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Myeloid neoplasms after follicular helper T-cell lymphomas: a real, but limited risk

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Over the past decade, our understanding of follicular T-cell lymphomas (TFHL) has evolved considerably, revealing a complex interplay between lymphogenesis and clonal hematopoiesis (CH). What was once viewed as a malignancy confined to T cells is now recognized as, at least in half of cases, a disease originating from mutated hematopoietic stem and progenitor cells (HSPCs)[1,2]. Since the seminal report by Quivoron et al[3], which identified *TET2* mutations in neoplastic T-cells and in immature progenitors endowed with myeloid colony-forming potential, several studies have confirmed that a large proportion of patients harbor *TET2* and/or *DNMT3A* mutations not only in neoplastic T cells, but also in neighboring B cells and myeloid compartments[4]. These findings strongly suggest that TFHL arise on the background of multilineage CH, in which mutated HSPCs acquire additional lineage-specific mutations that drive their divergent evolution toward either TFHL and sometimes toward myeloid neoplasms (MN), both bearing common ancestral mutations[1,5].

This conceptual shift naturally raises clinical questions of interest: how frequently do patients with TFHL actually develop secondary MN? Are these events primarily treatment-related, or do they reflect intrinsic properties of the preexisting mutant clone? And can clinical or genomic markers identify the patients at greatest risk?

Until recently, available data were limited to small retrospective series and case reports, preventing any reliable estimation of risk. The Memorial Sloan Kettering group had documented cases in which MN and TFHL co-occurred and shared ancestral genotypes[1], as well as instances of TFHL arising after a prior MN[6]. Yet despite these important observations, robust incidence estimates of MN occurrence in TFHL patients remained unavailable.

In this issue of *Haematologica*, Lin, Yan, and colleagues present the largest characterized cohort to date examining the development of MN after TFHL diagnosis[7]. Their analysis of 208 patients treated over an 11-year period provides essential quantitative insights and prompts a re-evaluation of survivorship care in this population.

One of the most notable findings is the 5.3% cumulative incidence of MN at five years after TFHL diagnosis. Derived from a uniformly followed, well-characterized cohort, this estimate provides a more reliable benchmark than those previously available. Interestingly, this incidence is comparable with that seen in individuals with high-intermediate risk CH in the general population, suggesting that CH alone, even when present in the context of TFHL, does not necessarily confer a dramatically elevated risk of myeloid transformation[5]. Nevertheless, the study emphasizes that although such events are infrequent, they are clinically significant.

The median time between lymphoma diagnosis and the onset of MN was 2.2 years, overlapping with the classic timeframe of treatment-related MNs, particularly those associated with topoisomerase II inhibitors such as doxorubicin, a key component of first-line treatments for TFHL[1,8]. Although the present study was not designed to analyze the relative contributions of treatment-induced mutagenesis versus natural clonal evolution, its findings are consistent with a model in which preexisting *TET2*- or *DNMT3A*-mutated clones gain a selective advantage under chemotherapy [1,6,8].

Despite the strengths of the cohort, it did not allow identification of specific clinical predictors of MN development. Given the modest number of events, the study probably lacked the statistical power to detect subtle associations. Features such as the presence of multiple *TET2* mutations or coexistence of *TET2* and *DNMT3A* mutation in a clone, the size of the CH reflected by higher variant allele fractions, the complexity of the clonal hematopoeisis, or additional mutations could be implicated in myeloid progression. Whether these characteristics have predictive value in TFH lymphomas remains to be established, as does the performance of the CH risk score developed by Weeks et al. in the general population for identifying high-risk patients when applied to the more specific TFHL patients[5] (Figure).

This report could have practical implications for clinicians managing TFH lymphomas. First, the emergence of MN in approximately 5% of patients several years after diagnosis underscores the need for long-term follow-up, and surveillance for unexplained cytopenias, new dysplastic features, or evolving hematologic abnormalities should be routine.

Second, although the risk of MN is biologically grounded and clinically relevant, it does not justify modifying frontline therapy or surveillance management of standard risk patients solely on the basis of CH-associated mutations. Further research is warranted, particularly in patients undergoing autologous stem cell transplantation, a setting that may impose additional stress on clonal hematopoiesis. For now, the immediate priority remains achieving durable lymphoma control. Population-based analyses of secondary malignancies in T-cell neoplasms likewise support maintaining current treatment standards until prospective data suggest otherwise[9].

Third, given the need for more robust data, investigators are encouraged to assess for the presence of CH at TFHL diagnosis, in addition to bone marrow evaluation, and to collect data aiming to correlate the characteristics of the CH with treatment efficacy, treatment-related toxicities, disease outcome and MN development risk. Such efforts could help build more informed recommendations for the management of these patients, which remains largely theoretical.

In summary, the work of Lin, Yan, and colleagues provides the clearest evidence to date that MNs arising in TFHL survivors represent a measurable and biologically coherent risk driven by CH-related clonal evolution. These events remain infrequent but call for long-term, personalized surveillance, ideally guided by risk factors for myeloid progression that still need to be validated in this population.

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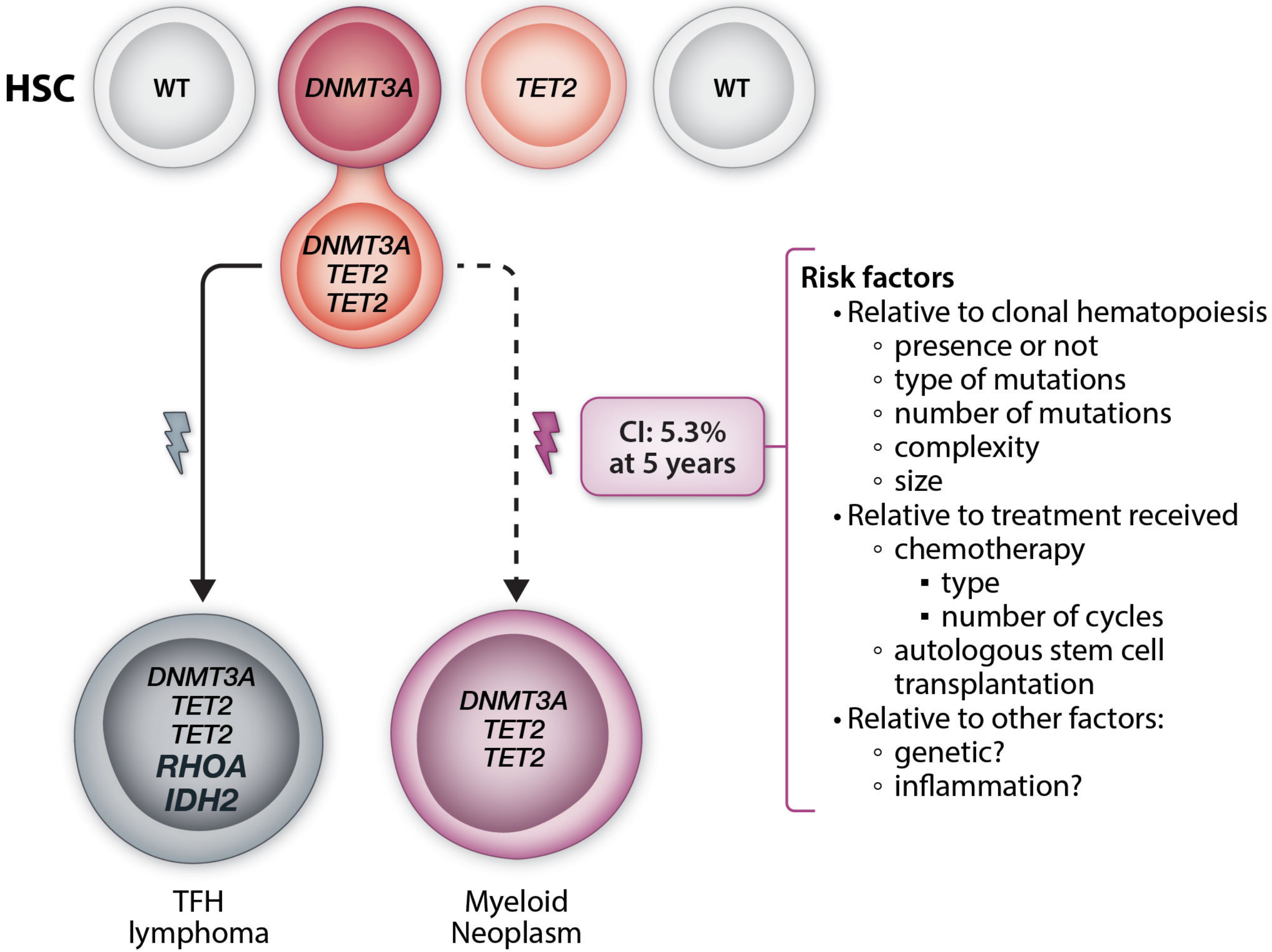
Figure legend:

Divergent evolutionary trajectories from clonal hematopoiesis toward follicular helper T-cell lymphoma (TFHL) and myeloid neoplasia. Patients with TFHL frequently harbor clonal hematopoiesis (CH), often characterized by multiple mutations with variable clonal complexity and/or the coexistence of several independent clones. The presence of CH may confer an increased risk of developing a myeloid neoplasm, estimated at approximately 5.3%. This risk is likely influenced by several clinical and biological factors that remain to be identified and validated.


HSC
WT
DNMT3A
TET2
WT
DNMT3A
TET2
TET2
CI: 5.3%
at 5 years
Risk factors
• Relative to clonal hematopoiesis
◦ presence or not
◦ type of mutations
◦ number of mutations
◦ complexity
◦ size
• Relative to treatment received
◦ chemotherapy
▪ type
▪ number of cycles
◦ autologous stem cell transplantation
• Relative to other factors:
◦ genetic?
◦ inflammation?
DNMT3A
TET2
TET2
RHOA
IDH2
DNMT3A
TET2
TET2
TFH lymphoma
Myeloid Neoplasm