Clinical staging and prognostic factors in folliculotropic mycosis fungoides

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GENERAL INTRODUCTION

PRIMARY CUTANEOUS T-CELL LYMPHOMAS

Primary cutaneous lymphomas represent a heterogeneous group of non-Hodgkin lymphomas (NHL) presenting in the skin without evidence of extracutaneous disease at diagnosis. After the gastro-intestinal tract lymphomas, primary cutaneous lymphomas are the second most common group of extra-nodal NHL with an estimated annual incidence of 1:100.000 individuals.[1] Primary cutaneous lymphomas often differ in clinical behavior, prognosis and biological features when compared to morphologically similar lymphomas arising in lymph nodes, and therefore require different types of treatment.[2] For this reason they have been included as separate entities in recent classification systems for non-Hodgkin lymphomas, such as the World Health Organization - European Organization for Research and Treatment of Cancer (WHO-EORTC) classification for cutaneous lymphomas and the WHO classification of lymphoid neoplasms in 2016.[3,4] Within these classifications two main groups of primary cutaneous lymphomas can be distinguished: primary cutaneous T-cell lymphomas (CTCL) accounting for 75% of the cases in the Western world, and primary cutaneous B-cell lymphomas (CBCL) that account for the remaining 25%.[3] (**Table 1**)

Mycosis fungoides (MF) is the most common type of CTCL. Folliculotropic mycosis fungoides (FMF) is recognized as a rare but distinct variant of MF in the WHO-EORTC classification due to its distinctive clinicopathologic and prognostic features. The studies in this thesis are focused on this folliculotropic variant of MF and will describe further insights into clinical staging, disease course, prognostic parameters and treatment of FMF patients. This introductory chapter starts with a brief overview on the characteristics of the classical type of MF, followed by a more extensive outline on the distinctive features of FMF.

Table 1. 2018 update of the WHO-EORTC classification for cutaneous lymphomas and relative frequencies.[3]

WHO-EORTC Classification 2018	Frequency (%)
Cutaneous T-cell lymphoma (CTCL)	
MF	39
MF variants:	
Folliculotropic MF	5
Pagetoid reticulosis	<1
Granulomatous slack skin	<1
Sézary syndrome	2
Adult T-cell leukemia/lymphoma	<1
Primary cutaneous CD30+ lymphoproliferative disorders	
C-ALCL	8
Lyp	12
Subcutaneous panniculitis-like T-cell lymphoma	1
Extranodal NK/T-cell lymphoma, nasal type	<1
Chronic active EBV infection	<1
Primary cutaneous peripheral T-cell lymphoma, rare subtypes	
Primary cutaneous γ/δ T-cell lymphoma	<1
CD8+ AECTCL (provisional)	<1
Primary cutaneous CD4+ small/medium T-cell lymfoproliferative disorder (provisional)	6
Primary cutaneous acral CD8+ T-cell lymphoma (provisional)	<1
Primary cutaneous peripheral T-cell lymphoma, NOS	2
Cutaneous B-cell lymphoma (CBCL)	
Primary cutaneous marginal zone lymphoma	9
Primary cutaneous follicle center lymphoma	12
Primary cutaneous diffuse large B-cell lymphoma, legtype	4
EBV+ mucocutaneous ulcer (provisional)	<1
Intravascular large B-cell lymphoma	<1

CD8+ AECTCL: primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, C- ALCL: primary cutaneous anaplastic large cell lymphoma, EBV: Epstein-Barrvirus, Lyp: lymphomatoid papulosis, MF: mycosis fungoides, NOS: not otherwise specified.

MYCOSIS FUNGOIDES

Clinical features

MF accounts for almost 50% of all primary cutaneous lymphomas and is clinically characterized by a slow evolution from patches to plaques to eventually tumors. A small minority of patients may develop extracutaneous dissemination.[2] MF typically affects older adults and occurs more frequently in males than in females. Skin lesions are preferentially localized on the buttocks and other non-sunexposed areas (**Figure 1 A-C**).

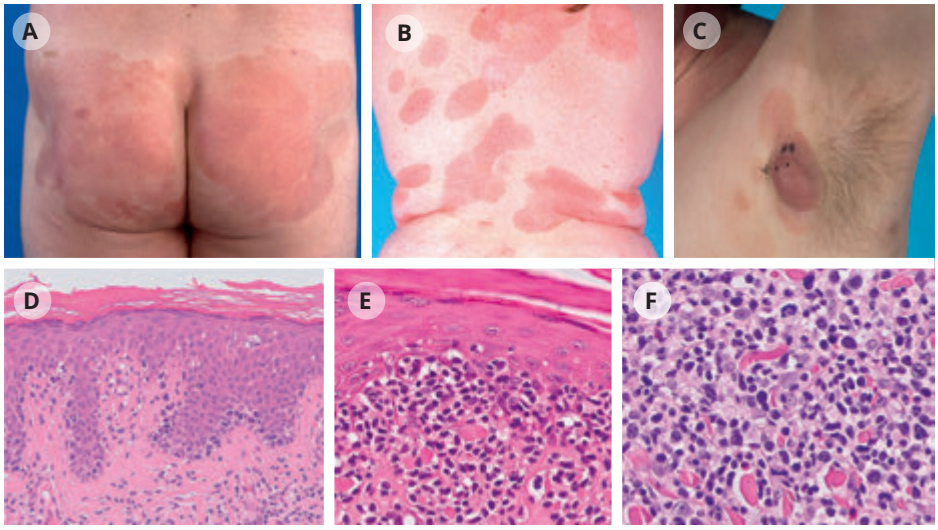

Figure 1. Examples of clinical manifestations of classic MF with limited patches (A), widespread patches, plaques (B) and a skin tumor (C) and their concordant histological pictures. Histopathologic pictures of patch- and plaque-stage MF (D and E) show sparse infiltration of atypical hyperchromatic and cerebriform T-cells into the epidermis (epidermotropism) (D) and an increased infiltrate with Pautrier microabcesses (E). Picture of tumor-stage MF (F) shows a diffuse infiltrate containing large cerebriform and blast cells.

Histology and phenotype

Patches and plaques in MF are histologically characterized by a band-like or lichenoid infiltrate in the papillary dermis consisting of atypical small- to medium-sized T-cells with convoluted (cerebriform) nuclei that infiltrate the epidermis (epidermotropism).[2] A highly characteristic feature are intra-epidermal collections of cerebriform T-cells (Pautrier microabscesses), which is observed in only a minority of cases.[5] In

tumor-stage MF, the dermal infiltrate becomes more diffuse with an increase in the proportion of tumor cells (**Figure 1 D-F**). Infiltrates may contain variable numbers of small, medium-sized, to large cerebriform cells and blast cells with prominent nuclei, and epidermotropism may disappear. The atypical MF cells usually exhibit a CD4+CD8- phenotype, but CD4-CD8+, CD4-CD8- or CD4+CD8+ are sometimes found and loss of pan-T-cell antigens such as CD2, CD3, CD5 and CD7 is a common finding, particularly in the advanced stages of the disease.[6-10]

Prognosis and prognostic features

Prognosis and risk of disease progression in MF patients are closely correlated with clinical stage.[11] Staging occurs via the clinical staging system for patients with MF/SS, based on the tumor-node-metastasis-blood (TNMB) classification. This staging system classifies both type and extent of skin lesions, and the presence and degree of lymph node, visceral and blood involvement (**Table 2: TNMB classification** and **Table 3: Clinical staging in MF/SS**).[12] Patients with patches and/or plaques (stage IA–IIA) are considered to have early-stage disease, while patients with tumors, erythroderma or nodal, blood and/or visceral involvement (stage IIB-IV) have advanced-stage disease. Patients with early-stage disease commonly run an indolent disease course and survival of MF stage IA is even comparable with age-, race- and sex-matched controls.[13-15] The prognosis becomes less favorable in patients developing MF stage IIB (tumor stage), stage III (erythroderma) or stage IV (extracutaneous disease), which have been associated with a 10-year disease-specific survival of 42%, 45% and 20%, respectively.[11] Patients usually die of systemic involvement or infections. Apart from clinical stage, independent prognostic factors associated with reduced survival in MF are advanced age, male sex, elevated lactate dehydrogenase (LDH), large cell transformation and the folliculotropic variant of MF.[11,15-21] As the folliculotropic variant of MF is the main topic of this thesis, the next paragraphs will further discuss the distinctive clinicopathologic features, diagnosis, staging, treatment and prognosis of folliculotropic mycosis fungoides.

Table 2. TNMB classification of mycosis fungoides and Sézary syndrome[12]

T (skin)	
T_1	Limited patch/ plaque (< 10% of total skin surface)
T_2	Generalized patch/ plaque (≥ 10% of total skin surface)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Erythroderma (≥ 80% of total skin surface)
N (lymph node)	
N_0	No clinically enlarged lymph nodes
N_1	Clinically enlarged lymph nodes, histologically uninvolved
N_2	Clinically enlarged lymph nodes, histologically involved (nodal architecture uneffaced)
N_3	Clinically enlarged lymph nodes, histologically involved (nodal architecture (partially) effaced)
M (viscera)	
M_0	No visceral involvement
M_1	Visceral involvement
B (blood)	
B_0	No circulating atypical (Sézary) cells (or < 5% of lymphocytes)
B_1	Low blood tumor burden (≥ 5% of lymphocytes are atypical (Sézary) cells, but does not meet criteria B2)
B_2	High blood tumor burden (positive clone and either ≥1000/μL Sézary cells or CD4/CD8 ratio>10 or CD4+CD7- cells≥ 40% or CD4+CD26- cells ≥ 30%)

Table 3. Clinical staging system for mycosis fungoides and Sézary syndrome[12]

Early-stage disease				
IA	T_1	N_0	M_0	B_{0-1}
IB	T_2	N_0	M_0	B_{0-1}
IIA	T_{1-2}	N_{1-2}	M_0	B_{0-1}
Advanced-stage disease				
IIB	T_3	N_{0-2}	M_0	B_{0-1}
III	T_4	N_{0-2}	M_0	B_{0-1}
IVA_1	T_{1-4}	N_{0-2}	M_0	B_2
IVA_2	T_{1-4}	N_3	M_0	B_{0-2}
IVB	T_{1-4}	N_{0-3}	M_1	B_{0-2}

FOLLICULOTROPIC MYCOSIS FUNGOIDES

In large series, folliculotropic mycosis fungoides makes up approximately 10% of all MF patients.[2] In 2002, van Doorn et al. studied the differences between classic MF and FMF

and found that patients with FMF differ both clinically, histologically and prognostically. Folliculotropic MF is defined by the presence of folliculotropic (infiltration of hair follicles) instead of epidermotropic infiltrates and the preferential involvement of skin lesions in the head- and neck area. FMF is generally more resistant to therapy and associated with a worse prognosis when compared to classic MF.[22] These observations were confirmed by several other studies and in recent (cutaneous) lymphoma classifications FMF has therefore been included as a distinct variant of MF.[2,23,24]

Clinical features

Clinically, FMF patients may present with (grouped) follicular papules, acneiform lesions, infiltrated plaques and/or tumors, which preferentially involve and are often most pronounced in the head- and neck area.[22-30] Patients may show keratosis pilaris-like lesions, mainly on extremities and trunk.[30-32] Skin lesions are often associated with local alopecia. The presence of infiltrated plaques in the eyebrow region with concurrent alopecia is a common and a highly characteristic feature (**Figure 2 A-G**). In rare cases FMF may present with a solitary skin lesion or with erythroderma.[33-35] Patients are often diagnosed with secondary bacterial infections. Complaints of (extensive) pruritus are common which may be difficult to manage therapeutically, whereas pruritus is usually absent in the classical type of MF.[22] **See BOX 1 – Pruritus in CTCL patients.**

Histology

Histologically, FMF is characterized by the presence of perifollicular to confluent infiltrates with variable infiltration of the follicular epithelium (folliculotropism) by small, medium-sized or sometimes large cerebriform T-cells with hyperchromatic nuclei (**Figure 2 H-J**).[2] Infiltration of the follicular epithelium may be accompanied by infiltration of the eccrine sweat glands (syringotropism). Concurrent infiltration of the epidermis (epidermotropism), characteristic of early stage classic MF, is uncommon.[22,44] Many cases show mucinous degeneration of the follicular epithelium (follicular mucinosis), which can be visualized by Alcian blue or colloidal iron staining.

Formerly in literature, these cases had been designated as MF-associated follicular mucinosis. This term has been abandoned when van Doorn et al. found no differences in clinical presentation or clinical behavior between FMF cases with or without associated follicular mucinosis. Periadnexal infiltrates contain apart from neoplastic

T-cells, a variable number of small reactive T-cells, histiocytes and sometimes clusters of B-cells. There is often a considerable admixture with eosinophils and, in particular in cases with secondary bacterial infection, plasma cells.[22,44] Histology of FMF patients presenting with early, non-infiltrated lesions such as patches containing follicle- based papules, keratosis pilaris-like lesions or acneiform lesions, usually contain sparse neoplastic infiltrates, that may be limited to a thin shell around the hair follicle.[30,31,45] With increasing infiltration of the skin lesions such as tumor-stage, the periadnexal infiltrates become more confluent or completely diffuse and may contain increasing numbers of large cerebriform cells or blast cells and hair follicles may get (partially) destructed. Large cell transformation, defined by the presence of more than 25% of blast cells or the presence of clusters of blast cells, has been reported in more than 20% of FMF cases[23,46,47] and is more commonly found than in classic MF.[48,49] Similar to classic MF, most cases of FMF exhibit a CD4+CD8- T-cell phenotype. Admixed tumor blast cells are often CD30-positive.

BOX 1. Pruritus in CTCL patients

Pruritus or 'itching' is the uncomfortable feeling that causes the desire to scratch. The exact mechanism of pruritus in both general skin disease and in CTCL patients specifically are not fully understood. Pruritus may be present in up to 88% of CTCL patients and occurs most frequently in advanced stages of disease.[36] In severe cases pruritus impacts patients' quality of life while it may be challenging to manage symptoms therapeutically.[37] Various mediators, neuropeptides and interleukins have been investigated such as histamines, substance P, IL4, IL5, IL10, IL13 and IL31, but their exact role in the pathogenesis has not fully been elucidated.[38] Conventional antipruritic agents, such as antihistamines, gamma-aminobutyric acid analogs and antidepressants have not or only been partially effective in CTCL patients.[39] In search for novel therapies, several recent studies focused on the role of interleukin 31 (IL31), since a IL31 receptor antagonist (nemolizumab) has appeared on the market. IL31 is a cytokine that is predominantly produced by activated Th2 cells.[40,41] It signals through a heterodimeric receptor that is composed of IL31A receptor and Oncostatin M receptor (OSMR).[40] This receptor is present on keratinocytes, eosinophils and afferent neurons of the dorsal root ganglia.[40] In lymphocytes and mast cells interleukin 4 induces upregulation of IL31. In eosinophils, staphylococcus toxin, interleukins 3, 4, 13 and IL31 itself upregulate IL31.[42] Expression of IL31 may be also triggered by staphylococcus aureus superantigens and colonization by staphylococcus aureus may often occur in CTCL patients, including FMF patients.[43] The role of IL31 in CTCL patients is one of the topics that will be further addressed in **chapter 7** of this thesis.

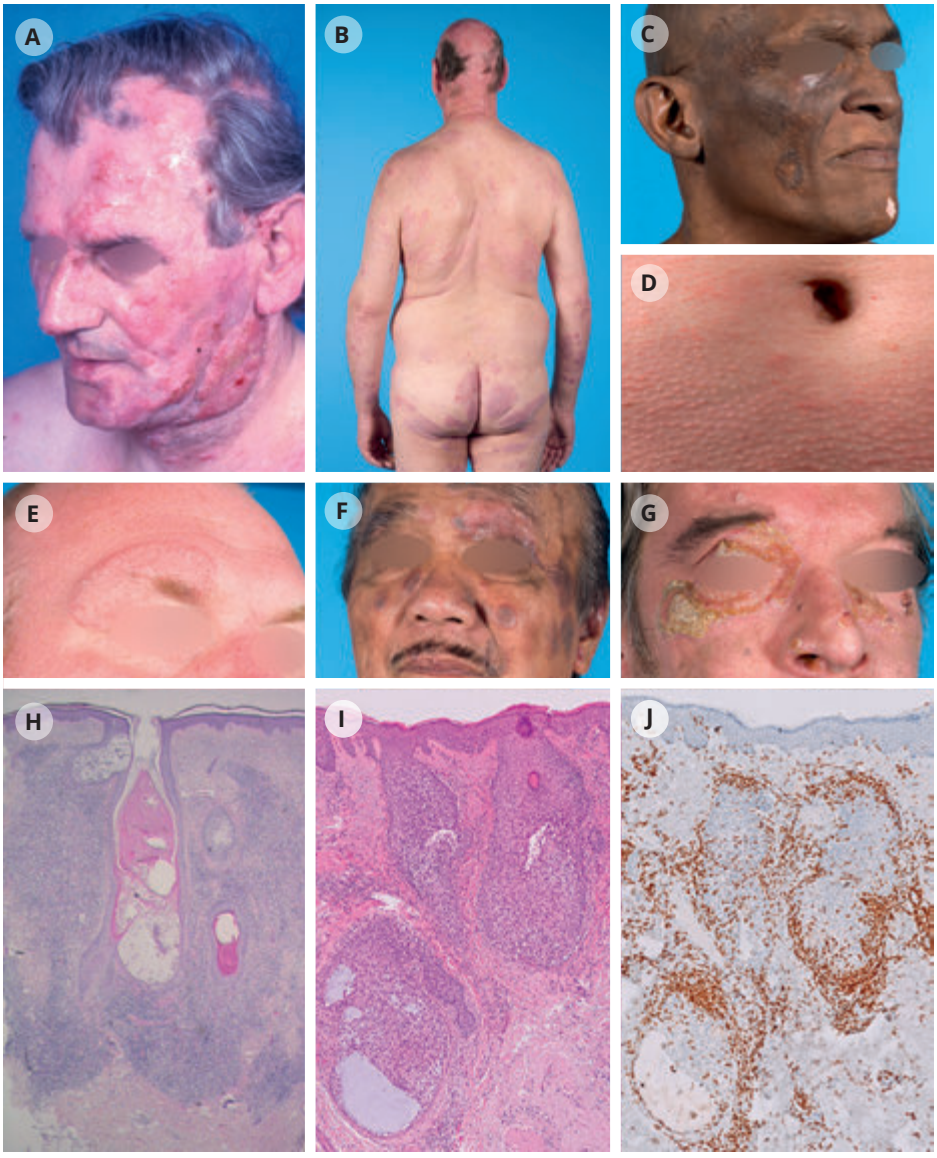

Figure 2. Clinical manifestations and histological pictures of FMF. A: pronounced tumorous skin lesions in head/neck area, B: marked alopecia on the scalp and widespread patches and plaques on the body, C: acneiform/cystic lesions on the cheek, D: characteristic keratosis pilaris-like skin lesions on the abdomen, E: facial plaque with lateral eyebrow hair loss, F: multiple facial plaques with concurrent eyebrow involvement, G: secondary bacterial infection of facial FMF lesions, H: histological picture of prominent perifollicular infiltrates with sparing of the epidermis, I: histological picture of sparse perifollicular infiltrates and mucinosis follicularis; CD3 staining shows distinct folliculotropism (J).

Staging

In classic MF the TNMB classification correlates well with survival, as previously stated (**Table 2**).[11] However, the clinical significance of this staging system for patients with FMF has been questioned. While it has been reported that patients with follicular papules, acneiform lesions or keratosis pilaris-like lesions may have early-stage disease (stage IA-IIA)[30,31,50] and patients presenting with tumors, erythroderma or extracutaneous disease have advanced FMF (stage IIB-IV), it is uncertain if patients presenting with plaques should be classified as early-stage FMF or advanced-stage FMF. Because of the deep perifollicular localization of the dermal infiltrates, it has been suggested that such patients should always be considered to have tumor-stage disease and should be treated accordingly.[22] As criteria to differentiate early- and advanced FMF are not clear, the first study in **chapter 2** will address this issue and evaluates clinical and histological characteristics of a large cohort of FMF patients in order to define criteria for early- and advanced-stage disease in FMF.

Treatment

Reports on treatment results in FMF are very scarce and controlled studies have never been performed. Management of FMF patients follows a similar therapeutic approach as used in patients with classic MF which is aimed at long-term disease control while limiting toxicity.

In general, early aggressive chemotherapy is not desirable in (F)MF patients as it is associated with considerable side effects and does not improve survival nor induces long-term remissions. Also other available treatments rarely induce durable remissions and therefore a stepwise, stage-adapted therapeutic approach is recommended.[51,52] However, as FMF has been associated with more resistance to those therapies, used in classic MF, it has been suggested that patients with FMF should be treated more aggressively, according to tumor-stage disease.[22,23] In this thesis, treatment results in a large cohort of FMF patients will be evaluated, aimed to formulate treatment recommendations in FMF. The results are presented in **chapter 3.**

Prognosis and prognostic factors

Many studies reported that patients with FMF have a worse prognosis as compared to patients with classic MF.[22-24,47] Also in large retrospective cohort studies FMF was found

to be an independent risk factor for reduced survival.[11,16,53] Independent risk factors in classic MF have been well identified, whereas prognostic factors in FMF are currently unknown and these have been the subject of further study throughout this thesis. One of the methods that has recently been used and studied for its prognostic significance in CTCL is high-throughput sequencing of the T-cell receptor (HTS-TCR). **See BOX 2 – High-throughput sequencing of the T-cell receptor in CTCL patients.**

BOX 2. High-throughput sequencing of the T-cell receptor in CTCL patients

T-cell receptors (TCRs) are translationally expressed on mature T-cells as heterodimer receptors. These heterodimer receptors are built from a combination of either α and β chains or γ and δ chains. In peripheral blood, a majority of T-cells possesses αβ TCRs, while a smaller fraction (1–5%) consists of γδ TCRs.[54] TCR formation occurs during lymphocyte development by the combination of variable (V), diversity (D), and joining (J) gene segments and deletion or insertion of nucleotides at the junctions of those segments (C, Constant gene segments). This randomized process allows for the unique T-cell receptor complimentary determining region 3 (CDR3) nucleotide sequences that enables recognition and tracking of a specific T-cell clone (**Figure 3**)**.** Four gene complexes are responsible for the variety of expressed TCRs and rearrange sequentially in a highly ordered manner, starting with *TRD*, followed by *TRG*, *TRB*, and finally *TRA*.

High-throughput sequencing (HTS) of the T-cell receptor (HTS-TCR) is a technique that allows identification and quantification of every distinct T-cell clone present within a biological sample.[55] HTS-TCR technology is based on the specific sequencing of the CDR3 region on one of the two chains of the TCR heterodimer by bias controlled multiplexed polymerase chain reaction (PCR). It is possible to identify and quantify the CDR3 segments and the V(D)J genes based on previously described sequences that can be accessed within data banks. HTS may thus give insight into the diversity of the TCR repertoire in different tissues under non-pathologic and pathologic conditions and the relative frequency of each individual clone within the full T-cell repertoire can be studied (**Figure 4**).[55] This technique has been studied in CTCL patients and shown to have both diagnostic and prognostic value. In MF, HTS of the TCR β and γ alleles was found more sensitive and specific than TCRγ PCR in detecting the pathogenic expanded T-cell clone and HTS-TCR was also found to accurately predict disease progression in early stage MF patients.[56,57] These findings prompted us to further study this HTS-TCR technique in FMF patients and results are presented in **chapter 5**.

BOX 2. *(continued)*

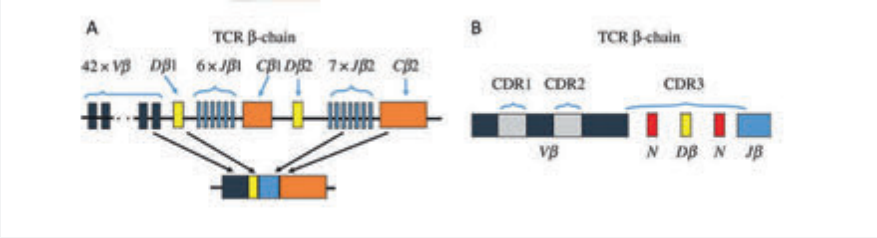

Figure 3. T-cell receptor gene rearrangement. A: Variable (V), joining (J) and constant regions (C) constitute the TCR β-chain, with additional diversity (D) regions (yellow). Segments from each region are recombined, with additional nucleotide additions, to generate each rearranged TCR. These processes generate substantial T-cell diversity. B: Hypervariable complementarity-determining regions (CDR1-CDR3) of the β-chain. CDR1 and CDR2 regions are encoded on the V region, while the most variable CDR3 region straddles the V(D)J junction.

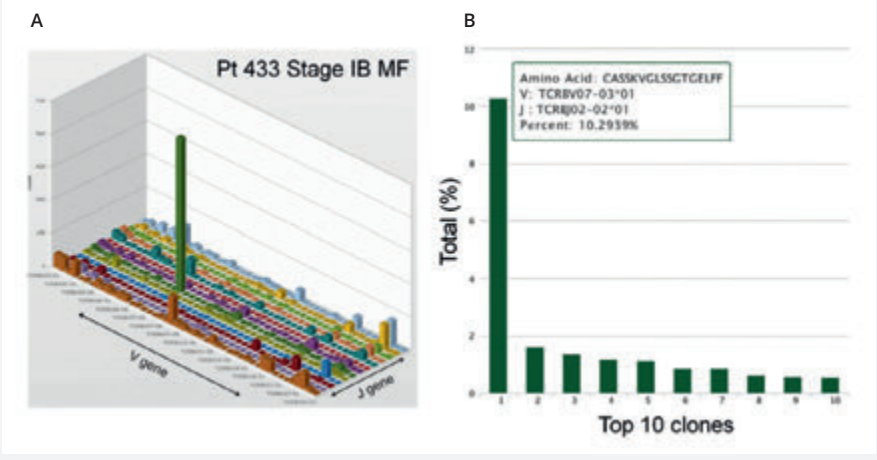

Figure 4. HTS-TCR identifies expanded populations of clonal malignant T-cells and V vs. J gene usages of T-cells from a lesional skin sample (example in A). The green peak includes the clonal malignant T-cell population, as well as other benign T-cells that share the same V and J gene usage. The individual T-cell clone sequence is shown with detailed information on the CDR3 amino acid sequence and V and J gene usage (B). The nine most frequent benign infiltrating T-cell sequences are also shown. In this example, the malignant T-cell clone makes up 10.3% of the total T-cell population in lesional skin.
Adapted from Kirsch et al, *Sci Transl Med.* 2015 October 7; 7(308). Reprinted with permission from AAAS.

AIMS AND OUTLINE OF THIS THESIS

The studies presented in this thesis were aimed to address questions regarding clinical staging, disease course, treatment and prognosis in folliculotropic mycosis fungoides.

Chapter 2 studies the clinicopathologic characteristics and disease course in a cohort of 203 FMF patients in order to identify criteria that could be used to differentiate between FMF cases with an indolent and an aggressive disease course. This study resulted in the identification of early-stage and advanced-stage FMF subgroups, implicating that these may require a different therapeutic approach. As a result, **Chapter 3** evaluates treatment results in early- and advanced-stage FMF and formulates treatment recommendations for different FMF subgroups.

Results from chapter 2 reinforced the impression that FMF patients presenting with plaques represent a prognostically heterogeneous group and that histological criteria may be helpful to differentiate indolent from aggressive cases. This patient group is further studied in chapters 4 and 5. **Chapter 4** evaluates detailed histopathologic features of FMF patients presenting with plaques and provides prognostic factors. **Chapter 5** analyses the prognostic value of T-cell receptor β gene sequencing in FMF patients presenting with plaques.

Chapter 6 describes the clinicopathologic characteristics, prognosis and treatment of a rare subgroup of FMF patients: those cases that present with a solitary skin lesion at time of diagnosis. **Chapter 7** analyses the role of interleukin 31 in pruritus and disease stage in several types of CTCL, including FMF, classic MF and Sézary syndrome.

Chapter 8 summarizes and discusses the findings described in the preceding chapters.

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