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Should we be imaging lymph nodes at initial diagnosis of early-stage mycosis fungoides? Results from the PROCLIP international Study

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Running head: Lymph node imaging in patch/plaque mycosis fungoides at initial diagnosis

What's already known about this topic?

- The indication for imaging in presentation of early mycosis fungoides (MF) without clinical lymphadenopathy is controversial.
- The literature on the outcome of imaging in early-stage presentation of MF is strikingly sparse.

What does this study add?

- Physical examination seems to be a poor determinant of radiological lymphadenopathy.
- Whereas enlarged LNs were palpated only in 5%, imaging detected 18% with at least stage IIA, mostly with plaques, and even rare cases with extensive lymphomatous nodes, stage IVA2.

Abstract

Background: Early-stage mycosis fungoides (MF) includes patients with dermatopathic lymph nodes (LNs) or early lymphomatous LN involvement. There is lack of unanimity among current guidelines regarding the indications for initial staging imaging in early-stage presentation of MF in the absence of enlarged palpable LNs.

Methods: Review of clinicopathologically confirmed newly diagnosed patients with cutaneous patch/plaque (T1/T2) MF from PROspective International Cutaneous Lymphoma Prognostic Index (PROCLIPi) data.

Results: PROCLIPi enrolled 375 patients with T1/T2 MF: 304 classical-MF and 71 folliculotropic-MF. Imaging was performed in 169 patients (45%; 83=CT, 18=PET/CT, 68=U/S); only 9 (5%) had palpable enlarged (≥ 15 mm) LNs, with an over-representation of plaques, irrespective of the 10% body-surface-area cutoff which distinguishes T1 from T2. Folliculotropic-MF was not more frequently imaged than classical-MF. Radiologically enlarged LNs (≥ 15 mm) were detected in 30 patients (18%); only 7 had clinical lymphadenopathy. On multivariate analysis, plaque presentation was the sole parameter significantly associated with radiologically enlarged LNs. Imaging of only clinically enlarged LNs upstaged 4% of patients (7/169) to at least IIA, whereas non-selective imaging upstaged another 14% (24/169). LN biopsy, performed in 8/30, identified N3 (extensive lymphomatous involvement) in 2, and N1 (dermatopathic changes) in 6.

Conclusion: Physical examination was a poor determinant of LN enlargement/involvement. Presence of plaques was associated with significant increase in identification of enlarged/involved LN in patients with early-stage presentation of MF, which may be important when deciding who to image. Imaging increases detection rate of stage-IIA, and identifies rare cases of extensive lymphomatous nodes, upstaging them to advanced-stage IVA2.

Introduction

Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma, is staged in 4 compartments: skin (T), node (N), metastasis (M), and blood (B)¹ (Table 1). Early-stage MF is characterized by the presence of cutaneous patches and/or plaques (T1ab, T2a,b) with no or low level MF blood involvement (B0, B1; N0, M0: stages IA-IB) or with a dermatopathic/low level MF nodal involvement (N1-N2,M0: stage IIA). The prognosis is typically good. However, patients with advanced-stage MF, particularly those with lymphomatous nodal disease (IVA2), have a very poor prognosis² requiring intensive immunotherapy/chemotherapy regimens. Hence detecting patients with early-stage skin lesions but lymphomatous nodes is of prognostic and therapeutic implications.

The 2007 guidelines of the International Society of Cutaneous Lymphoma and the European Organization of Research and Treatment of Cancer (ISCL/EORTC) recommend computed tomography (CT) or whole-body integrated positron emission tomography (PET)/CT, for all patients except those staged T1N0M0B0 and selected patients with limited T2N0M0B0 disease, in whom ultrasound (U/S) study of peripheral LNs is optional.¹ However, there is still a lack of unanimity among other guidelines regarding the indications for initial staging imaging in early-stage presentation of mycosis fungoides (MF) in the absence of enlarged palpable LNs, and the optimal type of imaging³⁻⁵ (Table S1).

The literature on the outcome of imaging in early-stage presentation of MF is strikingly sparse. The 2 most cited studies were published in 1986 and 1990 included a small series of patients with newly diagnosed early MF. All underwent CT of the abdomen and pelvis only, and findings were normal.^{6,7} The largest series of MF published so far lack any information on imaging.⁸⁻¹¹ It remains unclear if imaging is useful in the management of early-stage presentation of MF and if there are disease characteristics which should favor imaging.

Meaningful studies in rare diseases require large-scale international collaborations to power them. This study analysed data collected from the PROCLIP (PROspective

International Cutaneous Lymphoma Prognostic Index) database for MF which includes prospective pre-defined datasets collected at 29 expert skin lymphoma centres from 15 countries across 5 continents. We aimed to investigate how often imaging is performed in patients with early-stage presentation of MF, to assess the yield of LN imaging, and to determine what disease characteristics promoted imaging.

Methods

The cohort included all newly diagnosed patients with early-stage presentation of MF (T1/T2) who were enrolled in the PROCLIP study from July 2015 to June 2018. Patients require to pass a vigorous central clinicopathological review process for inclusion as described previously.¹² The relevant parameters were retrieved from the PROCLIP master database. Imaging reports of enlarged LNs and histopathologic reports of LN biopsies were reviewed, and the LN biopsies were examined by a Central Review Committee member (R.W.).

Patients were staged according to ISCL/EORTC/USCLC criteria^{1,13} (Table 1). A palpable peripheral LN measuring $\geq 15\text{mm}$ was considered clinically enlarged.¹ A LN site was considered radiologically positive if any LN measured $\geq 15\text{mm}$ in its long-axis diameter, as defined by the ISCL/EORTC/USCLC.¹ The short-axis LN diameter was also recorded, in line with the suggestion that LNs with a short axis ($>10\text{mm}$) may also be regarded as enlarged in MF.¹³ Radiologically, 6 peripheral sites (right/left supraclavicular-cervical, axilla, inguino-femoral) and 2 central sites (thoracic, abdominopelvic) were measured, if possible/relevant.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or median and range. The nonparametric Mann-Whitney test was used to compare median values of non-normally distributed data between groups, and Fisher's exact test was used to compare dichotomous data. T-class was compared between patients with and without LN enlargement using chi-square test. Univariate logistic and multivariate regression models were formulated to analyze the association of clinical parameters with enlarged LN on imaging. A two-tailed P value <0.05 was considered statistically significant. The statistical analysis was conducted with SPSS ver. 21 and SAS ver. 9.4.

Results

Clinical characteristics

The cohort included 375 patients with confirmed early-stage skin and histology from 29 centres. The median age was 56 years (range, 5-97): 304 (81%) had classical MF (or variants) and 71 (19%) had folliculotopic MF (FMF). Median score on the modified Severity Weighted Assessment Tool (mSWAT) was 11 (range 0.5-120). The distribution of T-classes is shown in Table 2. In 10 patients (2.7%), enlarged LNs were detected by clinical examination, including 7 with T2b disease and 1 each with T2a, T1b, and T1a; none was suspected to have systemic extranodal involvement.

One additional patient with patch/plaque presentation of MF was excluded from the analysis because he was found to have B2 (high blood burden) disease on initial investigation.

Predictors of imaging

LN imaging was performed in 169 patients (45%), including 9/10 patients with clinically enlarged LNs: CT ($n=83$) or PET/CT ($n=18$) in 101 and U/S in 68.

Comparison of the imaged and non-imaged patients showed that the frequency of imaging significantly differed by T-class; patients with plaque presentation underwent imaging more often than patients with patch MF, irrespective of the 10% BSA cutoff that distinguishes T1 from T2 (Table 2). There was no difference in the distribution of the types of MF (classical, FMF, Table 2), age (median 57 years vs. 55 years; mean 56.2 years vs. 54.2 years, $P=0.265$, logistic regression) or mSWAT score (median 10 vs 11; mean 18.7 ± 19.9 vs 21.1 ± 24.9 , $P=0.290$, logistic regression) between the imaged and non-imaged patients.

CT or PET/CT was used significantly more often for T2b disease, and U/S, for T1a disease (Table S2). Patients with plaques were more frequently evaluated by CT or PET/CT than patients with patch MF (73.3% vs. 26.7%, $P=0.001$, Fisher's exact test).

Analysis by site revealed differences in regional (institution-based) staging approaches in terms of imaging modality and frequency. In most of the centres, at least one type of imaging was done (U/S in 12 and CT or Pet/CT in 18) whereas in 7 centres, no imaging was done (Fig. 1). In none of the 3 participating institutions from the USA was U/S used in the staging workup.

Radiological findings and characteristics of patients with radiologically enlarged LNs

Imaging revealed enlarged LNs in 30 patients (17.8% of all imaged patients): CT in 18, PET/CT in 5, U/S in 7. The mean long-axis LN diameter was 22.2 ± 5.9 mm (median 21 mm; range 15-43 mm), and the mean short-axis, 12.5 ± 5.4 mm (median 11 mm; range 4-25 mm). Both diameters were provided for each site in 28 cases; in 16, both were considered abnormal (Table S3). The T-class distribution was as follows: 53% T2b, 30% T1b, 10% T1a, and 7% T2a. Twenty-four patients had classical MF (6 with clinically enlarged LNs) and 6 had FMF (1 with clinically enlarged LNs). Two patients had B1 disease.

There was no difference in the distribution MF types (classic, FMF) between patients with or without radiologically enlarged LNs ($P=0.797$, Fisher's exact test). On univariate regression (Table 3) analysis of images, LN enlargement was significantly associated with plaque (T2b- 31%, T1b- 17%) than patch (T2a- 9% T1a- 7%) disease, T2b than T1a class, and T2b than all the other classes. Positive imaging was also associated with a significantly higher median mSWAT score compared to no enlarged LNs on imaging (26 versus 10, mean 35.4 ± 33.1 vs. 18.1 ± 21.7). LN enlargement was not associated with B (0,1) class or blood clonal status. On multivariate analysis (Table 3) the presence of plaques was the sole significant parameter associated with radiologically enlarged LN.

Imaging detected peripheral lymphadenopathy in 29/30 patients, usually at the axilla and inguinal regions, and central lymphadenopathy alone in 1 patient. A median of 2 positive nodal regions (range 1-5) were detected. The distribution of the number of regions (≥ 2) with enlarged LNs across T-classes is presented in Table 2.

LN biopsy

Eight patients underwent LN biopsy (Table 4). Seven had radiologically enlarged LNs (6, both diameters and 1, long diameter only). In the eighth patient, LN measured <15 mm on PET-CT and U/S, but an abnormal LN structure was detected on U/S (patient #4). Half the patients did not have lymphadenopathy based on physical examination (including patient #4). All but 1 patient had plaque MF. Excision biopsy, considered the gold standard of LN sampling, was performed in 6 patients, and image-guided core biopsy, recently reported to be an accurate alternative sampling method,¹⁴ in 2 patients. Central pathology review confirmed 2 patients to have N3 disease, both T1b, only 1 with palpable LNs (and the other 1 with palpable LNs and large cell transformation in the skin), and were therefore upstaged to IVA2. The other 6 had N1 disease and were stage IIA.

The reason why 23 of the 30 patients with radiologically enlarged LNs did not undergo LN biopsy was not recorded. There were no significant differences in any of the following parameters between those who underwent LN biopsy and those who did not: age (median 49.5 years vs. 66 years; mean 51.6 years vs. 62.9 years, $P=0.102$, logistic regression) median maximal long-axis diameter (20mm, range: 15-33mm vs 23mm, range: 20-43mm; Mann Whitney, $P=0.133$), median maximal short-axis diameter (10mm, range: 4-25mm vs 12mm, range: 6-22mm; Mann Whitney, $P=0.221$), and mSWAT (30, range 6.0-99.8 vs. 22, range 1.8-100; Mann Whitney, $P=0.540$).

Post-imaging final staging

The final staging of the 169 patients who underwent imaging was as follows: IA/IB, 136 patients (80.5%); IIA, 31 (18.3%); IVA2, 2 (1.2%) (Fig. 2). Imaging-based upstaging to at least IIA occurred in 4% of patients (7/169) with clinically enlarged LNs and an additional 14% of patients (24/169) who underwent nonselective imaging (i.e., in the absence of clinically enlarged LNs).

Discussion

Analysis of cases of early-stage presentation (patches/plaques) of MF in the PROCLIFI Study database provided a unique opportunity to examine how clinicians implement the current imaging guidelines in daily practice and the yield of imaging in this patient group. This is the first large registry study of the frequency and methods of LN assessment in patients with clinicopathologically confirmed patch/plaque MF. We found that only a small fraction of early-stage MF patients (2.7%) had palpable enlarged LNs. The highest prevalence was found in patients with T2b (6.8% of all T2b patients). Almost half the 375 patients underwent imaging at diagnosis. Although the ISCL and NCCN guidelines recommend imaging for T2 disease, in our cohort, patients with plaques were more frequently imaged than those with patches, irrespective of T stage (T1 or T2). Another striking deviation from the NCCN guidelines was the similar imaging frequency for the variant FMF as for classical MF.³

Regarding the selected imaging modality, CT or PET /CT was used more often for plaque-type MF, and U/S, for patch-type MF, although imaging type also varied between institutions. The type of imaging selected might also be dictated by insurance policies in some countries, which may explain the more frequent use of CT than PET/CT (83 vs 18 patients) in our cohort. The neck was included in the routine CT scan in almost all patients

despite the current recommendations that CT be routinely limited to the chest/abdomen/pelvis to avoid the additional radiation.^{1,3,4}

LN enlargement was detected in 18% (n=30) of the 169 patients who underwent imaging. The Imaging reports were reviewed centrally but not the scans which are open to interpretation. Only 7 patients selected for imaging had clinically enlarged LNs. Thus, our study indicates for the first time in a large cohort of patients with early-stage presentation of MF, that physical examination seems to be a poor determinant of enlarged LN and may provide false-negative results in up to 14% of patients. In addition, false-positive results (clinical enlarged LNs and radiological normal LNs) were found in 2 patients. Accordingly, in studies of systemic lymphoma, clinical evaluation missed 12-13% of the patients with adenopathy on US imaging.^{15,16} The highest rate of radiologically enlarged LNs was found in patients with plaques (T2b=31%, T1b=17%) and the lowest, in patients with patch-only MF. The mSWAT score, which combines the BSA with type of lesion, was significantly higher in patients with than without radiologically enlarged LNs. Multivariate analysis confirmed plaques as the only significant parameter associated with a likelihood of LN enlargement. Radiological lymphadenopathy was not more frequent with FMF than with classical MF, supporting the very recent studies suggesting that early-FMF does not behave more aggressively than early-classical MF.^{17,18}

All major current guidelines recommend LN biopsy for accurate staging in patients with proven lymphadenopathy^{1,3,4} because this affects prognosis and management. However, only about a quarter of the 30 patients with radiological lymphadenopathy underwent LN biopsy. This low rate is not unexpected.^{9,19} Reasons for not performing LN biopsy include, among others, procedural morbidity, patient refusal, and inaccessible enlarged LN.¹⁹ Similar to a previous report on rare cases of lymphomatous LNs in patch/plaque disease,⁸ central histological review confirmed that 2 of 8 biopsied patients had N3 disease, upstaging them to IVA2. This is important because these patients generally require immediate systemic therapy and have a predicted median survival of 1 year.² The other 6/8 had confirmed dermatopathic nodes (N1). The prognostic implication of N1 is not well established. In the sole large single-centre retrospective study comparing N0 and N1 classification by T-class,⁸ N1 was found to affect disease-specific survival in patients with stage T2 (T2N1, n=56 compared to T2N0 n=133), but there were too few T1 cases for analysis. Future long-term follow-up study of our PROCLIP cases will help to determine the accurate prognosis of stage IIA.

The study has several limitations. First, less than half the patients underwent imaging. It is unknown if the 206 patients who were not imaged had a similar prevalence of

radiological lymphadenopathy as the imaged patients. However, we assume it was lower, because the non-imaged group included fewer patients with plaque presentation/disease. Second, the majority of cases staged IIA were based on Nx designation, as no LN biopsy was performed; thus, their accurate final stage is lacking and the possibility that some of them may in fact have N3 and thus advanced -stage disease cannot be ruled out. Thirdly the imaging scans were not subject to central review and only the written reports of those with radiologically enlarged LN were reviewed. Forth, in some patients, biopsies were not obtained from the largest LN, possibly missing N3. Last, the number of patients who underwent LN biopsies was too small to establish a profile of patients at increased risk of N3 disease.

In summary, the results of this PROCLIP study of early-stage presentation of MF show that clinical palpation seems to be a poor determinant of radiological lymphadenopathy. Enlarged LNs on imaging are more frequently associated with plaques and a higher mSWAT, but not FMF and this may be considered when selecting early-stage patients for imaging. Most enlarged LNs were dermatopathic but 2/8 had extensive LN involvement indicating stage IVA2 disease. Therefore, for accurate staging of patients with patch/plaque MF, imaging is needed to detect at least IIA disease, especially in the presence of plaques, as palpation for clinical lymphadenopathy is unreliable. Clinicians should be aware that although rare, patients with early-stage presentation of MF may have extensive lymphomatous nodes.

Appendix A. Supplementary data

Supplementary data attached.

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Legends to Figures

Fig. 1 Imaging approach in the 29 sites participating in PROCLIP study

Fig. 2 Flow diagram of outcome of LN radiological evaluation in 169 imaged patients with patch/plaque presentation of MF

Table 1 Modified ISCL/EORTC revisions to the staging of mycosis fungoides/Sézary syndrome¹

Stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1,2, X	0	0, 1
IIB	3	0-2, X	0	0, 1
IIIA	4	0-2, X	0	0
IIIB	4	0-2, X	0	1
IVA ₁	1-4	0-2, X	0	2
IVA ₂	1-4	3	0	0-2
IVB	1-4	0-3, X	1	0-2

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organization for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; X, clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories

¹ adapted from Olsen E. *blood*. 2007

Table 2. The distribution of the T classes, type of lesions, T1/T2, and mycosis fungoides type and the results of physical examination and imaging findings of lymph nodes in patch-plaque mycosis fungoides patients

	Parameter	Imaged cases n (% of total)	P	Odds ratio 95% confidence limits	Clinically enlarged LN n (% of total)¶	Radiologically enlarged LN n (% of total)¥	LN sites ≥2 n (% of total)¶
Total (%)	375 (100)	169 (45.2)			10 (2.7)	30 (8.0)	18 (4.8)
T class, n	T1a, 103	41 (39.8)	0.003*		1 (1.0)	3 (2.9)	1 (1.0)
	T1b, 96	54 (56.3)			1 (1.0)	9 (9.4)	6 (6.3)
	T2a, 73	22 (30.1)			1 (1.4)	2 (2.7)	1 (1.4)
	T2b, 103	52 (50.5)			7 (6.8)	16 (15.5)	10 (9.7)
Type of lesion, n	Patch, 176	63 (35.8)	0.001**	1.471 (1.167-1.855)	2 (1.1)	5 (2.8)	2 (1.1)
	Plaque, 199	106 (53.3)			8 (4.0)	25 (12.6)	16 (8)
T1 vs. T2, n	T1, 199	95 (47.7)	0.299**	0.898 (0.908-1.408)	2 (1.0)	12 (6.0)	7 (3.5)
	T2, 176	74 (42.0)			8 (4.5)	18 (10.2)	11 (6.3)
MF type, n	Classic, 304	138 (45.4)	0.895**	0.987 (0.895-1.088)	9 (3.0)	24 (7.9)	13 (4.3)
	FMF, 71	31 (43.7)			1 (1.4)	6 (8.5)	5 (7.0)

Abbreviations: MF, mycosis fungoides; FMF, folliculotropic MF; LN, lymph node; n, number

*Chi square test.

**Fisher's exact test.

¶Statistical analysis was not performed due to limited number of patients.

¥See Table 3 for statistical analysis.

Table 3. Univariate and multivariate analyses of the associations between radiologically enlarged lymph nodes of type of lesion (patch vs plaque) or T class

Analysis	Parameter	Odds ratio	P	95% confidence limits
Univariate	Plaque vs patch	3.580	0.014*	1.294-9.905
	T1b vs T1a	2.533	0.186	0.640-10.031
	T2a vs T1a	1.267	0.804	0.195-8.213
	T2b vs T1a	5.630	0.010*	1.512-20.962
	T2b vs others	3.270	0.004*	1.542-7.361
	T2b vs T1b	2.891	0.091	0.880-5.614
	T2 vs T1	2.223	0.052	0.994-4.974
	mSWAT score	1.023	0.001*	1.009-1.037
	B stage	1.170	0.848	0.236-5.807
	Relevant blood clone**	1.143	0.859	0.261-5.005
Multivariate	Plaque vs patch	3.300	0.023*	1.183-9.209
	T2 vs T1	1.986	0.102	0.874-4.516

*Statistically significant.

**Identical clone in blood and skin.

Table 4. Summary of patch/plaque mycosis fungoides cases undergoing lymph node biopsy

Pt	PRC No.	Sex/age	WHO class	T	B	Blood clone	Skin clone	Clinical ≥15mm	Imaging	Image ≥15mm	Enlarged LN sites	Max length	Max width	Biopsy site	Biopsy Type	LN length	LN width	Calc N	LN clone	Final Stage
1	103	F/70	FMF*	T1b	B1	***	+	No	PET/CT	Yes	1	23	21	Rt cervical/supraclavicular	Excision	23	21	N3	NR	IVA2
2	275	F/42	Class.	T2b	B0	-	+	No	CT	Yes	2	20	6	Rt axilla	Excision	20	5	N1	NR	IIA
3	462	M/72	Class.	T2b	B0	NR	-	No	PET/CT***	No	0	12	NR	Lt inguinal/femoral	Excision	NR	NR	N1	+^	IIA
4	552	M/55	Class.	T1b	B0	-	+	No	CT	Yes	3	25	11	Rt axilla	Excision	25	11	N1	NR	IIA
5	637	M/61	Class.	T2b	B0	-	+	Yes	CT	Yes	4	43	17	Rt axilla	Excision	20	10	N1	-	IIA
6	719	M/44	FMF	T2b	B0	-	+	Yes	CT	Yes	5	27	12	Rt axilla	Excision	22	12	N1	-	IIA
7	908	M/28	Class.	T1b	B0	-	NR	Yes	CT	Yes	2	20	20	Rt axilla	Guided core	20	20	N3	NR	IVA2
8	913	M/41	Class.	T2a	Bx	NR	NR	Yes	CT	Yes	1	21	12	Axilla	Guided core	21	12	N1	NR	IIA

Abbreviations: + positive; - negative; LN, lymph node; NR, not recorded; class, classic; FMF, folliculotropic MF

*had large cell transformation in the skin lesion.

**identical to skin.

***U/S of inguinal LN showed features "typical for lymphoma"

^non-identical to skin.

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Fig. 1.

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