Review

Follow-up of Mycosis Fungoides

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Abstract

Mycosis fungoides (MF) is the most common form of primary cutaneous T-cell lymphoma with an indolent course. The tumor, node, distant metastasis, and blood (TNMB) staging system is still the best method for determining prognosis. Individualized, TNMB-compliant conservative treatment approach is the basis of MF patient management. Treatment responses should be evaluated according to standardized guidelines based on objective criteria. There is no consensus on the follow-up of patients with cutaneous lymphoma, and the frequency of follow-up should be planned individually for life, depending mainly on disease stage; primary cutaneous lymphoma subtype; and the treatment agent used.

Keywords: Mycosis fungoides, follow-up, TNMB staging, precision medicine

Introduction

Primary cutaneous lymphomas are non-Hodgkin lymphomas of T- and B-cells that typically present in the skin without any extracutaneous disease findings upon diagnosis. Cutaneous T-cell lymphomas (CTCL) constitute approximately 75-80% of primary cutaneous lymphomas. Mycosis fungoides (MF) accounts for 54-72% of primary CTCL (Figure 1). The primary cutaneous lymphoma classification revised by the World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) in 2018 is still accepted (Table 1).[1-3] Given that CTCLs have a different clinical presentation and prognosis compared to nodal lymphomas that secondarily involve the skin, patient management requires distinct approaches. A personalized, TNMB-compliant (Table 2) conservative treatment strategy is the cornerstone of managing patients with MF. The treatment of each case diagnosed with MF based on clinical, histopathological, and immunohistochemical findings should be individually planned in accordance with the current literature. According to the TNMB staging system, early-stage cases (IA-IIA) can be managed with skin-directed therapies, whereas advanced-stage cases (IIB-IVB) should be treated with systemic therapies, either as monotherapy or in combination with skin-directed therapies, utilizing a multidisciplinary approach.[4-6]

In this section, the key aspects of MF patient management are discussed in accordance with the current literature.

Which Examination is Right for Which Patient?

The primary objectives of the tests conducted during the diagnosis and follow-up of patients are to determine the stage of the disease, identify whether the clinical course is aggressive or indolent, assess the suitability of metabolic parameters for the planned treatment, detect any comorbidities that may accompany the condition, evaluate the treatment response (complete/partial response, stable disease, progression, and relapse), and monitor treatment-related side effects.[4-6]

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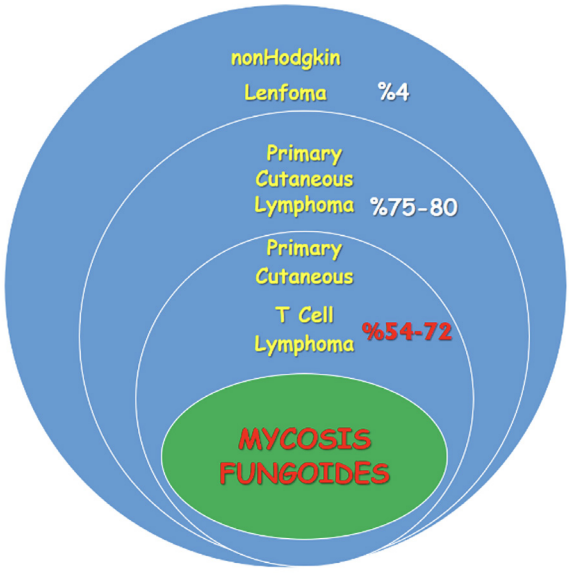

Figure 1. Frequency of primary cutaneous lymphomas

Detailed physical examination: From the first presentation of the patient, a detailed physical examination including scalp and mucosa examination is required at each visit for initial staging and follow-up visits, lesion type; extent; suspicious (≥ 1.5 cm) palpable lymph node (LN) and organomegaly evaluation.[4-6]

Histopathological and İmmunohistochemical examination: Histopathological and immunohistochemical diagnostic criteria for MF were first defined in 2005 for clinically suspicious skin lesions and are still widely accepted today.[7] For histopathological examination during the initial presentation and follow-up, at least two skin biopsies should be taken from different anatomical regions and lesions with varying morphologies (indurated and scaly), using a punch biopsy instrument of at least 4 mm. In cases with high clinical suspicion in which a diagnosis cannot be confirmed histopathologically and immunohistochemically at the initial staging, close follow-up with repeat biopsies is crucial. Clinicopathological correlation is essential for an accurate diagnosis.[4,5]

Table 1. Cutaneous T-cell lymphoma WHO-EORTC classification, frequency and prognosis

Revised WHO 2018 classification	Frequency, (%)	5-y DSS, (%)
Cutaneous T- and NK-cell lymphomas		
MF	39	88
MF variants;		
Folliculotropic MF	5	75
Pagetoid reticulosis	< 1	100
Granulomatous slack skin	< 1	100
Sézary syndrome	2	36
Adult T-cell leukemia/lymphoma	< 1	NDA*
Primary cutaneous CD30⁺ LPDs;		
C-ALCL	8	95
LyP	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	< 1	16
Chronic active EBV infection	< 1	NDA*
Primary cutaneous peripheral T-cell lymphoma, rare subtypes;		
Primary cutaneous γ/δ T-cell lymphoma	< 1	11
CD8⁺ AECTCL (provisional)	< 1	31
Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder (provisional)	6	100
Primary cutaneous acral CD8⁺ T-cell lymphoma (provisional)	< 1	100
Primary cutaneus peripheral T-cell lymphoma, NOS*	2	15
Cutaneous B-cell lymphomas		
Primary cutaneous marginal zone B-cell lymphoma	9	99
Primary cutaneous follicle center lymphoma	12	95
Primary cutaneous large B-cell lymphoma (leg type)	4	56
EBV1 mucocutaneous ulcer (provisional)	< 1	100
Intravascular large B-cell lymphoma	< 1	72

WHO: World Health Organization, DSS: Disease-specific survival, NK: Natural killer, MF: Mycosis fungoides, NDA*: No data available, LPDs: Lymphoproliferative disorders, C-ALCL: Cutaneous anaplastic large-cell lymphoma, LyP: Lymphomatoid papulosis, EBV: Epstein-Barr virus; **γ/δ**: Gamma/delta, AECTCL: Aggressive epidermotropic cytotoxic T-cell lymphoma, NOS*: Not otherwise specified

Table 2. Mycosis fungoides TNMB staging

Clinical stage	T(skin)	N(node)	M(Visceral)	B(blood involvement)
IA (limited skin involvement)	T1 (patches, papules, and/or plaques covering < 10% BSA)	N0	M0	B0 or B1
IB (skin only disease)	T2 (patches, papules, and/or plaques covering ≥ 10% BSA)	N0	M0	B0 or B1
IIA	T1-2	N1-2	M0	B0 or B1
IIB (tumor stage disease)	T3 [one or more tumors (≥ 1 cm in diameter)]	N0-2	M0	B0 or B1
IIIA (erythrodermic disease)	T4 (confluence of erythema ≥ 80% BSA)	N0-2	M0	B0
IIIB (erythrodermic disease)	T4 (confluence of erythema ≥ 80% BSA)	N0-2	M0	B1
IVA1 (Sézary syndrome)	T1-4	N0-2	M0	B2
IVA2 (Sézary syndrome or non-Sézary)	T1-4	N3	M0	B0 or B1 or B2
IVB (visceral disease)	T1-4	N0-3	M1A or M1B	B0 or B1 or B2

BSA: Body surface area, T: Tumor, N: Node, M: Metastasis, B: Blood

In the evaluation of treatment response, histopathological confirmation is required in cases of suspected residual disease, the presence of resistant lesions, a different clinical presentation, lack of response or progression, aggressive clinical behavior, or suspicion of relapse in patients who have achieved complete remission. If the disease remains stable, performing a biopsy is left to the clinician's discretion.[7,8]

Additionally, the prognosis of the folliculotropic MF variant, as defined in the WHO-EORTC classification, differs from that of classic MF.[1,9,10] Another significant histopathological finding is large cell transformation (LCT), which may indicate a poor prognosis. Therefore, histopathological and immunohistochemical examination is necessary to differentiate between MF with LCT and other $CD30^+$ clinicopathological conditions.[5,11]

1.3. Laboratory examination: In the first admission and follow-up, blood tests should include complete blood count [including lactate dehydrogenase (LDH)]; comprehensive biochemical tests; liver and kidney function tests, and viral serology [hepatitis markers, human immunodeficiency virus, human T-cell lymphotropic virus 1 (HTLV-1)] at the first admission. Given the potentially advanced age of patients with MF and immunosuppressive nature of the disease, secondary malignancies that may accompany metabolic comorbidities should be considered. Each patient should be approached holistically, and necessary tests should be conducted in accordance with national and international guidelines to rule out age- and sex-appropriate malignancies.[5,12-14]

Peripheral blood smear and flow cytometric analysis: Although peripheral blood smear is performed at the initial evaluation and during follow-up visits, as needed, to assess Sézary cells, it provides subjective results. The use of flow cytometry to determine the absolute counts of Sézary cells is becoming increasingly widespread. According to EORTC and European Society for Medical Oncology (ESMO) guidelines, flow cytometry is recommended for the diagnosis and follow-up of all patients suspected of having blood involvement.[6,15]

Flow cytometric analysis should be performed in cases of stage IIB and advanced stages, generalized patch or plaque involvement (stage T2A/T2B), erythroderma, persistent pruritus, lymphocytosis, elevated serum LDH levels, and treatment resistance. In patients with initial pathological flow cytometry, follow-up flow cytometric evaluation every 3 months is recommended.[16,17]

***TCR* gene clonality:** *TCR* gene clonality can be observed in both malignant and benign conditions and may not be present in all MF lesions. While demonstrating identical clones in the skin, blood, and/or LN simultaneously can be useful in the diagnosis and differential diagnosis of MF, it is not absolutely recommended in guidelines due to its limited availability.[4-6]

Evaluation of Treatment Response

In patients with MF, decisions regarding whether to continue, discontinue, or change treatment are primarily based on clinical evaluation, although treatment responses may vary between compartments (skin, LN, blood, internal organs). The International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the EORTC have published Consensus Guidelines for Treatment Response Evaluation Criteria. Depending on the initial characteristics of the case, treatment responses may differ across compartments; therefore, the treatment responses of the skin, LN, blood, and internal organs should be evaluated separately.[18]

Evaluation of treatment response in skin involvement: Complete clearance of the skin lesions after treatment is considered complete response. A biopsy of clinically normal-appearing skin is not required to confirm complete response. However, if there is any suspicion of residual disease (persistent erythema/pigmentary changes), the response should be evaluated histopathologically. If histopathological examination reveals finding indicative of MF, the treatment response is considered a partial response. In patients with isolated skin involvement who are not in the tumoral stage (T3), a 50-99% improvement in lesions without the development of new tumors is considered a partial response in T1, T2, and T4 stages. A reduction of less than 50%, no change in lesions, or up to a 25% increase is considered stable disease. The development of a new tumor (T3) in patients with T1, T2, or T4 skin involvement or an increase of more than 50% in the skin score in patients who achieved a complete or partial response is considered progressive disease. The emergence of any clinical signs associated with MF during follow-up of patients who achieved complete response is considered a relapse.

Evaluation of treatment response in lymph node involvement: Patients with LN involvement that are the largest in the draining area near the lesion, show high positron emission tomography (PET) uptake, and have a long axis ≥ 1.5 cm, short axis ≥ 1 cm, hard, irregular, clustered, or fixed, an excisional biopsy should be performed. The excised material should be evaluated histopathologically, immunohistochemically, and if possible, for TCR clonality. In the presence of multiple LNs, the decision for excisional biopsy should prioritize Cervical > Axillary > Inguinal LNs.

Although physical examination is a valuable method in the evaluation of LNs, it is insufficient on it's own for accurately determining their size.[19] Given the variations among evaluators, the use of contrast-enhanced computed tomography (CT) (cervical, thoracic, abdominal, pelvic) provides more objective results in the evaluation of LNs compared with ultrasound.[20]

In the PROspective Cutaneous Lymphoma International Prognostic Index (CLIPi) study, which examined the long-term follow-up of early-stage patients, it was emphasized that physical examination alone is a poor predictor of LN enlargement or involvement; the presence of plaque lesions may indicate LN involvement in early-stage MF patients and is important in deciding who should undergo imaging. Additionally, imaging could increase the detection rate of stage IIA MF and identify patients with rare extensive LN involvement, potentially upgrading them to advanced stage (IVA2).[20] PET/CT has been identified as more sensitive than CT alone in detecting lymphoma-related LN involvement for MF staging, and the intensity of PET activity has been shown to correlate with the histological grade of LN involvement. It has been reported that PET/CT can provide more accurate staging and prognostic information.[21,22]

In the assessment of LN treatment response, the initial method considers a complete response when, after treatment, the largest transverse diameter (long axis) of all LNs is ≤ 1.5 cm. For LNs classified as N3 prior to treatment, where the long axis is ≤ 1.5 cm but the short axis is > 1 cm, a complete response is defined as the short axis being reduced to ≤ 1 cm after treatment or an LN biopsy result that is negative for lymphoma.

A partial response to treatment is defined as a ≥ 50% reduction in the Sum of the Product of Perpendicular Diameters (SPD), calculated by multiplying the largest transverse and vertical diameters of each pathological LN compared with baseline. Additionally, no new pathological LN should develop with a long axis greater than 1.5 cm, or if the long axis is between 1 and 1.5 cm, no new LN should have a short axis greater than 1 cm.[23] Progressive disease is defined as a ≥ 50% increase in the SPD of pathological LNs compared with baseline, the development of a new pathological LN proven to be N3 histologically with a long axis greater than 1.5 cm or a long axis between 1-1.5 cm with a short axis greater than 1 cm, or a > 50% increase in the SPD of LNs that previously met the criteria for partial response. Cases that do not meet the criteria for complete response, partial response, or progressive disease are classified as stable disease. In a patient who achieved complete response to treatment, the development of a new LN was proven to be N3 histologically, with a long axis of 1.5 cm is considered a disease relapse.

Evaluation of treatment response in visceral disease: In the evaluation of organ involvement, it is recommended to confirm organ involvement, except for liver and spleen involvement, which can be determined by appropriate imaging methods, through biopsy at the initial assessment.[5] The assessment of bone marrow involvement as either organ involvement or a separate prognostic factor in patients with Sézary syndrome (SS) has not been clearly established in the studies conducted. Therefore, in many studies, bone marrow involvement is considered part of blood involvement and does not need to be taken into account when evaluating the treatment response of visceral involvement.[24] In cases in which imaging is insufficient for the initial assessment of organ involvement, the diagnosis should be confirmed by biopsy.

Criteria for complete response after treatment: any organ that initially showed involvement should not appear enlarged on physical examination or imaging and should be observed as normal. Nodules should be present on liver or spleen imaging. Any mass observed on post-treatment imaging should be

biopsied to rule out a lymphoma diagnosis. An increase in liver or spleen size without new sites of involvement, along with a reduction of 50% or more in the SPD value of pre-existing liver and spleen nodules or any organ involvement after treatment, is considered a partial response. The presence of new organ involvement, more than 50% progression in the organ previously affected before treatment (to be determined by SPD value), or a loss of more than 50% of the response in a patient who had previously achieved partial response, constitute progressive disease. Conditions that do not meet the criteria for complete response, partial response, or progressive disease are classified as stable disease, whereas the observation of new organ involvement in a patient who previously achieved complete response should be considered a relapse.

In cases of localized skin recurrence in which no tumoral lesions are present, existing tumors show signs of regression, and no organ symptoms are evident; therefore, imaging is not necessary in asymptomatic early-stage patients. However, in patients with stage ≥ IIB, imaging should be used to evaluate the patient if new lymphadenopathy develops, in case of unexplained laboratory findings, histopathological examination reveals LCT or folliculotropism, or if clinical progression is detected.[4-6]

Prognosis

Rare cases of MF usually present with early-stage disease with a median survival of 10-35 years, but more than 25% progress to advanced disease with a median survival of less than 4 years.[25]

The CLIPi, developed from another retrospective cohort study of 1,502 patients with MF and SS in the United Kingdom, identified unfavorable factors in patients with early stage (IA-IIA) as male gender; age > 60 years; presence of plaque lesions; folliculotropic disease, and N1/Nx classification, whereas unfavorable factors in advanced stage (IIB-IVB) disease were male gender; age > 60 years, B1/B2, N2/3, and visceral involvement. In a retrospective study of 1,275 patients with advanced-stage MF or SS from 29 international centers, extracutaneous disease (stage IV), age > 60 years, transformation to large cell histology and increased LDH levels were independently associated with worse overall survival.[26,27]

Although clinical, demographic, hematologic, histopathologic, and genetic abnormalities associated with poor prognosis have been identified in addition to the TNMB staging system, these studies are small, single-center cohorts with inconsistencies. Therefore, the findings should be validated through large-scale, prospective, multicenter international studies. The TNMB staging system remains the best method for determining prognosis.

Follow-up Frequency

In patients with MF, cutaneous lymphoma, follow-up recommendations are for patients in complete remission, and treatment should be continued in patients with stable disease or partial remission. The goals of follow-up in patients with cutaneous lymphoma are to detect relapses and metastases, identify secondary lymphomas, and monitor for treatment-related side effects (such as psoralen photochemotherapy associated tumors). All patients with cutaneous lymphoma should be educated to regularly perform self-examination of their skin and palpation of LNs. Follow-up should be individualized based on clinical needs, and should be conducted throughout life.

There is no consensus regarding the follow-up of patients with MF and cutaneous lymphoma, and the follow-up intervals should be individually tailored according to the disease stage, primary cutaneous lymphoma subtype, and treatment agents used. According to the ESMO guidelines, for indolent types of cutaneous lymphoma, follow-up is recommended every 6-12 months for patients with stable disease or those in complete remission, whereas for active and progressive disease, follow-up visits are recommended every 4-6 weeks. These visits should primarily be based on patient history and physical examination, with additional tests (blood tests, histopathological examination, imaging) conducted only when necessary. Since relapses after complete remission or tumor response are often localized to the skin, there is generally no need to routinely use imaging methods in all follow-up visits after treatment.[6]

According to the S2k Guidelines, patients initially diagnosed with stage IA and IB should undergo detailed history-taking and physical examinations every 6 months for the first 5 years and annually thereafter. In this patient group, imaging methods such as LN ultrasound, CT, PET/CT, and blood tests are not necessary unless there is a suspicion of recurrence based on physical examination and history. Patients with stage IIA should undergo detailed history and physical examination every 3 months for the first 2 years, every 6 months in the 3rd, 4th, and 5th years, and annually thereafter. Regular LN ultrasonography and laboratory tests, including complete blood count and LDH levels, are recommended for follow-up. For patients with blood involvement beyond B0, Sézary cell counts and flow cytometric analysis are required during follow-up after remission. The frequency of follow-up for patients with advanced-stage disease should be determined on an individual basis.[4,15]

Conclusion

In the National Comprehensive Cancer Network Guidelines, although there are no specific recommendations regarding the follow-up frequency for patients with MF, the 2024 version of the Peripheral T-cell Lymphoma Guidelines suggests clinical and histopathological evaluations every 3-6 months during the first 2 years, followed by as-needed evaluations based on clinical necessity. Imaging methods are recommended every 6 months for the first 2 years, once annually between years 2 and 5, and thereafter only as clinically indicated.[5]

Footnotes

Authorship Contributions

Concept: S.Y., E.A., Design: S.Y., E.A., Data Collection or Processing: S.Y., E.A., Analysis or Interpretation: S.Y., E.A., Literature Search: S.Y., E.A., Writing: S.Y., E.A.

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