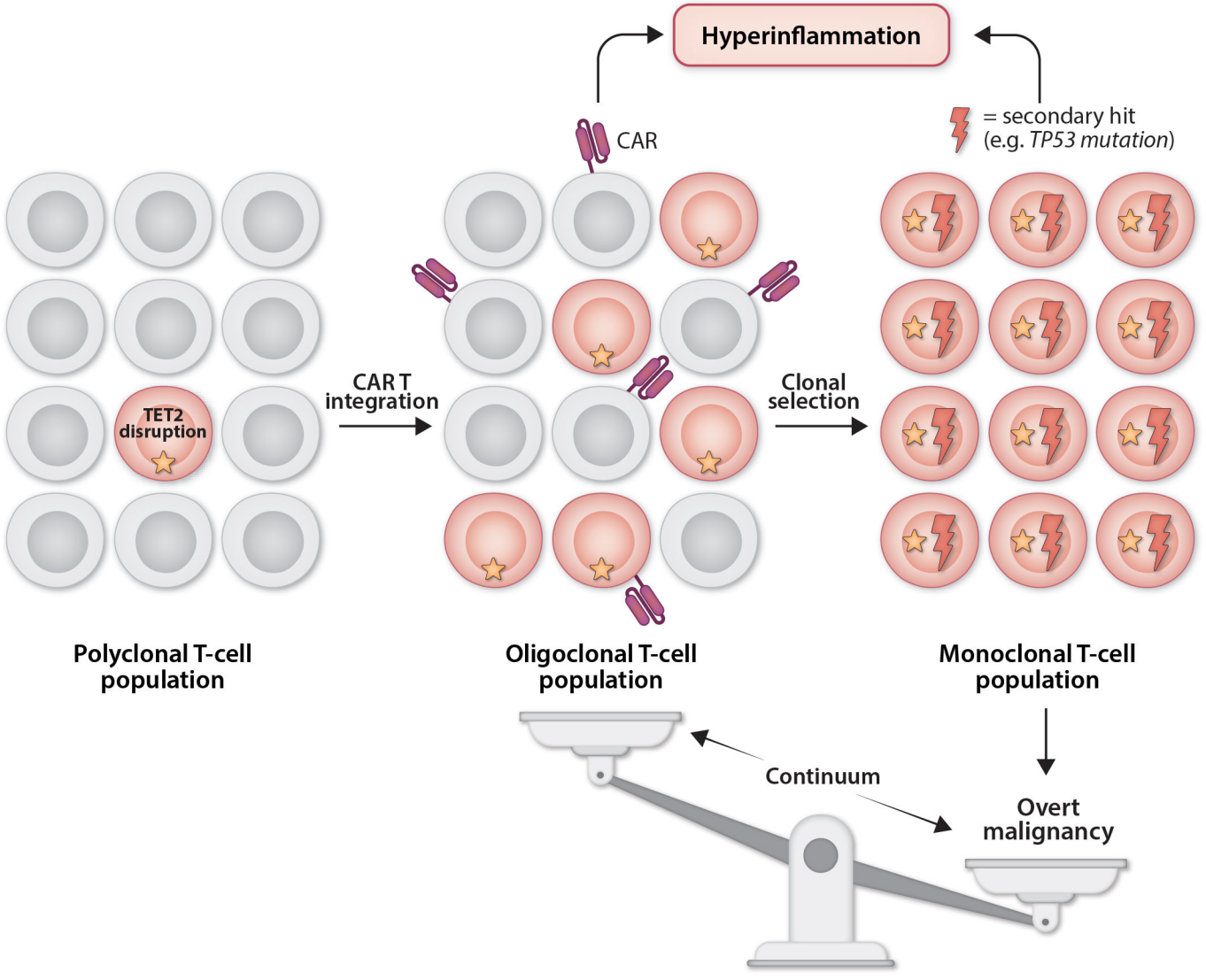
Clinical spectrum of CAR$^-$ T-cell lymphoma.

Summary of clinical and genomic information on seven cases of CAR$^-$ T-cell lymphomas that have been published to date. r/r: relapsed/refractory, DLBCL: diffuse large B-cell lymphoma, B-NHL: non-Hodgkin B-cell lymphoma, tisa-cel: tisagenlecleucel, liso-cel: lisocabtagene maraleucel, axi-cel: axicabtagene ciloleucel, cilta-cel: ciltacabtagen-autoleucel, HLH: hemophagocytic lymphohistiocytosis, PTCL-NOS: peripheral T cell lymphoma, not otherwise specified, TFH: T follicular helper.

Indication	CAR T product	Bispecific Antibody	Timepoint	Clinical presentation	T cell phenotype	T cell clonality	Mutational burden	Classification	Reference
r/r DLBCL	tisa-cel	epcoritamab	1 month	Non-nodal, **association with HLH**	CD8$^+$, **CD5$^-$**, CD30$^-$ T cells	Yes	*TP53*, ***TET2 CNV***	PTCL-NOS	*Terakawa et al., Haematologica, 2026*
r/r DLBCL	liso-cel	no	8 months	Nodal, subcutaneous, and splenic infiltration	CD8$^+$, **CD5$^-$**, CD30$^+$ T cells	Yes	n.a.	PTCL-NOS	*Tatetsu et al., Int. J. Hemat., 2025*
r/r DLBCL (transformed follicular lymphoma)	axi-cel	no	2 years	Nodal	CD4$^+$, CD8$^+$, CD5$^+$, CD30$^-$ T cells	Yes	***TET2***, *HIP3K*	Nodal TFH cell lymphoma, NOS	*Maurer et al., Nat. commun., 2025*
r/r multiple myeloma	cilta-cel	no	6 months	Cutaneous	CD8$^+$, CD5$^+$, CD30$^-$ T cells	n.a.	n.a.	n.a.	*Maurer et al., Nat. commun., 2025*
r/r DLBCL	axi-cel	no	2 months	Nodal, **association with HLH**	CD4$^+$, CD30$^-$ T cells	Yes	***TET2***, *DNMT3A, FYN*	PTCL-NOS	*Hamilton et al., NEJM, 2024*
r/r B-NHL	axi-cel	no	3 months	Nodal	CD8$^+$, **CD5^{dim}**, CD30$^+$ T cells	Yes	*JAK3*	PTCL-NOS	*Ghilardi et al., Nat. med., 2024*
r/r multiple myeloma	Arcellx ddBCMA CAR-T cells	no	1 month	Hepatic	CD4$^+$, **CD5^{dim}**, CD30$^-$ T cells	Yes	n.a.	n.a.	*Mehr J., Chen M., eJHaem, 2024*

Figure Legend

Figure 1. Proposed pathogenetic concept of immune effector cell–associated clonal T-cell evolution. Left: A polyclonal T-cell compartment containing a pre-existing, burdened T-cell population harboring clonal hematopoiesis–associated alterations, most prominently disruption of the epigenetic regulator TET2 (highlighted in red). These altered clones may persist at low frequency without overt clinical manifestation. Middle: Following immune effector cell therapy, including CAR-T cell manufacturing and integration, antigenic and inflammatory selective pressure promotes oligoclonal T-cell expansion. At this stage, both CAR-positive and CAR-negative T-cell populations with shared TET2 disruption may coexist, reflecting therapy-driven clonal selection rather than CAR transgene–dependent transformation. Right: Under sustained selective pressure, analogous to Darwinian evolution, as exemplified by adaptive radiation in Darwin's finches, acquisition of a secondary oncogenic hit enables the outgrowth of a dominant monoclonal T-cell population. In the case reported by Terakawa et al., this step is exemplified by the acquisition of a pathogenic TP53 mutation, resulting in overt peripheral T-cell lymphoma. Notably, both oligoclonal and monoclonal T-cell expansions may present with HLH, indicating that IEC-associated hyperinflammation and overt T-cell malignancy represent different points along a shared biological spectrum shaped by immune-mediated selection.


Hyperinflammation
CAR
= secondary hit
(e.g. TP53 mutation)
TET2
disruption
CAR T
integration
Clonal
selection
Polyclonal T-cell
population
Oligoclonal T-cell
population
Monoclonal T-cell
population
Continuum
Overt
malignancy