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Cumulative incidence and factors associated with subsequent myeloid neoplasms in patients with nodal T-follicular helper cell lymphomas

Kai Shiang Lin,[1*] Mingfei Yan,[2*] Nivetha Ganesan,[1] Tiffany Chang,[1] Ahmet Dogan,[2] Zachary Epstein-Peterson,[1] Ozgur Can Eren,[2] Paola Ghione,[1] Varun Iyengar,[1] William Johnson,[1,3] Katie Ksanznak,[1] Alison Moskowitz,[1] Benedetta Sordi,[1] Steven Horwitz,[1,3] Wenbin Xiao,[2#] Robert Stuver[1#]

1. Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA

2. Hematopathology Service, Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, USA

3. Cellular Therapy Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA

Running Head: Myeloid Neoplasms and TFH Lymphomas

Corresponding Author:

Robert Stuver

Lymphoma Service, Department of Medicine

Memorial Sloan Kettering Cancer Center

530 E. 74th Street

New York, NY 10021

e-mail: stuverr@mskcc.org

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T-follicular helper cell lymphomas (TFHLs) are now understood to arise upon a background of clonal hematopoiesis (CH).[1] We and others have shown that divergent evolution of stem cells harboring CH mutations can result in both TFHLs and myeloid neoplasms (MN) within the same patient.[1,2] As TFHLs are typically treated with chemotherapy, there is a risk that selective treatment pressure allows CH clones to expand and evolve to MNs. The frequency at which this occurs, as well as factors that may be associated with this phenomenon, are not established. We assessed a large cohort of patients with TFHLs to understand the incidence of this phenomenon and associated risks.

Patients with nodal TFHLs who were sequentially treated at Memorial Sloan Kettering between 2012 and 2023 were identified. All cases underwent pathology review for diagnostic confirmation. TFHLs were defined using consensus World Health Organization (WHO) and International Consensus Classification (ICC) pathology criteria, with at least two TFH markers positive to assign a TFH phenotype.[3,4] Cases with concomitant TFHL and MN at diagnosis, or cases in which the MN preceded the TFHL,[5] were excluded (n=12, described elsewhere[5]). In addition, patients with less than six months of follow up (in the absence of death) were omitted (eight patients). Relevant patient- and treatment-related factors were collected. When available, next-generation sequencing results from MSK-IMPACT Heme panel (MSK-Integrated Mutation Profiling of Actionable Cancer Targets Heme) were noted.[6] The cumulative incidence of developing a MN was calculated using the competing risks method treating death as a competing risk. Univariate analyses were performed to evaluate risks associated with developing a MN. All research was conducted under an IRB-approved retrospective research protocol.

A total of 208 patients were identified. Baseline characteristics are shown in **Table 1**. The median age of all patients was 69. Except eight patients who were managed expectantly with observation, all patients received upfront anthracycline-based induction (96%). Ninety-six patients (46%) received an etoposide-containing induction regimen, such as CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone). Eighty-one patients received autologous stem cell transplant (ASCT) in first remission

(39%). The median follow up time among survivors was 2.7 years (IQR: 1.6-4.4). In terms of follow up surveillance, patients were observed as per National Comprehensive Cancer Network (NCCN) recommendations, with clinical exams and laboratory studies every three months for two years and then at least every six to 12 months, and surveillance imaging every six months for two years and then annually up to five years.

Among these 208 patients, 10 developed a MN, resulting in a cumulative incidence at two and five years of 1.5% and 5.3%, respectively (**Figure 1**). The median time to developing a MN was 2.2 years. The specific MNs were acute myeloid leukemia (AML) (n=4), myelodysplastic syndrome (MDS) (n=4), chronic myelomonocytic leukemia (n=1), and chronic neutrophilic leukemia (n=1). All patients had received prior anthracycline-based therapy, eight had received multiple treatments for TFHL, and five had received prior ASCT. No patients had received prior allogeneic transplant for lymphoma, though one patient proceeded with allogeneic transplant for AML. Except for two patients, all of these patients had undergone a baseline bone marrow (BM) biopsy at the time of TFHL diagnosis. Details of these patients are shown in **Supplementary Table 1**. Specifically, of the eight patients with a baseline BM at the time of TFHL diagnosis, none had evidence of the MN and each demonstrated mature trilineage hematopoiesis without dysplasia. Patient 6 (81/F) was noted to have occasional small hypolobated megakaryocytes and patient 10 (74/M) was noted to have a mildly hyperplastic myeloid lineage without dysplasia, both of which are consistent with expected secondary BM findings in TFHLs.[7] Peripheral hematological parameters at the time of TFHL diagnosis were largely unrevealing, with most patients have a normal white blood cell count, hemoglobin, and platelet count (**Supplementary Table 1**). Notable exceptions include patient 5 (72/M) with hemoglobin 7.3, though this patient had a concomitant diagnosis of multiple myeloma with 20% bone marrow involvement, and patient 9 (58/M) with hemoglobin of 6.4, though this patient had diffuse splenic involvement and positive direct Coombs testing, suggesting a paraneoplastic autoimmune hemolytic anemia associated with the lymphoma.

In addition, the results of mutational profiling for these patients are shown in **Table 2**, comparing the genetic profiles of each TFHL with the subsequent MN. Particular note is made for shared mutations and changes in variant allele frequency (VAF) within the MN. Aside from one patient without sequencing results, all patients had *TET2* mutations in the TFHLs, and all patients with sequencing of both the lymphoma and MN shared at least one *TET2* mutation. Aside from *TET2*, the only other shared mutation was *DNMT3A.* Notably, among these cases, none of the TFHLs harbored mutations in *TP53*, *SF3B1*, *SRSF2*, *ZRSR2*, *RUNX1*, *JAK2*, *IDH1*, or *PPMD1*, known CH mutations previously identified as conferring increased cumulative risk of MNs.[8,9] Two patients had baseline genetic studies on peripheral blood or BM samples at the time of lymphoma diagnosis. Patient 1 (73/M) underwent BM testing with an unmatched 30-gene panel which detected no mutations (at that time, the BM was only minimally involved with lymphoma at < 5%). Over eight years later, this patient developed MDS, which shared a *TET2* C1396R mutation with the preceding lymphoma. Of note, three years prior to the MDS diagnosis (and five years after the lymphoma diagnosis), unmatched MSK-IMPACT testing on a BM sample detected mutations in *U2AF1* Q157P (VAF: 6.6%) and *ASXL1* H782Lfs*2 (VAF: 36.5%) (at that time, there was no definitive evidence of MDS). Three years later, upon formal MDS diagnosis, the same *U2AF1* and *ASXL1* mutations were detected, with a notably large increase in the VAF of the *U2AF1* variant to 31.7%. The second patient, patient 5 (72/M), underwent peripheral blood testing at the time of lymphoma diagnosis with an unmatched 49-gene panel. At the time of lymphoma diagnosis, peripheral blood testing detected mutations in *TET2* p.Y1128* (VAF: 5.1%) and *DNMT3A* p.R736C (VAF: 7.2%). Only a minute abnormal T-cell population was detected in the blood at this time (0.9% of total white cells), indicating that these mutation were present in the myeloid compartment. These same mutations were concomitantly present in the lymphoma at diagnosis at high VAFs (*TET2* VAF: 45.8%, *DNMT3A* VAF 47.8%), and were eventually detected in the MN at the time of MN diagnosis over two years later, again at high VAFs (*TET2* VAF: 35.8%, *DNMT3A* VAF 39.6%). Of note, this patient's only intervening therapy was CHOP. These patients are displayed in **Supplementary Figure 1**. None of the other eight patients had baseline

sequencing performed on the blood and/or bone marrow at the time of lymphoma diagnosis, primarily due to normal bone marrow examination at baseline (and no perceived need to sequence normal tissue).

To evaluate whether certain patient- and treatment-related factors were significantly associated with developing a MN, the effects of age, sex, receipt of ASCT, and receipt of etoposide were measured (**Supplementary Table 2**). On univariate analyses, no factor was significantly associated with subsequent MN (age > 60, HR 1.2, 95% CI 0.3-5.8; male sex, HR 1.8, 95% CI 0.5-6.8; CHOP induction versus etoposide-containing, HR 0.6, 95% CI 0.2-21.1; ASCT, HR 1.5, 95% CI 0.4-5.2; etoposide use, HR 0.9, 95% CI 0.2-3.2).

Divergent clonal evolution of CH can lead to both TFHLs and MNs within the same patient. Herein we reviewed a large cohort of patients with TFHLs, showing that this is a relatively infrequent though not trivial event, with a cumulative incidence of 5.3% at five years, which is slightly less than or similar to estimates in patients with high-risk CH or clonal cytopenias of undetermined significance (and no lymphoma), though higher than estimates in patients with low-risk CH.[8,10] Given that CH is a well-established risk factor for developing MNs,[10] and that cancer therapies exert selective pressure on premalignant clones that can increase the risk of MN,[11–13] one may expect the incidence among patients with TFHLs to be higher.

Several factors may explain the incidence observed in this cohort despite the uniformity of CH in TFHLs and use of chemotherapies. First, there is a lack of mutations considered high-risk for progression to a MN in TFH lymphomas. For example, in a large cohort of healthy participants from the U.K. Biobank (N=438,890),[8] single mutations in *TET2* or *DNMT3A*, which are most frequent in TFHLs, carried a low risk of subsequent MN (HR 0.189, 95% CI 0.147-0.243) compared to mutations in splicing factors, such as *SRSF2*, *SF3B1* and *ZRSR2* (HR 13.77, 95% CI 10.31-18.42), and AML-like genes, such as *FLT3* and *RUNX1* (HR 9.26, 95% CI 5.29-16.18). These high-risk mutations are generally not observed in TFHLs.[13]

Similarly, in a cohort of over 300 patients with Hodgkin lymphoma undergoing ASCT, while patients with *TP53* and/or *PPMD1* CH mutations at the time of ASCT had a very high incidence of MN (8-year cumulative incidence of 63.2%, 95% CI 17.5 to 88.6), those with other mutations had a risk near what was observed in our cohort (8-year cumulative incidence of 5.8%, 95% CI 1.0 to 17.2).[9] While *TP53* mutations are observed in TFHLs, they are not very common and are more frequently encountered in non-TFH histologies, such as peripheral T-cell lymphoma, not otherwise specified.[14,15] Additional reasons for the incidence observed here are a high competing risk of death from lymphoma and the use of allogeneic transplant for relapsed lymphoma, which could in theory eliminate pre-existing recipient CH clones. In our cohort, thirty patients (14%) received an allogeneic transplant.

Our series is limited in its retrospective nature and the low number of events, potentially hindering our ability to detect any significant factors associated with developing a MN. In addition, as mutational profiling had not been performed on all patients, we were not able to compare the mutational profiles of patients who did and did not develop a MN. In particular, not being able to fully characterize the molecular makeup of each myeloid component at the time of lymphoma diagnosis hinders the ability to assess whether certain risk profiles (such as those calculatable through the clonal hematopoiesis risk calculator[8]) hold true in this population. Still, as all patients in this cohort had TFHLs, which are generally genomically similar,[14] we would expect that established genetic risk factors, such as the presence of high-risk mutations, high VAFs within such mutations, and multiple high-risk mutations, to be applicable to patients with lymphoma.[8] As the patients in our series generally did not have these features, it remains somewhat elusive why MNs developed. Moreover, recent work has shown that patients can develop MNs *before* lymphoma or have a concomitant presentation in the absence of treatment pressures.[6] Collectively, our data and these findings appear to suggest that yet unrealized intrinsic genetic susceptibilities in addition to therapy-related selective pressure, may be driving clonal evolution. Prospective studies that involve sequential sequencing to evaluate changes in VAFs and capture additive mutational events may further elucidate this phenomenon.

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Table 1. Characteristics of Cohort.

Variable	Total Cohort, No. (N = 208)	No Myeloid Neoplasm, No. (N = 198)	Myeloid Neoplasm, No. (N = 10)
Diagnosis			
TFH, NOS	25	24	1
TFH, AITL	182	173	9
TFH, follicular	1	1	0
Age at lymphoma diagnosis, median (IQR)	69 (61-74)	68 (61-74)	72 (63-74)
Sex			
Male	112	105	7
Female	96	93	3
Stage			
I/II	17	17	0
III/IV	191	181	10
Induction			
CHOP	63	58	4
Etoposide-based	96	91	5
BV-CHP	30	30	0
Other	11	11	1
Observation	8	8	0
ASCT			
Yes	81	76	5
No	127	122	5
Number of lines of therapy, median (range)	2 (0-11)	2 (0-11)	3 (1-5)
Etoposide use (any time)	146	139	7
Other agents used			
azacitidine	18	16	2
EZH inhibitor	14	12	2
HDAC inhibitor	80	74	6
JAK inhibitor	21	19	2
lenalidomide	22	20	2
PI3K inhibitor	58	54	4

Note: Other includes investigational regimens, including lenalidomide-CHOEP, azacitidine-CHOP, duvelisib-CHOP, and BV-C(H)EP. The 1 patient in the Myeloid Neoplasm group with Other as Induction received lenalidomide-CHOEP.

ASCT, autologous stem cell transplant; BV-CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; IQR, interquartile range; No., NOS, not otherwise specified; TFH, T-follicular helper cell.

Table 2. Genomic Profiles of Patients with TFH Lymphoma and Myeloid Neoplasm.

Pt	TFH Genetics				Myeloid Neoplasm Genetics				
	Tissue Source	**Gene**	**Mutation**	**VAF**	**Dx**	**Tissue Source**	**Gene**	**Mutation**	**VAF**
73/M	lymph node	***TET2*** *RHOA*	**C1396R** G17V	**0.171** 0.050	WHO: MDS-LB ICC: MDS, NOS	bone marrow: MDS, +flow abnormal T-cell population (1.0% of WBC)	***TET2*** *U2AF1* *RUNX1* *ASXL1* *PTPN11*	**C1396R** Q157P T92Afs*31 H782Lfs*2 D61G	**0.160** 0.317 0.223 0.311 0.021
72/M	lymph node	***TET2*** ***TET2*** *EPHA5*	**C484*** **L757Sfs*56** D136N	**0.250** **0.230** 0.097	WHO: MDS-IB1 -> AML, MR; ICC: MDS-EB -> AML, NOS progression from MDS	bone marrow: AML, no TFH lymphoma	***TET2*** ***TET2*** *WT1*	**C484*** **L757Sfs*56** S189*	**0.449** **0.455** 0.408
63/F	bone marrow, **flow sorted abnormal T-cells from bone marrow**	***DNMT3A*** ***TET2*** ***TET2*** *NFE2* *ROBO1* *ARID1B* *DDX3X*	**R771*** **L1899Sfs*9** **C1289Y** T318A G904R S914N V526A	**0.510** **0.446** **0.506** 0.341 0.516 0.349 0.234	WHO: AML, MR ICC: AML with MR gene mutation	bone marrow: AML and TFH lymphoma; genetics are **flow sorted CD34+ myeloid blasts**	***DNMT3A*** ***TET2*** ***TET2*** *RUNX1* *DNMT3A*	**R771*** **L1899Sfs*9** **C1289Y** A329Sfs*271 C861Y	**0.400** **0.320** **0.481** 0.621 0.406
74/M	lymph node	***TET2*** *TET2* ***TET2*** *SETBP1* *VAV1* *CUX1*	**S577Pfs*3** C1289F **F1300V** L1421P Y174C E555L	**0.373** 0.243 **0.072** 0.300 0.334 0.296	WHO/ICC: CMML-1	bone marrow: CMML, +flow abnormal T-cell population (0.036% of WBC)	*SRSF2* ***TET2*** ***TET2*** *FBXO11* *CHEK2*	P95H **S577Pfs*3** **F1300V** Y692H D134G	0.479 **0.426** **0.468** 0.437 0.443
72/M	bone marrow, **flow sorted abnormal T-cells from bone marrow**	*IDH2* *RHOA* ***TET2*** ***DNMT3A*** ***TET2*** *KMT2B* *ATR*	R172K G17V **Q810*** **R736C** **Y1128*** Q757* Q757*	0.406 0.459 **0.463** **0.478** **0.458** 0.248 0.206	WHO: MDS-IB2 ICC: MDS/AML	bone marrow: MDS, no TFH lymphoma	*RUNX1* ***TET2*** ***DNMT3A*** ***TET2*** *BTG1* *BRCA2* *SETD5* *SPEN* *RET* *CEBPA* *MET* *MET* *NBN*	D198N **Q810*** **R736C** **Y1128*** K29* A2306S Y987F P3008Q Q70K H260N P210Q R592K H328N	0.042 **0.440** **0.396** **0.358** 0.024 0.013 0.027 0.022 0.017 0.024 0.542 0.599 0.015

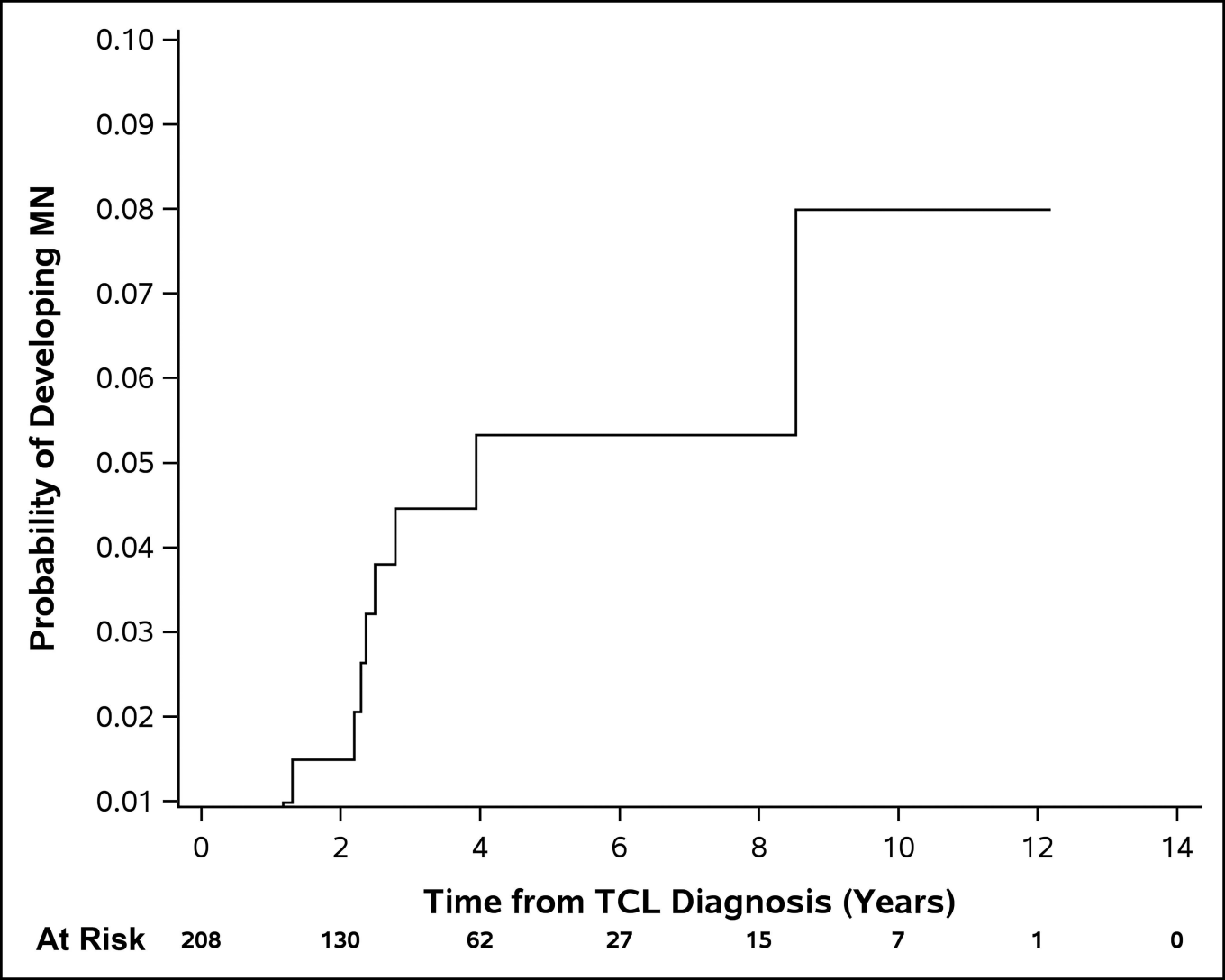
							VAV2	G106*	0.015
81/F	lymph node	*RHOA* ***TET2*** ***TET2*** ***TET2***^	G17V **N752Kfs*60** **K1500Qfs*72** **N598Ifs*3**	0.195 0.180 0.194 0.007	WHO: AML, MR ICC: AML, NOS	bone marrow: AML, +flow abnormal T-cell population (0.1% of WBC), genetics are **flow sorted CD34+ myeloid blasts**	*ATR* *TET2* ***TET2***^ ***TET2***^	Q631* N598Ifs*3 **N752Kfs*60** **K1500Qfs*72**	0.697 **0.717** **0.008** **0.008**
55/M	lymph node	*TET2*	E1082*	0.408	WHO: MDS, LB ICC: MDS, NOS	Not performed.			
71/F	lymph node	*IDH2* *RHOA* ***TET2*** ***DNMT3A*** *TET2* *HLA-A* *CCND3* *MYCN* *HDAC4* *HGF*	R172K G17V **W1198*** **Y724*** A379Vfs*6 X25_splice R271Pfs*53 S369G G362A S145G	0.146 0.147 0.452 **0.364** 0.115 0.076 0.134 0.363 0.154 0.090	WHO/ICC: CNL	bone marrow: CNL, +flow abnormal T-cell population (0.0043% of WBC), also 5% plasma cell neoplasm by CD138	***DNMT3A*** *JAK2* ***TET2***	**Y724*** V617F **W1198***	**0.493** 0.412 **0.792**
58/M	Not performed.				WHO: AML, MR ICC: AML with MR gene mutation	Not performed.			
74/M	lymph node	*IDH2* *RHOA* ***TET2*** ***TET2*** ***DNMT3A*** *NCOR2* *SETD1B*	R172S G17V **Q778*** **D1384N** **V296M** A989T E612*	0.063 0.070 **0.420** **0.277** **0.410** 0.067 0.054	WHO: MDS-LB ICC: MDS, NOS	bone marrow: MDS, +flow abnormal T-cell population (0.014% of WBC)	***TET2*** ***TET2*** ***DNMT3A***	**Q778*** **D1384N** **V296M**	**0.515** **0.490** **0.520**

NOTE: Shared mutations between the TFH lymphoma and myeloid neoplasm are bolded. Differences in VAF less than 10% are marked in red, changes within 10% are marked in yellow, and changes greater than 10% are marked in green.

^ These mutations are below the technical sensitivity of the performed assay though were detected upon manual review.

Dx, Diagnosis; AML, acute myeloid leukemia; CNL, chronic neutrophilic leukemia; EB, excess blasts; F, female; ICC, International Consensus Criteria; LB, low blasts; M, male; MDS, myelodysplastic syndrome; MR, MDS-related; NOS, not otherwise specified; Pt, patient; TFH, T-follicular helper call; VAF, variant allele frequency; WHO, World Health Organization.

Figure 1. Cumulative incidence of myeloid neoplasm. Cumulative incidence plot of developing a myeloid neoplasm over time from T-cell lymphoma (TCL) diagnosis. Cumulative incidence calculated using the competing risks method, treating death as a competing risk.


Probability of Developing MN
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
2
4
6
8
10
12
14
Time from TCL Diagnosis (Years)
At Risk
208
130
62
27
15
7
1
0

Supplementary Table 1. Individual Patient Characteristics.

Pt	Other PMH	TFHL subtype	Baseline BM & CBC findings at TFHL diagnosis	Treatment prior to MN	Myeloid Neoplasm (MN)	Time from TFHL to MN, y	Subsequent Course (after MN diagnosis)
73/M	localized prostate cancer (monitored)	AITL	BM: <5% AITL; hypocellular 10-20%; mature trilineage hematopoiesis CBC: WBC 10.2, HGB 10.7, MCV 80, RDW 13.4, PLT 379	CHOEP, BEAM ASCT, romidepsin, duvelisib/bortezomib, EZH2 inhibitor	WHO: MDS-LB ICC: MDS, NOS	8.5	active TFHL and MDS, pursued supportive care, died of disease
72/M	—	AITL	BM: no lymphoma; normocellular 30%; mature trilineage hematopoiesis CBC: WBC 4.0, HGB 12.6, MCV 84, RDW 14.6, PLT 139	CHOEP, romidepsin/ carfilzomib/lenalidomide	WHO: MDS-IB1 -> AML, MR; ICC: MDS-EB -> AML, NOS progression from MDS	3.1	no evidence of TFHL, trial of azacitidine for MDS -> AML, died of disease
63/F	—	AITL	BM: no baseline bone marrow CBC: WBC 5.9, HGB 12.3, MCV 92, RDW 13.1, PLT 205	CHOEP, BEAM ASCT, belinostat, azacytidine	WHO: AML, MR ICC: AML with MR gene mutation	2.6	active TFHL and AML, trial of azacitidine for both, died of disease
74/M	EBV+ B-cell LPD	AITL	BM: no lymphoma; limited specimen, mature trilineage hematopoiesis CBC: WBC 6.6, HGB 13.9, MCV 86, RDW 13.3, PLT 125	lenalidomide-CHOEP, BEAM ASCT, cerdulatinib	WHO/ICC: CMML-1	2.8	CMML observed/not treated, active TFHL and progressive EBV+ B-cell LPD treated with rituximab, died of disease
72/M	IgG λ MM	AITL	BM: <5% AITL; 20% MM; hypercellular 50%, mature trilineage hematopoiesis w/o dysplasia CBC: WBC 6.8, HGB 7.3, MCV 97, RDW 22.2, PLT 224	CHOP	WHO: MDS-IB2 ICC: MDS/AML	2.2	no evidence of TFHL, MDS observed/not treated, progressive DLBCL treated with rituximab, died of disease and infection
81/F	—	TFHL, NOS	BM: +flow TFHL, NOS; mildly hypercellular, mature trilineage hematopoiesis w/ occasional small hypolobated megakaryocytes	mini-CHOP, romidepsin/duvelisib, investigational SIRPα-IgG1 Fc (anti-CD47)	WHO: AML, MR ICC: AML, NOS	1.8	AML treated with azacitidine/venetoclax with CR, then progressive TFHL, died of disease

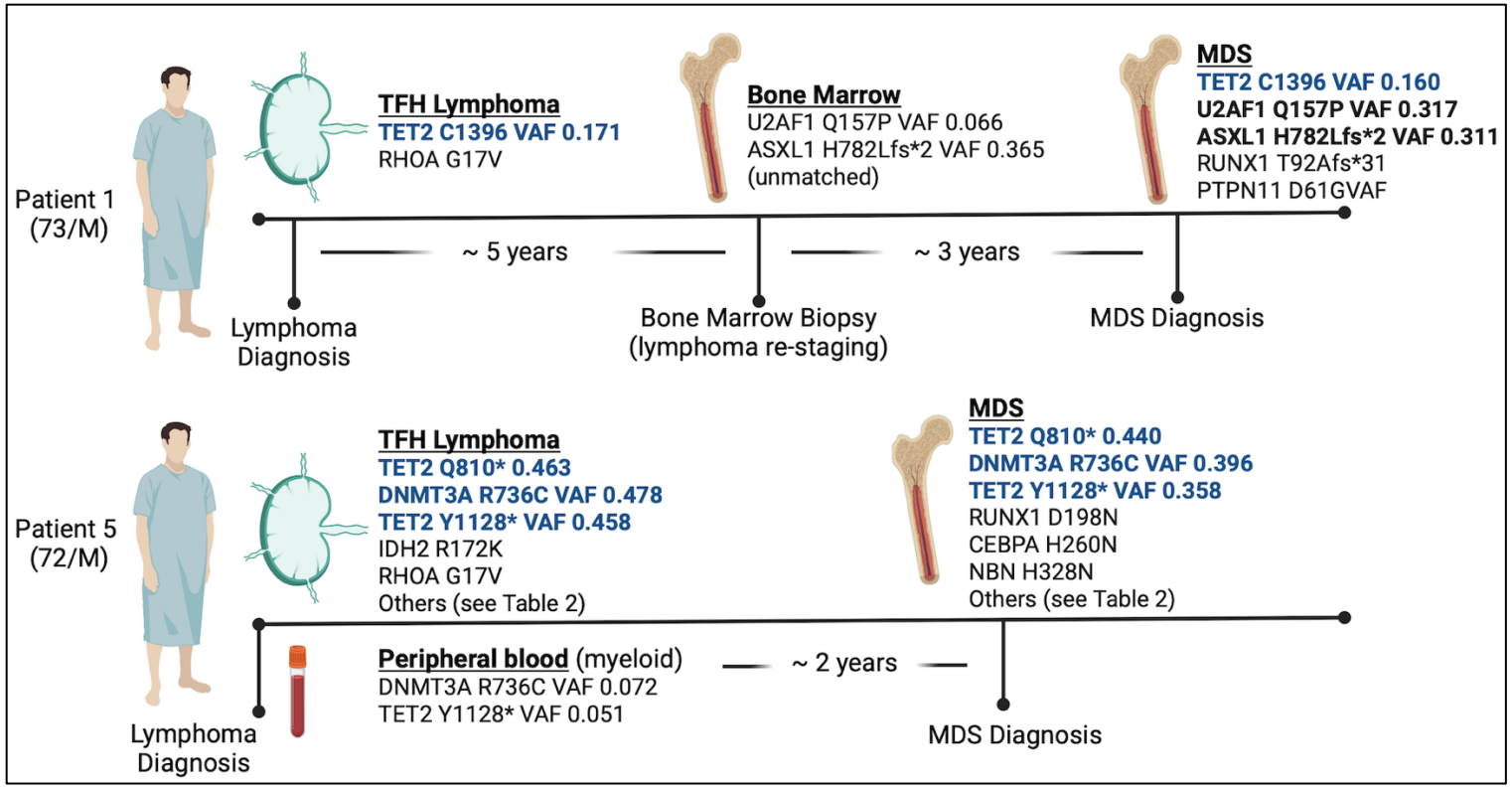
			CBC: WBC 9.6, HGB 10.1, MCV 96, RDW 14.7, PLT 360				
55/M	psoriasis, prior adalimumab	AITL	BM: limited specimen with crush artifact, involved w/ AITL; no overt dysplasia CBC: missing baseline values (started treatment outside of institution)	CHOEP/CHOP (CHOEP x 1, then CHOP), BEAM ASCT, romidepsin	WHO: MDS-LB ICC: MDS, NOS	1.2	active TFHL and MDS, pursued supportive care, died of disease and infection
71/F	breast ca s/p TAC 12 y pre-T-cell dx	AITL	BM: no baseline bone marrow CBC: WBC 7.3, HGB 12.5, MCV 89, RDW 13.9, PLT 331	BV-CEP, romidepsin/duvelisib, EZH2 inhibitor	WHO/ICC: CNL	2.2	CNL observed, active TFHL, pursued supportive care, died of disease
58/M	—	AITL	BM: <5% AITL; hypercellular 60%, mature trilineage hematopoiesis, unremarkable myeloid and megakaryocytic elements CBC: WBC 8.6, HGB 6.4, MCV 89, RDW 15.1, PLT 216	CHOEP, BEAM ASCT	WHO: AML, MR ICC: AML with MR gene mutation	1.3	no evidence of TFHL, AML treated with FLAG-IDA, died post-allogeneic transplant for AML
74/M	head/neck SCC s/p RT 7 m pre T-cell dx	AITL	BM: 10-15% AITL; hypercellular 90% w/ mature trilineage hematopoiesis; mildly hyperplastic myeloid lineage without frank dysplasia or morphologic evidence of MN CBC: missing baseline values (started treatment outside of institution)	CHOP, ruxolitinib/duvelisib, azacitidine	WHO: MDS-LB ICC: MDS, NOS	1.0	active TFHL and MDS, continued treatment with azacitidine, died of disease

AITL, angioimmunoblastic type; AML, acute myeloid leukemia; ASCT, autologous stem cell transplant; BV, brentuximab vedotin; BEAM, carmustine, etoposide, cytarabine, melphalan; CBC, complete blood count; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CMML, chronic myelomonocytic leukemia; CNL, chronic neutrophilic leukemia; DLBCL, diffuse large B-cell lymphoma; dx, diagnosis; EB, excess blasts; EBV, Epstein-Barr virus; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; IB, increased blasts; HGB, hemoglobin, g/dL; LB, low blasts; LPD, lymphoproliferative disorder; MDS, myelodysplastic syndrome; M, male; MCV, mean corpuscular volume, fL; MM, multiple myeloma; MR, MDS related; NOS, not otherwise specified; PLT, platelets, K/mcL; PMH, past medical history; RDW, red blood cell distribution width, %; RT, radiotherapy; SCC, squamous cell carcinoma; TAC, docetaxel, doxorubicin, cyclophosphamide; TFH, T-follicular helper cell; w/, with; w/o, without; WBC, white blood cell count, K/mcL; y, years.

Supplementary Table 2. Univariate Analysis for Patient- and Treatment-Related Factors.

Variable	UVA HR (95% CI)	P Value
Age at diagnosis > 60	1.2 (0.3-5.8)	0.8
Sex		
Male	1.8 (0.5-6.8)	0.4
Female	Ref.	
Induction		
CHOP	Ref.	0.5
Etoposide-based	0.6 (0.2-2.1)	
BV-CHP	—	
Other	—	
Observation	—	
ASCT		
Yes	1.5 (0.4-5.2)	0.5
No	Ref.	
Etoposide use (any time)	0.9. (0.2-3.3)	0.8

ASCT, autologous stem cell transplant; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; UVA HR, univariate analysis hazard ratio.



Supplementary Figure 1. Schematic representation of two representative patients. Patient 1 was a 73-year-old male with TFH lymphoma who subsequently developed myelodysplastic syndrome (MDS) eight years after lymphoma diagnosis. At baseline, this patient had *TET2* and *RHOA* mutations detected in lymphoma. Five years after diagnosis, restaging bone marrow for lymphoma treatment purposes showed new *U2AF1* and *ASXL1* mutations (note that this was an unmatched sample). This marrow was without morphological evidence of MDS. Three years later, the patient was diagnosed with MDS, which showed the same *TET2* mutation detected eight years prior in the lymphoma, as well as the *U2AF1* and *ASXL1* mutations detected in the bone marrow three years prior. Patient 2 was a 72-year-old male with TFH lymphoma who subsequently developed MDS two years later. At baseline, this patient had two TET2 mutations and a DNMT3A mutation (among others) in lymphoma. In the peripheral blood, there was a shared TET2 and DNMT3A mutation, though at elevated VAF consistent with presence in the myeloid component, as there was only a minute abnormal T-cell population detected by flow cytometry. Two years later, the patient was diagnosed with MDS, which showed the same TET2 and DNMT3A mutations which had been previously detected, in addition to several other mutations.