

TITLE PAGE

Manuscript category: Review

Title (English)

Concomitant Hematologic Malignancies in Patients with Mycosis Fungoides

Authors (English)

Athanasiou Nikolaos ¹, Papadavid Evangelia², Nikolaidou Elektra³, Jahaj Edison⁴, Motsios Dimitrios⁵, Stratigos Alexandros⁶, Nikolaou Vasiliki⁷

Affiliations (English)

¹Postgraduate Programme in Cutaneous Oncology, Medical School, National and Kapodistrian University of Athens, 1st Department of Dermatology and Venereology, Andreas Sygros Hospital, Athens, Greece

²Professor of Dermatology and Venereology, National and Kapodistrian University of Athens, Director, 2nd Department of Dermatology and Venereology Attikon University General Hospital

³Professor of Dermatology and Venereology, National and Kapodistrian University of Athens 1st Department of Dermatology and Venereology, Andreas Sygros Hospital, Athens, Greece

⁴Assistant Professor Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

⁵1st Department of Dermatology-Venereology, Faculty of Medicine, Andreas Sygros Hospital, National and Kapodistrian University of Athens, Athens, Greece

⁶Professor of Dermatology and Venereology, National and Kapodistrian University of Athens, Director, 1st Department of Dermatology and Venereology, Andreas Sygros Hospital, Athens, Greece

⁷Assistant Professor of Dermatology and Venereology, National and Kapodistrian University of Athens, 1st Department of Dermatology and Venereology, Andreas Sygros Hospital, Athens, Greece

Key words (English)

mycosis fungoides; cutaneous T-cell lymphoma; second primary neoplasms; Hodgkin lymphoma; chronic lymphocytic leukemia; clonal hematopoiesis

Title (Greek) / Τίτλος

Συνυπάρχουσες αιματολογικές κακοήθειες σε ασθενείς με σπογγοειδή μυκητίαση.

Authors (Greek) / Συγγραφείς

Αθανασίου Νικόλαος¹, Παπαδαυΐδ Ευαγγελία², Nikolaidou Elektra³, Jahaj Edison⁴, Motsios Dimitrios⁵, Stratigos Alexandros⁶, Nikolaou Vasiliki⁷

Affiliations (Greek) / Ιδρύματα

¹ Πρόγραμμα Μεταπτυχιακών Σπουδών «Κακοήθη Νεοπλάσματα Δέρματος», Α΄ Πανεπιστημιακή Κλινική Αφροδισίων και Δερματικών Νόσων, Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Νοσοκομείο Α. Συγγρός, Αθήνα, Ελλάδα

² Καθηγήτρια Δερματολογίας-Αφροδισιολογίας ΕΚΠΑ, Διευθύντρια της Β΄ Κλινικής Δερματικών και Αφροδισίων Νόσων Πανεπιστημιακό Γενικό Νοσοκομείο «Αττικών», Αθήνα, Ελλάδα

³ Καθηγήτρια Δερματολογίας-Αφροδισιολογίας ΕΚΠΑ Α΄ Πανεπιστημιακής Κλινικής Αφροδισίων & Δερματικών Νόσων, Νοσοκομείο Α. Συγγρός, Αθήνα Ελλάδα

⁴ Επίκουρος Καθηγητής Υγιεινής, Επιδημιολογίας και Ιατρικής Στατιστικής Ιατρικής Σχολής Αθηνών ΕΚΠΑ, Αθήνα, Ελλάδα

⁵ Α΄ Πανεπιστημιακή Κλινική Αφροδισίων και Δερματικών Νόσων, Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Νοσοκομείο Α. Συγγρός, Αθήνα, Ελλάδα

⁶ Καθηγητής Δερματολογίας-Αφροδισιολογίας ΕΚΠΑ Διευθυντής Α΄ Πανεπιστημιακής Κλινικής Αφροδισίων & Δερματικών Νόσων, Νοσοκομείο Α. Συγγρός, Αθήνα Ελλάδα

⁷ Επίκουρη Καθηγήτρια Δερματολογίας-Αφροδισιολογίας ΕΚΠΑ Α΄ Πανεπιστημιακής Κλινικής Αφροδισίων & Δερματικών Νόσων, Νοσοκομείο Α. Συγγρός, Αθήνα Ελλάδα

Key words (Greek) / Λέξεις-κλειδιά

σπογγοειδής μυκητίαση· δερματικό T-κυτταρικό λέμφωμα· δευτεροπαθή νεοπλάσματα·
λέμφωμα Hodgkin· χρόνια λεμφοκυτταρική λευχαιμία· κλωνική αιμοποίηση

Corresponding author / Υπεύθυνος αλληλογραφίας

Nikolaos Athanasiou, MD, MSc – Antinoros 16, 11634, Athens - 2107001516 –
sokinat@gmail.com

Νικόλαος Αθανασίου – Αντήνορος 16, 11634, Αθήνα - 2107001516 – sokinat@gmail.com

Conflict of interest / Σύγκρουση συμφερόντων

The authors declare that they have no conflicts of interest.

Οι συγγραφείς δηλώνουν ότι δεν υπάρχει σύγκρουση συμφερόντων.

Funding / Χρηματοδότηση

No funding. / Καμία χρηματοδότηση.

Word counts

Abstract (English): 188 words; abstract (Greek): 184 words. Main text: 5306 words. References:
34. Tables: 3. Figures: 0.

ABSTRACT

Mycosis fungoides (MF), the most common cutaneous T-cell lymphoma, is associated with an increased occurrence of additional hematologic neoplasms, although the strength of evidence varies markedly between entities and the underlying biology remains unresolved. We critically synthesized the literature and integrated descriptive observations from 39 patients with MF, or Sézary syndrome and an associated hematologic neoplasm or clonal disorder followed at a Greek center of expertise for cutaneous lymphomas.

Population-based and pooled data most consistently support excess Hodgkin lymphoma and non-Hodgkin lymphoma, whereas associations with CLL/SLL, plasma cell disorders and myeloid neoplasms rely mainly on institutional series and case reports. Two pathogenetic models are considered: immune permissiveness, favoring independent primary neoplasms in a host with impaired tumor surveillance, and a shared clonal progenitor. Distinct T- and B-cell clonotypes do not by themselves exclude an earlier common ancestor, but comprehensive paired tumor-normal genomic studies have not been performed systematically. In our cohort, B-lineage disorders predominated; antecedent diagnoses were most frequent, while synchronous and subsequent disorders were also well represented. Management should emphasize diagnostic precision, preservation of immune competence, and lifelong but proportionate clinical vigilance.

Key words

mycosis fungoides; cutaneous T-cell lymphoma; second primary neoplasms; Hodgkin lymphoma; chronic lymphocytic leukemia; clonal hematopoiesis

ΠΕΡΙΛΗΨΗ

Η σπογγιοειδής μυκητίαση (MF), το συχνότερο δερματικό T-κυτταρικό λέμφωμα, συνδέεται με αυξημένη εμφάνιση δευτεροπαθών αιματολογικών νεοπλασμάτων, αν και η ισχύς της τεκμηρίωσης διαφέρει σημαντικά μεταξύ των επιμέρους οντοτήτων και η υποκείμενη βιολογία παραμένει ασαφής. Πραγματοποιήσαμε ανασκόπηση της βιβλιογραφίας και ενσωματώσαμε περιγραφικές παρατηρήσεις από 39 ασθενείς με MF, ή σύνδρομο Sézary και συνοδό αιματολογικό νεόπλασμα ή κλωνική διαταραχή σε Ελληνικό κέντρο εμπειρογνωμοσύνης για τα δερματικά λεμφώματα.

Πληθυσμιακά και συγκεντρωτικά δεδομένα υποστηρίζουν περισσότερο την αυξημένη συχνότητα λεμφώματος Hodgkin και μη-Hodgkin λεμφώματος, ενώ οι συσχετίσεις με CLL/SLL, διαταραχές πλασματοκυττάρων και νεοπλάσματα του μυελού στηρίζονται κυρίως σε σειρές ασθενών και μεμονωμένες αναφορές. Εξετάζονται δύο παθογενετικά μοντέλα: η ανοσολογική επιτρεπτικότητα και ο κοινός κλωνικός πρόγονος. Διακριτοί T- και B-κυτταρικοί κλώνοτυποι δεν αποκλείουν από μόνοι τους έναν προγενέστερο κοινό πρόγονο, αλλά συστηματικές συζευγμένες γονιδιωματικές αναλύσεις του όγκου και του φυσιολογικού ιστού δεν έχουν πραγματοποιηθεί. Στη σειρά μας επικράτησαν οι B-κυτταρικές διαταραχές· οι προϋπάρχουσες διαγνώσεις ήταν συχνότερες, ενώ σύγχρονες και μεταγενέστερες διαταραχές ήταν επίσης παρούσες. Η αντιμετώπιση πρέπει να δίνει έμφαση στη διαγνωστική ακρίβεια, τη διατήρηση της ανοσολογικής επάρκειας και τη δια βίου ανάλογη κλινική επαγρύπνηση.

Λέξεις-κλειδιά

σπογγοειδής μυκητίαση· δερματικό T-κυτταρικό λέμφωμα· δευτεροπαθή νεοπλάσματα· λέμφωμα Hodgkin· χρόνια λεμφοκυτταρική λευχαιμία· κλωνική αιμοποίηση

1. INTRODUCTION

Mycosis fungoides (MF) is the most frequent primary cutaneous lymphoma and the prototype of cutaneous T-cell lymphoma (CTCL).¹ Most patients present with patches and plaques and follow an indolent course over many years; a minority develop tumors, erythroderma, nodal or blood involvement, large cell transformation (LCT) or visceral dissemination. Sézary syndrome (SS) is a distinct leukemic CTCL defined by erythroderma, lymphadenopathy and circulating malignant T cells. Current classification and management emphasize clinicopathologic correlation, TNMB staging and recognition of variants such as folliculotropic MF, pagetoid reticulosis and granulomatous slack skin.¹⁻³

Because many patients survive for years or decades, long-term complications have become clinically important, and additional primary neoplasms have attracted particular attention. Population-based studies, institutional cohorts and meta-analyses agree that patients with MF and other CTCLs develop additional cancers more often than expected, with the clearest hematologic signal involving lymphoid neoplasms.⁴⁻⁷ Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-

cell lymphoma (DLBCL) and, less often, plasma cell or myeloid neoplasms have been described before, at approximately the same time as, or after MF.

The association creates three clinical problems and poses one biological question. Clinically, a second neoplasm can be mistaken for MF progression and MF can be mistaken for cutaneous spread of a systemic lymphoma; treatment directed at one disease may destabilize the other; and standard MF follow-up does not address hematologic risk. Biologically, the question is whether the two neoplasms share a clonal origin or arise independently in a host whose tumor surveillance is impaired.

The literature is heterogeneous, and pooled standardized incidence ratios (SIRs) from population registries are often discussed alongside single case reports as though they carried equal weight. This article therefore uses a pragmatic evidence hierarchy to distinguish population-level signals from institutional observations and case-level hypotheses, compares the two principal pathogenic models against available clonality and genomic data, reports a descriptive single-center series of 39 patients from Greece, and derives clinical and research implications. Throughout, “antecedent”, “synchronous” and “subsequent” denote an associated hematologic disorder diagnosed more than 3 months before, within ± 3 months of, or more than 3 months after MF/SS, respectively; “composite lymphoma” denotes two distinct lymphomas in the same tissue specimen, whereas “discordant lymphoma” refers to distinct lymphomas at separate anatomic sites. “Associated hematologic disorder” is used for the full spectrum, while “hematologic malignancy” is reserved for overt malignant entities.

2. METHODS

Literature. The synthesis was narrative and selective rather than systematic. Evidence for individual associations was described as strong when supported by meta-analysis or reproducible population-based data, moderate when supported by consistent institutional series without population comparators, limited when based mainly on case reports or small series, and hypothetical when a biologically plausible mechanism had not been tested adequately in paired tissues. This pragmatic hierarchy is used for narrative interpretation.

Institutional series. The records of the 1st Department of Dermatology and Venereology, “Andreas Syggros” Hospital, National and Kapodistrian University of Athens, were reviewed retrospectively for patients with MF, folliculotropic MF or SS and a documented hematologic neoplasm, clonal

lymphoproliferative disorder or plasma cell disorder. Cases were assembled in two stages — a narrative chart review (n = 12) and structured capture using the EORTC retrospective registry template for CTCL with secondary hematologic neoplasia (n = 27) — with no overlap between the two groups. Timing was classified as defined above, using calendar year of diagnosis. Data were anonymized and analyzed descriptively. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of “Andreas Syggros” Hospital in November 2025.

3. EPIDEMIOLOGY AND MAGNITUDE OF RISK

Reported frequencies vary widely because studies differ in population, follow-up, diagnostic criteria, treatment era and whether solid tumors are counted together with hematologic neoplasms. Two measures are routinely conflated and should be kept apart: the proportion of patients in a cohort who develop any additional neoplasm, and the SIR, which compares observed with expected cancers in a reference population. Across systematic-review data, 5.9-16.8% of patients with CTCL developed a secondary malignancy;⁴ in a 2025 comparative single-center study, secondary neoplasms occurred in 13.9% of 252 patients with MF versus 3.6% of dermatologic controls, although most were solid tumors and only five were hematologic.⁸ These proportions describe cohort frequency; they are not directly interchangeable with population-based relative-risk estimates.

The strongest quantitative evidence comes from a meta-analysis of 10 studies (12 cohorts): the pooled SIR was 2.18 for all malignancies, 15.25 (95% confidence interval [CI] 7.70-22.79) for HL and 4.96 (95% CI 3.58-6.33) for NHL.⁴ Registry analyses agree in direction. In Huang et al., the HL SIR was 17.14 (95% CI 6.25-37.26) in SEER-9 and 27.27 (95% CI 5.35-77.54) in the Stanford cohort.⁵ A SEER-18 analysis of 6,742 patients with MF reported an overall SIR for second cancers of 10.15 (95% CI 9.29-11.07),⁶ approximately five times the pooled meta-analytic estimate, a discrepancy that reflects methodology rather than biology. A sex-stratified SEER analysis reported higher relative risks of HL, NHL and CLL among women than among men.⁹ Large relative risks must be read against low absolute incidence: a SIR of 15 for HL does not mean that patients with MF commonly develop HL.

The Dutch nationwide cohort is the most informative single dataset, because every diagnosis was histopathologically verified and neoplasms occurring before MF were also counted. Among 1,024

patients followed for a mean of 10 years, only cutaneous (odds ratio [OR] 2.54) and hematologic neoplasms (OR 2.62, 95% CI 2.00–3.42) exceeded population expectations; solid-organ tumors did not, and lung cancer was less frequent than expected (OR 0.54).⁷ Within the hematologic category, however, the excess was driven by lymphomatoid papulosis (LyP; OR 76.22) and HL (OR 6.28), whereas NHL (OR 1.60), CLL (OR 1.86) and plasma cell neoplasms (OR 2.41) did not reach statistical significance.⁷ Institutional series confirm an excess without quantifying hematologic-specific risk: among 672 patients with CTCL the risk of a subsequent cancer was increased 1.79-fold, with excesses of HL, NHL and acute myeloid leukemia (AML).¹⁰

Age is a consistent modifier. In the 2025 comparative study, patients with a secondary neoplasm had a higher mean age overall (62.71 vs 53.69 years; $p = 0.003$) and were older at MF diagnosis (56.23 vs 44.52 years; $p = 0.016$) than those without a secondary neoplasm.⁸ This is biologically plausible because immunosenescence, clonal hematopoiesis and the background incidence of lymphoid neoplasms all rise with age. Male predominance is common in MF cohorts, but sex has not emerged as a consistent independent predictor of additional neoplasia;^{4,8} the Dutch cohort found no difference in the frequency or type of associated neoplasm between men and women,⁷ whereas a sex-stratified SEER analysis reported higher relative risks of several secondary cancers, including CLL, HL and NHL, among women.⁹

Variant morphology influences clinical suspicion more than measured risk. Folliculotropic MF follows a more difficult course than early classical disease, but the available data do not demonstrate an independently increased risk of a second hematologic neoplasm once stage and age are taken into account; in the Dutch cohort, classical and folliculotropic MF did not differ in the frequency or type of associated malignancy.⁷ Granulomatous slack skin is the recognized exception, with a documented association with HL, and warrants careful long-term assessment despite its rarity.² SS should be analyzed separately from MF wherever numbers permit, since its blood involvement, immune dysfunction and treatment burden differ substantially.

Geographic comparisons require caution. Cohorts from the United States, the Netherlands, Turkey, Poland and Greece differ in referral patterns, ethnic composition, access to specialist dermatopathology, treatment era and completeness of cancer registration. Registry-based datasets estimate relative risk more reliably, whereas specialist-center series provide richer clinicopathologic detail at the cost of referral bias. These complementary designs explain why one

study may report a high proportion of secondary cancers with modest relative risks while another reports a low absolute frequency but a high standardized ratio for a single subtype. They argue for comparing like with like rather than pooling incompatible measures.

Three problems recur across the literature and account for much of the apparent disagreement. First, case definitions differ. Some cohorts count lymphomatoid papulosis (LyP) and other CD30-positive lymphoproliferative disorders among hematologic second neoplasms - in one 730-patient MF series, LyP accounted for 22 of 36 hematologic second neoplasms¹¹ - and many studies count only neoplasms diagnosed after MF, excluding antecedent disease.^{7,8} Second, ascertainment is unequal: excess risk is greatest near the time of CTCL diagnosis, when staging and medical contact are most intensive,¹² although elevated risk persists beyond the initial period.^{4,13} Third, cohorts labelled CTCL may pool MF with SS and other entities, diluting MF-specific estimates, while registry coding may miss composite lymphomas or classify synchronous cancers inconsistently. The reliable conclusion is therefore a pattern rather than a single percentage: MF carries a reproducible excess of additional malignancy, and the hematologic component is driven mainly by lymphoid neoplasms.

4. SPECTRUM AND TIMING OF ASSOCIATED HEMATOLOGIC DISORDERS

The disorders reported with MF are heterogeneous, and the distinction matters clinically: an indolent CLL clone, an aggressive DLBCL, a plasma cell precursor state and a therapy-related myeloid neoplasm have entirely different implications for treatment and survival. Table 1 summarizes the reported associations and the strength of the evidence supporting each.

Hodgkin lymphoma. Among overt hematologic malignancies, HL shows the largest and most consistently reproduced relative-risk signal in MF/CTCL cohorts.^{4,5,7} It may precede, coincide with or follow MF, and cutaneous HL has occasionally been reported in skin previously affected by MF.¹⁴ Because Hodgkin and Reed-Sternberg cells are sparse, molecular analysis of whole-biopsy DNA may fail to demonstrate clonality. In reported MF-cHL cases, microdissection of Hodgkin/Reed-Sternberg cells has enabled demonstration of B-cell clonality alongside a distinct T-cell clone in MF, supporting separate mature cellular origins.¹⁴ The practical difficulty is distinction from CD30-positive transformed MF, which requires integration of morphology, B-lineage markers such as PAX5, the background infiltrate and, when necessary, clonality studies.

B-cell neoplasms. CLL/SLL are among the B-cell neoplasms most frequently reported with MF, in either temporal order and with intervals extending beyond a decade.^{15,16} Among 23 patients with contemporaneous MF and a B-cell malignancy at one institution, MF was diagnosed first in 10, the B-cell neoplasm in 7 and both simultaneously in 6; no therapeutic factor explained the association.¹⁶ Two diagnostic pitfalls follow. First, CLL/SLL cells can express CD5 and CD43, so these markers alone cannot assign lineage within a mixed infiltrate; complementary B- and T-cell immunophenotyping and, in unresolved cases, molecular clonality analysis may be required. Gene-rearrangement studies in patients with coexistent CTCL and B-CLL have confirmed separate clonal B- and T-cell lineages.¹⁷ Second, an atypical cutaneous infiltrate in a patient with CLL/SLL should not be assumed to represent leukemia cutis: in a series of 12 patients with CLL/SLL who developed a distinct primary cutaneous lymphoma, four had MF (three classic and one folliculotropic) and 58% of the second cutaneous lymphomas were clinically aggressive.¹⁸ DLBCL is reported less often but is clinically consequential. In a 2024 case, tumor-stage LCT MF and nodal double-expressor DLBCL were diagnosed simultaneously, with a dominant T-cell clone in skin and a separate B-cell clone in the lymph node.¹⁹ Hairy cell leukemia and indolent B-cell lymphomas are documented mainly in case reports and small series.^{20,21}

T-cell neoplasms and plasma cell disorders. Reports of MF with a second T-cell neoplasm, including T-cell large granular lymphocytic (T-LGL) leukemia, are sparse but raise a specific methodological problem: when both neoplasms are T-cell derived, a TCR-versus-IgH comparison cannot adjudicate relatedness, and direct comparison of TCR clonotype sequences is required. Plasma cell disorders span a continuum from monoclonal gammopathy of undetermined significance (MGUS), a clonal precursor state, through smoldering disease to symptomatic myeloma; precursor states and overt malignancy should therefore be reported separately. In a heterogeneous cohort of 26 patients with a T-cell neoplasm and concomitant plasma cell dyscrasia, treatment directed at the T-cell neoplasm eradicated the plasma cell clone in 15.4% and CTCL outcomes did not differ from historical controls, but MF represented only a minority of the cohort and MF-specific outcomes were not reported separately.²² The observation is biologically interesting but cannot be generalized directly to MF.

Myeloid neoplasms. AML was among the malignancies observed in excess in a 672-patient institutional CTCL cohort¹⁰ and has been reported synchronously with MF and DLBCL.²³ Myelodysplastic neoplasia remains supported mainly by anecdotal evidence, including a 2025

report of folliculotropic MF with concurrent MDS.²⁴ Some myeloid neoplasms arise after cytotoxic therapy and may be therapy-related, whereas others occur without prior leukemogenic exposure. Given their rarity, these reports are more useful as mechanistic clues than as evidence for a common clinical pathway.

Timing. Classifying associations as antecedent, synchronous or subsequent separates biologically different scenarios. An antecedent B-cell malignancy establishes chronic immune dysfunction before MF appears, and its treatment may itself contribute; a synchronous diagnosis raises the question of shared predisposition but also of simultaneous ascertainment; a subsequent diagnosis may reflect intrinsic immune dysregulation, aging, treatment exposure or a combination. No single sequence predominates across the literature. In the Dutch cohort, 43 of 61 hematologic neoplasms were diagnosed before MF,⁷ a distribution that also reflects the diagnostic delay characteristic of early MF, which may exceed several years.

5. PATHOGENESIS: TWO COMPETING MODELS

Two models can account for these associations (Table 3), and they are not mutually exclusive.

Model A: immune permissiveness. MF is accompanied by progressive local and systemic immune dysfunction, including impaired cytotoxic T-cell and natural killer cell activity, defective dendritic cell antigen presentation and expansion of regulatory T cells.^{2,3} Single-cell transcriptomic analysis of MF skin describes a microenvironment organized for tolerance rather than rejection, with chemokine-mediated recruitment of CCR4-positive malignant T cells through the CCR4-CCL17/CCL22 axis, immunosuppressive myeloid and dendritic cell populations, and an activated, angiogenic fibroblast compartment.²⁵ The systemic component is probably more relevant to a second hematologic neoplasm than the cutaneous one: reduced cytotoxic capacity and impaired antigen presentation weaken surveillance outside the skin, so that a B-cell or myeloid clone which would otherwise remain controlled can expand. In such a host, a second neoplasm need not share any genetic lesion with MF; it need only escape surveillance. Cytokine cross-talk may add a second layer, since neoplastic B cells and plasma cell clones can chronically stimulate T cells and may in turn depend on T-cell-derived signals - an interaction that requires no shared clonal origin.^{20,22}

Model B: a shared clonal progenitor. MF carries recurrent alterations in signaling, cell-cycle control and chromatin regulation, involving pathways that also recur across hematologic neoplasia.^{3,26} In a small next-generation sequencing series of MF, DNMT3A was among the

previously reported MF-associated pathogenic variants detected, illustrating overlap between MF biology and genes also encountered in broader hematologic clonal processes.²⁶ The hematogenous-seeding model proposes that, in at least a subset of MF/SS, disease-initiating events may occur earlier in T-cell development than traditionally assumed, with circulating precursors subsequently colonizing permissive skin sites.²⁷ In principle, an early mutated hematopoietic progenitor could generate T-, B- or myeloid descendants after lineage-specific second hits. However, the frequently cited report of synchronous MF, DLBCL and AML does not demonstrate this mechanism: targeted TET2 sequencing of the available MF and DLBCL tissues found no somatic TET2 mutation and therefore provided no molecular evidence that those two malignancies arose from a common TET2-mutated ancestor.²³

Adjudication. Distinct B- and T-cell gene rearrangements have confirmed separate mature clonal populations in coexistent CTCL/B-CLL,¹⁷ and separate T- and B-cell clones have also been demonstrated in MF/DLBCL reports.¹⁹ These findings exclude simple transformation of one mature neoplasm into the other, but they do not by themselves exclude a shared pre-lineage ancestor because antigen-receptor rearrangement occurs after lineage commitment. A common progenitor could therefore generate different TCR and IgH rearrangements after divergence. The stronger test would be comprehensive paired genomic analysis of both tumors, ideally together with germline DNA and sorted non-neoplastic hematopoietic cells, to determine whether shared somatic variants predate lineage divergence. Such analyses have not been performed systematically across MF-associated hematologic pairs. Timing is likewise non-discriminatory, because both independent oncogenesis and a shared ancestral clone can produce antecedent, synchronous or subsequent disease.

Three considerations nevertheless favor host-level immune permissiveness as the more general explanation. First, immune dysfunction and a tolerogenic tumor microenvironment are directly documented in MF, whereas a shared hematopoietic ancestor remains unproven for most MF-associated pairs. Second, patients with MF also show excesses of non-hematopoietic cancers such as melanoma and keratinocyte carcinomas in some datasets,^{4,7} which points to mechanisms extending beyond a common hematopoietic progenitor; this does not exclude a shared ancestor in selected hematologic pairs. Third, alteration of a candidate gene by itself is insufficient to prove common ancestry: DNMT3A is one of several pathogenic variants reported in a small MF sequencing series,²⁶ while targeted TET2 analysis in the Miyatake MF/DLBCL case was negative

in the malignant tissues examined.²³ A convincing common-progenitor model would require shared somatic variants with a compatible phylogenetic pattern, not merely the presence of biologically plausible candidate genes. Model B is therefore best regarded as a testable hypothesis, perhaps most relevant to myeloid or multilineage presentations, rather than a general explanation.

Pathogenesis is thus best considered layered rather than binary. Host immune dysfunction reduces surveillance; the cutaneous and systemic microenvironment supports survival and immune escape; genomic and epigenetic abnormalities may create additional susceptible clones; therapy may add mutagenic or immunosuppressive pressure; and in selected patients two malignant populations may interact through cytokine or stromal signals.^{3,25,26} These mechanisms are not mutually exclusive, and their relative importance probably differs from patient to patient.

6. CONTRIBUTION OF MYCOSIS FUNGOIDES-DIRECTED THERAPY

Treatment is a plausible modifier of risk but cannot be the principal driver, since second hematologic neoplasms occur in patients who never received systemic therapy, frequently precede MF, and remain in excess in population-based data. In the Dutch cohort, 43 of 61 hematologic neoplasms antedated the MF diagnosis,⁷ and in the Mayo Clinic series no therapeutic exposure explained the co-occurrence.¹⁶

Phototherapy. Narrowband UVB has a favorable long-term profile and has not been convincingly linked to secondary hematologic malignancy, although very long follow-up data in MF remain limited.³ Cumulative psoralen plus UVA (PUVA) exposure is associated primarily with cutaneous carcinogenicity at high treatment burdens; the evidence that PUVA independently causes systemic hematologic neoplasia is weak.²⁸ In the 2025 comparative MF study, neither phototherapy modality nor cumulative NB-UVB or PUVA dose was significantly associated with secondary neoplasm development.⁸ PUVA should therefore be discussed primarily as a cumulative skin-cancer risk rather than as an established cause of secondary leukemia or lymphoma.

Radiotherapy. Localized radiotherapy and total skin electron beam therapy give rapid cutaneous control. One retrospective study reported an association between electron beam therapy and secondary neoplasms ($p = 0.032$), but the signal arose within a subgroup of 44 patients who had received no phototherapy, involved seven patients and predominantly non-hematologic tumors, and was not significant in the cohort as a whole.⁸ It should be read as hypothesis-generating;

comparative long-term data for secondary hematologic cancers after modern lower-dose regimens are lacking.

Systemic therapy. Alkylating agents, purine analogues and anthracyclines can damage marrow progenitors and have recognized leukemogenic or immunosuppressive potential. Multi-agent chemotherapy also tends to provide relatively short remissions in advanced MF and is reserved for selected aggressive settings.^{3,29} When another hematologic malignancy is present, additive marrow toxicity and infection risk become major practical constraints. Targeted and immunomodulatory approaches - including brentuximab vedotin in appropriate CD30-positive disease, mogamulizumab in suitable advanced MF/SS, interferon-based therapy and extracorporeal photopheresis - can reduce reliance on nonspecific genotoxic chemotherapy, although long-term second-cancer data for modern agents remain limited.^{3,29}

7. INSTITUTIONAL EXPERIENCE: A 39-PATIENT SERIES

Thirty-nine patients met the criteria (33 classical MF, 3 folliculotropic MF, 3 SS; 26 men and 13 women; median age at MF/SS diagnosis approximately 65 years, range 20–83). Among the 27 patients whose stage was systematically recorded, 22 (81%) had stage IA–IB disease at diagnosis and 5 (19%) stage IIIA or higher.

B-lineage disorders predominated (24 of 39, 62%), led by the CLL/SLL/monoclonal B-cell lymphocytosis (MBL) spectrum (10, 26%) and HL (6, 15%), which together accounted for 41% of all associations. Plasma cell disorders accounted for 7 cases (18%; 3 multiple myeloma and 4 MGUS or IgM paraproteinemia, none of which progressed during follow-up), T-lineage disorders for 6 (15%; 5 T-LGL-spectrum clonal expansions and 1 peripheral T-cell lymphoma) and myeloid neoplasms for 2 (5%; one chronic myeloid leukemia and one myelodysplastic syndrome).

The distribution by timing is shown in Table 2. The associated disorder was antecedent in 17 patients (44%), synchronous in 8 (21%) and subsequent in 10 (26%); timing was not determinable in 4. Intervals extended beyond 30 years in both directions. Antecedent diagnoses were the most frequent, but all three temporal categories were well represented. Because the associated disorder was antecedent or synchronous in 25 patients (64%), MF-directed therapy cannot have caused it in those cases. Treatment exposure was heterogeneous: most patients had received skin-directed phototherapy at some point and subsets had received methotrexate, bexarotene, interferon-alpha or topical mechlorethamine over many years, but these exposures cannot be interpreted causally for

patients whose hematologic disorder was already present. All five T-LGL-spectrum expansions were synchronous or subsequent; this distribution may partly reflect ascertainment during MF staging or follow-up, including blood immunophenotyping and TCR clonality testing, and should not be interpreted as evidence of a specific biological sequence.

Vital status was systematically available for the 27 registry-template patients, of whom 17 (63%) had died. Among the 14 deaths with an attributed cause, 7 were due to MF/CTCL, 4 to the associated hematologic neoplasm and 3 to other causes, with none attributed to treatment toxicity. Counting the two deaths documented in the chart-review stage, observed mortality across the whole cohort was at least 19 of 39. Two additional patients with LyP and classical HL were identified in the same registry and excluded from this analysis.

These observations are descriptive and hypothesis-generating. Without a denominator they cannot estimate prevalence or relative risk; they are subject to referral and survivor bias; and data completeness differed between the two collection stages, particularly for vital status. Their value lies in documenting the spectrum and timing of associations in a tertiary cutaneous lymphoma center: B-lineage disorders predominated, antecedent disease was the largest temporal group while synchronous and subsequent presentations were also common, and the associated neoplasm accounted for a meaningful minority of attributed deaths.

8. DIAGNOSTIC AND PROGNOSTIC IMPLICATIONS

Diagnosis. The most useful practical rule is that neither disease should be assumed. A new nodule, plaque or lymph node in a patient with MF should not automatically be labelled MF progression when morphology, distribution or tempo is atypical, and a new cutaneous infiltrate in a patient with CLL or DLBCL should not automatically be labelled secondary involvement by the known B-cell neoplasm.^{18,19} Conversely, a rapidly growing tumor in established MF may represent LCT and requires evaluation for transformation while a second lymphoma remains in the differential. LCT is defined histologically by large atypical cells comprising at least 25% of the infiltrate and is associated with a more aggressive course.³ Molecular abnormalities described in transformed disease include disruption of TP53 and other cell-cycle or genomic-control pathways, and transformed lesions may become strongly CD30-positive, creating overlap with other CD30-positive lymphomas.³⁰

CD30 expression does not assign lineage because it occurs in transformed MF, LyP, anaplastic large cell lymphoma and HL. The decision to use CD30-directed therapy is phenotype-driven; the decision to pursue clonality testing is context-driven and should arise when morphology, site or clinical course remains unexpected after standard clinicopathologic assessment.³ Diagnosis should integrate clinical distribution, morphology and a broad immunophenotypic panel. Combined TCR and IgH clonality studies can provide decisive supportive evidence when mixed T- and B-cell infiltrates remain ambiguous; in HL, microdissection may be necessary because the neoplastic Hodgkin/Reed-Sternberg cells can be sparse within a reactive background.¹⁴ T-cell/T-cell pairs require direct comparison of clonotype sequences. Nodes requiring lymphoma classification should generally be sampled by core or excisional biopsy rather than fine-needle aspiration alone.

Prognosis. Outcome data are confined to small, heterogeneous cohorts, and a single survival figure would be misleading: early patch-stage MF with an asymptomatic monoclonal B-cell population is a different disease from tumor-stage MF with DLBCL or AML. Small series of concurrent CLL/SLL and CTCL suggest worse outcomes than expected for early MF alone, but the numbers are too small for estimates.³¹ In 14 patients with CTCL and CLL, 10 had died at last follow-up, from lymphoma, MF, pneumonia or respiratory failure — a distribution in which infection is as prominent as tumor burden, consistent with the compounded T-cell and natural killer cell dysfunction produced by both diseases and by their treatment.³² Population-level survival estimates for specific MF–hematologic pairings do not exist, and the cause-of-death distribution in our own series suggests a meaningful but not dominant contribution from the associated neoplasm.

9. CLINICAL MANAGEMENT AND SURVEILLANCE

No prospectively validated program exists specifically for detecting secondary hematologic malignancy in MF. Surveillance therefore must distinguish evidence-based MF staging from proportionate vigilance for a second disease. Routine extensive imaging, bone marrow examination or repeated molecular testing in every asymptomatic patient with stable early-stage MF is not supported by current evidence. The Dutch investigators likewise concluded that routine screening with imaging and laboratory testing in the absence of clinical suspicion was of low additional value.⁷

At diagnosis, history and full examination remain the foundation, including assessment of disease extent, lymph node examination, constitutional symptoms, recurrent infection, previous

malignancy and prior cytotoxic or radiation exposure. A complete blood count with differential and lactate dehydrogenase are reasonable baseline investigations, and peripheral blood flow cytometry is appropriate when erythroderma, lymphocytosis, atypical circulating cells or SS is suspected.^{3,29} During follow-up, new persistent lymphadenopathy, unexplained cytopenias, marked lymphocytosis, a monoclonal protein, organomegaly, constitutional symptoms or an unexpected change in disease behavior should prompt targeted evaluation rather than attribution to MF.²⁸ Vigilance should be lifelong, since associated neoplasms occur decades before and after MF, but proportionate: an elevated relative risk does not justify intensive testing of asymptomatic patients with stable early-stage disease. Closer coordination with hematology is reasonable for advanced MF/SS, previous hematologic malignancy, large-cell transformation, unexplained blood abnormalities or a high-risk variant such as granulomatous slack skin, and age-appropriate screening for solid tumors should continue in parallel.

Treatment decisions should be multidisciplinary and governed by the need to avoid unnecessary additive immunosuppression while treating the biologically dominant disease. Early-stage MF coexisting with an indolent hematologic disorder that does not itself require treatment - for example CLL under observation or MGUS - can usually be managed with skin-directed therapy.^{3,29} When DLBCL, acute leukemia or another aggressive systemic neoplasm is active, control of that disease generally takes priority while MF therapy is simplified to preserve skin comfort and barrier function. Where both diseases require systemic treatment, less myelotoxic MF-directed options may be preferable to multi-agent chemotherapy when clinically appropriate. In erythrodermic MF/SS, extracorporeal photopheresis or interferon-based strategies may be attractive when deep immunosuppression is undesirable. Allogeneic hematopoietic cell transplantation remains the only potentially curative option for selected advanced or refractory MF/SS: pooled 1-year and 3-year overall survival are 51% and 40%, relapse occurs in 47% and non-relapse mortality is 18%.³³ Current European recommendations emphasize early transplant consultation for eligible patients with advanced-stage, transformed, relapsed or refractory disease and N3 nodal involvement.³⁴ A coexisting hematologic neoplasm complicates eligibility, conditioning and treatment sequencing and requires joint planning by cutaneous lymphoma, hematology and transplant teams.

10. CONTROVERSIES, GAPS AND RESEARCH PRIORITIES

Five questions remain open. The first is the true magnitude of risk for individual entities: population data are robust for HL and for NHL as a category but unreliable for rarer pairings, and many series come from tertiary centers where advanced MF and complex second malignancies are overrepresented. The second is causality. Treatment-related carcinogenesis is an attractive explanation, but antecedent and synchronous diagnoses are too common for it to be the unifying mechanism; prospective studies should capture cumulative exposure — psoralen plus UVA session counts and dose, radiation fields and dose, systemic agents, transplant conditioning — so that treatment effects can be separated from age, stage and immune dysfunction.

The third question is clonal relatedness, and it is the most tractable. Comprehensive paired sequencing of MF and the associated neoplasm, combined with germline control and, where possible, sorted non-neoplastic hematopoietic cells, has not been performed systematically across MF-associated pairs. Such studies should integrate TCR/IgH clonality with genomic phylogeny and targeted analysis of clonal-hematopoiesis genes. The answer need not be uniform: some patients may share an ancestral hematopoietic clone while others may have two unrelated cancers favored by the same host environment. The fourth gap is prognosis: reliable survival estimates for specific pairings such as MF-CLL, MF-HL or MF-DLBCL remain absent, and future analyses should report overall and disease-specific survival, infection-related mortality, transformation and cause of death with the stage and treatment of both diseases specified. The fifth gap is surveillance, where current proposals are extrapolated mainly from MF staging and clinical experience. Prospective work should test whether age, stage, variant, blood involvement, persistent LDH elevation, previous hematologic malignancy, treatment exposure or measurable clonal hematopoiesis identify a subgroup in whom additional screening is justified. Once sufficiently large multicenter datasets exist, interpretable prediction models - including machine-learning approaches - could integrate clinical, treatment and paired molecular variables, but such models should follow rather than substitute for standardized prospective data collection.

Underlying all five is terminology. Studies should distinguish antecedent, synchronous and subsequent disease; separate overt malignancy from precursor states such as MBL and MGUS; exclude or report LyP explicitly; and differentiate large-cell transformation from a true second lymphoma. As the Dutch data show, the inclusion of LyP alone can dominate an estimate of

hematologic risk. A prospective multicenter registry with harmonized definitions, systematic stage and treatment capture and paired tissue banking would address the epidemiologic, mechanistic and prognostic gaps simultaneously.

11. CONCLUSIONS

The excess of HL in MF is established and the excess of NHL as a broad category is well supported, whereas associations with CLL/SLL, plasma cell disorders and myeloid neoplasms remain much less precisely quantified. Associated hematologic disorders can precede, coincide with or follow MF/SS; in the Syggros series antecedent diagnoses were the largest group, but all three temporal patterns were represented. This breadth of timing, together with population-level excess risk in patients without a uniform treatment exposure, makes a purely therapy-driven model inadequate. Host immune permissiveness is the better-supported general framework, while a shared clonal progenitor remains biologically plausible in selected patients but requires properly designed paired genomic studies before it can be accepted as a common mechanism.

In practice, the implications are straightforward: maintain a low threshold for biopsy when lesions or nodes behave unexpectedly; use molecular clonality as an adjunct when morphology and immunophenotype do not resolve lineage; choose treatment sequences that minimize avoidable additive immunosuppression; and maintain lifelong but proportionate clinical vigilance rather than a fixed intensive screening schedule for every patient. The institutional cohort adds descriptive support to the international literature by demonstrating B-lineage predominance, wide temporal variability and clinically meaningful mortality attributable to the associated hematologic neoplasm, while remaining unable to estimate population risk.

REFERENCES

1. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019;133:1703-1714.
2. Miyashiro D, Sanches JA. Mycosis fungoides and Sézary syndrome: clinical presentation, diagnosis, staging, and therapeutic management. *Front Oncol*. 2023;13:1141108.
3. Hristov AC, Tejasvi T, Wilcox RA. Cutaneous T-cell lymphomas: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2023;98:193-209.

4. Goyal A, O'Leary D, Goyal K, et al. Cutaneous T-cell lymphoma is associated with increased risk of lymphoma, melanoma, lung cancer, and bladder cancer: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2021;85:1418-1428.
5. Huang KP, Weinstock MA, Clarke CA, McMillan A, Hoppe RT, Kim YH. Second lymphomas and other malignant neoplasms in patients with mycosis fungoides and Sézary syndrome: evidence from population-based and clinical cohorts. *Arch Dermatol*. 2007;143:45-50.
6. Goyal A, O'Leary D, Goyal K, et al. Increased risk of second primary hematologic and solid malignancies in patients with mycosis fungoides: a Surveillance, Epidemiology, and End Results analysis. *J Am Acad Dermatol*. 2020;83:404-411.
7. Ottevanger R, Vermaas E, Willemze R, et al. Mycosis fungoides and associated malignancies in a Dutch nationwide retrospective cohort study. *Acta Derm Venereol*. 2024;104:adv40065.
8. Acar A, Ozturk A, Ozturk G, et al. Secondary neoplasms in mycosis fungoides: evaluating risk factors and phototherapy impact in a comparative study. *Ann Hematol*. 2025;104:3829-3836.
9. Almukhtar R, Gill F, Soine R, McBurney E. Gender differences in the risk of secondary malignancies in patients with mycosis fungoides and Sézary syndrome. *J Am Acad Dermatol*. 2020;83:647-648.
10. Brownell I, Etzel CJ, Yang DJ, et al. Increased malignancy risk in the cutaneous T-cell lymphoma patient population. *Clin Lymphoma Myeloma*. 2008;8:100-105.
11. Atci T, Yerlioğlu Ak D, Baykal C. Evaluation of secondary malignancies in a large series of mycosis fungoides. *An Bras Dermatol*. 2024;99:370-379.
12. Amber KT, Bloom R, Nouri K. Second primary malignancies in CTCL patients from 1992 to 2011: a SEER-based, population-based study evaluating time from CTCL diagnosis, age, sex, stage, and CD30+ subtype. *Am J Clin Dermatol*. 2016;17:71-77.
13. Błażewicz I, Olszewska B, Stawczyk-Macieja M, et al. The incidences of other primary cancers in patients with mycosis fungoides and Sézary syndrome. *Postepy Dermatol Alergol*. 2021;38:289-294.
14. Zanelli M, Ricci S, Sanguedolce F, et al. Cutaneous localization of classic Hodgkin lymphoma associated with mycosis fungoides: report of a rare event and review of the literature. *Life (Basel)*. 2021;11:1069.

15. Barzilai A, Trau H, David M, et al. Mycosis fungoides associated with B-cell malignancies. *Br J Dermatol.* 2006;155:379-386.
16. Herro E, DiCaudo DJ, Davis MDP, et al. Review of contemporaneous mycosis fungoides and B-cell malignancy at Mayo Clinic. *J Am Acad Dermatol.* 2009;61:271-275.
17. Harland CC, Whittaker SJ, Ng YL, Holden CA, Wong E, Smith NP. Coexistent cutaneous T-cell lymphoma and B-cell chronic lymphocytic leukaemia. *Br J Dermatol.* 1992;127:519-523.
18. Liu YA, Finn AJ, Subtil A. Primary cutaneous lymphomas in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma: a series of 12 cases. *J Cutan Pathol.* 2021;48:617-624.
19. Rohan TZ, Suriano J, Tekmen V, et al. Coexistence of large cell transformed mycosis fungoides and diffuse large B-cell lymphoma in one patient. *J Cutan Pathol.* 2024;51:761-766.
20. Paolini R, Poletti A, Ramazzina E, et al. Co-existence of cutaneous T-cell lymphoma and B hairy cell leukemia. *Am J Hematol.* 2000;64:197-202.
21. Wong E, Mahmood MN, Salopek TG. Concomitant B hairy cell leukemia and mycosis fungoides in an elderly man. *Case Rep Dermatol.* 2017;9:103-107.
22. Braunstein Z, McLaughlin E, Ruiz M, et al. Incidence, treatment, and survival of patients with T-cell lymphoma, T-cell large granular leukemia, and concomitant plasma cell dyscrasias. *Front Oncol.* 2022;12:858426.
23. Miyatake J, Inoue H, Serizawa K, et al. Synchronous occurrence of mycosis fungoides, diffuse large B cell lymphoma and acute myeloid leukemia. *Intern Med.* 2018;57:1445-1453.
24. Benchekroun L, Darghal H, Hammoud F, Ismaili N, Meziane M, Benzekri L. Folliculotropic mycosis fungoides associated with myelodysplastic syndrome: a rare association. *MedPeer.* 2025. doi:10.70780/medpeer.000QGNS.
25. Gaydosik AM, Stonesifer CJ, Tabib T, et al. The mycosis fungoides cutaneous microenvironment shapes dysfunctional cell trafficking, antitumor immunity, matrix interactions, and angiogenesis. *JCI Insight.* 2023;8:e170015.
26. Shrestha S, Newsom K, Chaffin JM, Seifert RP. Pathogenic variants of mycosis fungoides identified using next-generation sequencing. *J Hematopathol.* 2024;17:209-214.

27. Gniadecki R, Guenova E, Querfeld C, et al. Haematogenous seeding in mycosis fungoides and Sézary syndrome: current evidence and clinical implications. *Br J Dermatol*. 2025;192:381-389.
28. Goyal A, O'Leary D, Goyal K, Rubin N, Janakiram M. Screening for second malignancies in mycosis fungoides: non-Hodgkin lymphoma, Hodgkin lymphoma, lung cancer, bladder cancer and melanoma. *J Eur Acad Dermatol Venereol*. 2021;35:1821-1829.
29. Latzka J, Assaf C, Bagot M, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2023. *Eur J Cancer*. 2023;195:113343.
30. Flerova E, Alpdogan O, Bhatti S, Nikbakht N, Wang ZX, Gong JZ. Anaplastic large cell transformation of mycosis fungoides: case report and review of the literature. *Am J Dermatopathol*. 2023;45:e74-e82.
31. Singh L, Boulavsky JL, Duvic M. Concurrent chronic lymphocytic leukemia and cutaneous T cell lymphoma: a case series. *Leuk Lymphoma*. 2014;55:2192-2195.
32. Chang MB, Weaver AL, Brewer JD. Cutaneous T-cell lymphoma in patients with chronic lymphocytic leukemia: clinical characteristics, temporal relationships, and survival data in a series of 14 patients at Mayo Clinic. *Int J Dermatol*. 2014;53:966-970.
33. Goyal A, O'Leary D, Foss F. Allogeneic stem cell transplant for treatment of mycosis fungoides and Sézary syndrome: a systematic review and meta-analysis. *Bone Marrow Transplant*. 2024;59:41-51.
34. Damaj G, de Masson A, Dreger P, et al. Allogeneic hematopoietic cell transplant in cutaneous T-cell lymphomas: recommendations from the EBMT PH&G Committee. *Bone Marrow Transplant*. 2025;60:1565-1573.

TABLES

Table 1. Hematologic neoplasms reported in association with mycosis fungoides, with the strength of the supporting evidence.

Associated neoplasm	Principal evidence	Key data	Strength of evidence
Hodgkin lymphoma	Meta-analysis; population registries; molecular case studies	Pooled SIR 15.25 (95% CI 7.70-22.79) ⁴ ; SIR 17.14 in SEER-9 and 27.27 in the Stanford cohort ⁵ ; OR 6.28 in the Dutch cohort ⁷ ; MF-cHL reports support distinct mature B- and T-cell clones ¹⁴	Strong
Non-Hodgkin lymphoma (as a group)	Meta-analysis; population registries	Pooled SIR 4.96 (95% CI 3.58-6.33) ⁴ ; increased risk in SEER analyses ^{5,6} , but not statistically significant in the Dutch cohort (OR 1.60) ⁷	Strong overall; heterogeneous by dataset
CLL / SLL	Institutional series; composite-lymphoma reports; sex-stratified registry analysis	Bidirectional timing and intervals >10 years ^{15,16} ; higher relative risk among women in one SEER analysis ⁹ ; OR 1.86 (not significant) in the Dutch cohort ⁷	Moderate
DLBCL and other B-cell lymphomas; hairy cell leukemia	Case reports and small series	Synchronous LCT MF and nodal DLBCL with separate T- and B-cell clones ¹⁹ ; hairy cell leukemia reported with CTCL/MF ^{20,21}	Limited
T-cell neoplasms (T-LGL spectrum, PTCL)	Case-level literature; single-center observations	Relatedness requires comparison of TCR clonotypes rather than TCR-versus-IgH logic; MF-specific population estimates are unavailable	Limited
Plasma cell disorders (MGUS, myeloma)	Mixed T-cell cohort; case reports	Plasma cell clone disappeared in 15.4% after T-cell-directed therapy in a heterogeneous T-cell-neoplasm cohort ²² ; MF-specific results not separately reported	Limited

Myeloid neoplasms (AML, MDS, CML)	Institutional cohort; case reports	AML in excess in one 672-patient CTCL cohort ¹⁰ ; synchronous MF/DLBCL/AML reported without evidence of a shared TET2-mutated origin ²³ ; MDS evidence remains anecdotal ²⁴	Limited
-----------------------------------	------------------------------------	--	---------

CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; IgH, immunoglobulin heavy chain; LCT, large cell transformation; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; OR, odds ratio; PTCL, peripheral T-cell lymphoma; SIR, standardized incidence ratio; TCR, T-cell receptor; T-LGL, T-cell large granular lymphocytic leukemia.

Table 2. Distribution of associated hematologic disorders by timing relative to MF/SS diagnosis in the institutional cohort (n = 39).

Associated hematologic disorder	n	Antecedent	Synchronous	Subsequent	Not determinable
Hodgkin lymphoma	6	2	2	2	0
CLL / SLL / MBL spectrum	10	5	2	1	2
Indolent B-cell NHL (marginal zone, follicular)	4	2	0	2	0
B-cell NHL, other or not otherwise specified	3	3	0	0	0
Hairy cell leukemia	1	0	0	0	1
Multiple myeloma	3	2	0	1	0
MGUS / IgM paraproteinemia	4	2	2	0	0
T-LGL leukemia / clonal T-cell lymphoproliferation	5	0	2	3	0
Peripheral T-cell lymphoma, NOS	1	0	0	1	0
Chronic myeloid leukemia	1	1	0	0	0
Myelodysplastic syndrome	1	0	0	0	1
Total	39	17	8	10	4

Antecedent, >3 months before MF/SS; synchronous, within ± 3 months; subsequent, >3 months after; not determinable, year of diagnosis missing for one of the two disorders. MBL, monoclonal B-cell lymphocytosis; MGUS, monoclonal gammopathy of undetermined significance; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; T-LGL, T-cell large granular lymphocytic leukemia.

Table 3. Two non-exclusive models for the association between mycosis fungoides and concomitant hematologic neoplasia.

	Model A: immune permissiveness	Model B: shared clonal progenitor
Proposition	Two independent primary neoplasms arise in a host with impaired tumor surveillance.	An early mutated hematopoietic progenitor gives rise to both neoplasms after lineage-specific divergence and additional hits.
Supporting evidence	Documented immune dysfunction and a tolerogenic/angiogenic MF microenvironment ^{3,25} ; excess of non-hematopoietic malignancies in several datasets ^{4,7} .	MF sequencing studies demonstrate genomic/epigenetic alterations including DNMT3A among multiple pathogenic variants ²⁶ ; early-development/hematogenous-seeding models have been proposed for MF/SS ²⁷ .
Interpretation of distinct TCR and IgH clonotypes	Consistent with independent oncogenesis.	Also compatible with a pre-lineage common ancestor because antigen-receptor rearrangement occurs after lineage commitment; distinct clonotypes exclude one mature tumor directly transforming into the other, not necessarily an earlier ancestor.
Timing prediction	Any sequence; risk may accumulate with age and immune dysfunction.	Any sequence; latency depends on lineage divergence and acquisition of additional lesions.
Most informative future test	Paired tumors show no shared founding somatic variants beyond unrelated background alterations.	Shared somatic variants with a compatible phylogeny in both tumors, assessed with germline control and, where feasible, sorted non-neoplastic hematopoietic cells.
Current status	Better supported as a general explanation for most patients.	Biologically plausible in selected cases but unproven as a general mechanism; the Miyatake MF/DLBCL/AML case found no somatic TET2 mutation in the analyzed MF and DLBCL tissues ²³ .

AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; IgH, immunoglobulin heavy chain; MF, mycosis fungoides; TCR, T-cell receptor.