The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients


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Summary

Background Survival in mycosis fungoides (MF) is varied and may be poor. The PROCLIPI (PROspective Cutaneous Lymphoma International Prognostic Index) study is a web-based data collection system for early-stage MF with legal data-sharing agreements permitting international collaboration in a rare cancer with complex pathology. Clinicopathological data must be 100% complete and in-built intelligence in the database system ensures accurate staging.

Objectives To develop a prognostic index for MF.

Methods Predefined datasets for clinical, haematological, radiological, immunohistochemical, genotypic, treatment and quality of life are collected at first diagnosis of MF and annually to test against survival. Biobanked tissue samples are recorded within a Federated Biobank for translational studies.

Results In total, 430 patients were enrolled from 29 centres in 15 countries spanning five continents. Altogether, 348 were confirmed as having early-stage MF at central review. The majority had classical MF (81.6%) with a CD4 phenotype (88.2%). Folliculotropic MF was diagnosed in 17.8%. Most presented with stage I (IA: 49.4%; IB: 42.8%), but 7.8% presented with enlarged lymph nodes (stage IIA). A diagnostic delay between first symptom development and initial diagnosis was frequent (85.6%; median delay 36 months (interquartile range 12–90)). This highlights the difficulties in accurate diagnosis, which includes lack of a singular diagnostic test for MF.

Conclusions This confirmed early-stage MF cohort is being followed-up to identify prognostic factors, which may allow better management and improve survival by identifying patients at risk of disease progression. This study design is a useful model for collaboration in other rare diseases, especially where pathological diagnosis can be complex.
Mycosis fungoides (MF) is a rare skin cancer, with an incidence of < 1 per 100,000 but a much higher prevalence given the long survival in early-stage disease (stages IA–IIA). Meaningful studies in rare diseases require large-scale international collaborations to power them. Such collaboration requires expert coordination, accessible data-collection systems and legal data-share agreements to be implemented, which is challenging. Here we present the PROCLIPI (PROspective International Cutaneous Lymphoma Prognostic Index) study for early-stage MF as a prototype study for international collaborations in rare disease and present our initial findings and central review process.

Diagnosis of early-stage MF (IA–IIA) is complex owing to a number of factors, including varied clinical appearance and similarity to inflammatory skin diseases such as eczema/psoriasis, subtle variations in pathological/immunohistochemical features and lack of a singular specific diagnostic test. Indeed, interobserver variation for diagnosis of T-cell lymphomas, including MF, is well recognized and a definite diagnosis often requires careful clinicopathological correlation, with discordance in diagnosis of ~20%. Hence, misdiagnosis and diagnostic delay are frequent. To confirm diagnosis in PROCLIPI, all recruited patients were subject to expert central clinicopathological review. This is of paramount importance to ensure patients meet criteria for a diagnosis of early-stage MF and those with benign inflammatory dermatoses are rejected.

Patients with early-stage MF typically have a slowly progressive evolution over years, or even decades, to widespread patches or more infiltrated plaques. Morbidity can be considerable, with pain, pruritus and disfigurement experienced, and patients have been demonstrated to have a poor quality of life. However, disease-specific mortality may occur in some patients, and up to one-third of patients presenting with early-stage disease progress within 10 years to advanced stage disease (IIB–IVB), characterized by cutaneous tumours or erythroderma and/or nodal/leukemic/visceral involvement. If patients with a poor prognosis could be preselected and referred for more intensive management there may be improved disease control and, potentially, survival. Given the rarity of MF, only a large international multicentre prospective study will improve our understanding and allow better diagnostic tests for more efficient diagnosis.

Specific clinical characteristics have been associated with a worse prognosis in MF. However, most are associated with advanced-stage disease and their relevance in early-stage disease is unknown. These include male sex, higher age, raised serum lactate dehydrogenase (LDH) and histological features, such as folliculotropism and large-cell transformation (LCT). Some favourable prognostic factors have been identified for early-stage disease and include poikiloderma, hypopigmented patches, a CD8+ phenotype and coexisting lymphomatoid papulosis. However, these studies are typically single-centre cohorts and there is frequent discordance between reports. Benton et al. developed a cutaneous lymphoma prognostic index, but future publications could not validate this, and large international collaborations are required to develop useful prospective indices. An international prognostic index may select patients with early MF at higher risk of disease progression for improved management choices.

**Patients and methods**

**Study design and patients**

Datasets (Appendix S1; see Supporting Information) were prospectively defined by the Cutaneous Lymphoma...
International Consortium over a series of meetings and teleconferences (2012–14). A secure web-based data system was designed by University Hospital Birmingham (UHB) with in-built intelligence to stage patients that does not allow data to be saved unless clinicopathological datasets are complete. (This database is housed on a secure UHB server, which is a secure SQL Server housed behind Threat Management Gateway and firewalls. The security of both the web application and technical infrastructure has been penetration-tested by an independent ethical hack/security company.) Selected fields are duplicated to cross-check for data consistency. No patient-identifiable data are shared and patients are anonymised centrally.

Specialist international centres treating MF were selected via membership to expert international groups (European Organisation for Research and Treatment of Cancer, International Society for Cutaneous Lymphoma). A data-sharing agreement was signed between each participating centre and UHB. (On most occasions the generic agreement was signed, but owing to the complexity of data sharing and different stipulations between countries, if required, minor amendments were made.)

Since July 2015, all patients referred to the participating centres with a new diagnosis of early-stage MF within the prior 6 months were eligible. The study was reviewed and approved by local ethical committees/institutional review boards prior to recruitment. Patients were given verbal and written patient information about PROCLIPI in their native language. Written consent for participation in this study, analysis of data and use of blood, skin and lymph tissue for future study was signed between each participating centre and UHB. (On most occasions the generic consent was signed, but owing to the complexity, a Data Monitoring Committee (Appendix S3; see Supporting Information) manually reviews data for inaccuracies. Queries are raised to the respective institutions if data inaccuracies are suspected and for missed updates.

Central review

All patients were subject to a clinicopathological review prior to the patient’s data being included in the analysis. This was performed to confirm early-stage MF and prevent inclusion of patients with either reactive skin changes or advanced MF. Three internationally recognized leading dermatologists and dermatopathology specialists formed the central review panel (R.W., L.C., W.K.). The diagnosis of early-stage MF was based on a combination of clinical, histopathological and immunophenotypical criteria, as published previously. An initial virtual review of representative clinical photographs of cutaneous lesions together with photomicrographs of haematoxylin and eosin, CD3, CD4 and CD8 stains was performed. In unclear cases, slides were requested to have a real-time central review. Details of the review processes are described in Appendix S4 (see Supporting Information).

Statistical analysis

The Kruskal–Wallis test was used to analyse difference in medians for the nonparametric continuous variables. The $X^2$-test was used to determine differences in categorical variables. Nonparametric continuous variables are presented as medians and interquartile ranges (IQR). Analyses were performed using STATA SE version 15 (StataCorp, College Station, TX, U.S.A.).

Results

Central review

Twenty-nine international centres enrolled 430 patients (Fig. 1). Centres unable to comply with the central review process were not eligible for inclusion. Virtual central review confirmed 329 patients as having early-stage MF. Sixty-four were referred for a real-time central review and 37 failed (13 advanced-stage MF and 24 nondiagnostic of MF). Real-time review was possible for 41 of 64 patients (64-1%), with 19 of 41 (46-3%) passing. At the time of writing, 23 are awaiting real-time review; thus, 407 of 430 patients (94-6%) have completed central review; 348 of 407 patients (85-5%) were confirmed as having early-stage MF, 16 of 407 (3-9%) had advanced-stage disease and 43 of 407 (10-5%) were diagnostic of MF (10-6%) (Fig. 2).

This report focuses on the 348 patients passing the central review process. However, all patients entered into the PROCLIPI database are followed-up as it is appreciated some of weighted assessment tool (mSWAT), which reflects skin tumour burden and provides a numerical value between 0 and 400, blood classification and overall stage (using TNMB). Additionally, a Data Monitoring Committee (Appendix S3; see Supporting Information) manually reviews data for inaccuracies. Queries are raised to the respective institutions if data inaccuracies are suspected and for missed updates.
these patients may develop MF or have true MF, which could not be confirmed by the central review process. In reality, all these patients may be receiving MF treatment at their local centre.

**Patient demographics**

Of the 348 patients, there was a male predominance [219 males, 129 females (ratio 1.7 : 1)]. Table 1 shows the clinical characteristics of the patients.

In total, 172 patients (49.4%) had clinical stage IA MF, 149 (42.8%) had stage IB MF and 27 (7.8%) had stage IIA MF. Median age at diagnosis was 57 years (IQR 44–67), without significant differences between stage IA (median age 54 years; IQR 44–66), stage IB (median age 57 years; IQR 45–67) and stage IIA [median age 61 years; IQR 44–73 (P = 0.285)]. In total, 298 patients (85.6%) reported a diagnostic delay, with a median delay of 36 months (IQR 12–9). This was similar for all stages (P = 0.141): 36 months (IQR 12–72) for stage IA; 48 months (IQR 24–100) for stage IB; and 33 months (IQR...
15–87) for stage IIA. Eastern Cooperative Oncology Group (ECOG) scores were 0 in 338 patients, 1 in eight patients, 2 in one patient and 4 in one patient.

The median mSWAT score at diagnosis of stage IA was 5 (IQR 2–8), 26 (IQR 17–45) for stage IB and 32.2 (IQR 11–70) for IIA. The clinical phenotype was patch-only lesions in 160 patients (46%), significantly more often in stage IA/B (53.5% and 42.3%, respectively) than IIA (18.5%; P = 0.002). Fifty-five patients (14.9%) had plaque-only lesions, 31 of 172 (18.0%) with stage IA MF, 18 of 149 (12.1%) with IB MF and three of 27 (11.1%) with IIA MF. The remaining 136 patients (39.1%) had coexisting patches and plaques. Other clinical features recorded included follicular lesions (24-4%), poikiloderma (15.2%) and hypopigmented lesions (8.0%).

Follicular lesions (clinical lesions of MF showing predilection for hair follicles and include follicular papules, plaques, alopecia, milia and cysts) were present in 85 patients; 67 received a diagnosis of folliculotropic MF (FMF), but follicular lesions also occur in classical MF. Follicular lesions were less common in patients with IA MF (14.4%) than type IB (32.2%) or IIA (26.0%) MF (P = 0.009). While poikiloderma and hypopigmentation were found at a similar frequency in all stages (P = 0.452 and P = 0.313, respectively), there was a positive association with patches. Twelve (3.4%) patients had coexisting lymphomatoid papulosis lesions, which is similar to what has previously been reported.15,16

### Skin histology and clonality

From central pathology review, 284 patients had classical MF (81.6%), 62 (17.8%) had FMF and two syringotropic MF (0.6%). The T-cell phenotype was CD4+ in 307 patients (88.2%). In the 41 with negatively staining CD4 tumour cells, 34 were CD4–CD8+. In addition to CD4 positivity, seven also had tumour cells that stained CD4+CD8+. Six patients (1.7%) had LCT in the skin, two of whom had FMF.

Not all sites perform T-cell receptor (TCR) gene analysis in the skin. This was recorded in 205 patients and was clonal in 132 patients (64.4%) at a similar percentage in all stages (P = 0.848); 70 of 109 (64.2%) with stage IA MF, 46 of 73 (63.0%) with stage IB MF and 16 of 23 (69.6%) with stage IIA MF.

### Haematological parameters and serum lactate dehydrogenase

B-classification data were available in 121 of 348 patients and was B0 in 96 of 121 patients (79.3%) and B1 in 25 of 121 patients (20.7%; Table 2). By staging definition, no patients had B2, which is a criterion for advanced-stage disease (≥ IV1A). Of the 25 patients with B1, 10 of 55 (18.2%) had stage IA MF, 12 of 46 (26.1%) had stage IB MF and three of 21 (14.3%) stage IIA MF. Only 33.6% had TCR in blood tested and this was clonal in 8.5% (n = 10). Full blood count and differential was tested in 68.7%. Lymphopenia was a frequent abnormality found in 10.3%; 1.7% had lymphocytosis.

LDH was recorded in 244 of 348 patients (70.1%) and was raised in 27 patients (11.1%), particularly in stage IIA (n = 10/23; 43.5%) with respect to stage IA (n = 8/120; 6.7%) and stage IB MF (n = 9/101; 8.9%) (P < 0.001).

### Lymph node involvement

Radiological imaging was not mandatory for this study. It was performed in 143 patients (41.1%); 23 of 143 patients (16.1%) had LN enlargement by computed tomography criteria for MF, defined as ≥ 15 mm in the greatest diameter (long
axis). By staging definition, these patients have stage IIA MF. No patients had visceral disease, which would be an advanced stage (IVB).

Of the 23 patients with enlarged LN on imaging, nine had enlarged nodes at one region, whereas the remaining had ≥2 (five at two regions, four at three regions, four at four regions and one at more than five regions). Lymphadenopathy was mostly found at peripheral sites (69.5% inguinal/femoral, 56.5% axillary and 21.7% cervical). Only one patient had centrally enlarged LN (one abdominal). Six patients had an LN biopsy: four were classed as N1 (dermatopathic lymphadenopathy) and two as N2 (early nodal involvement).25 The remaining 21 patients with stage IIA MF were recorded as Nx (four with LN identified by clinical exam alone, no imaging/biopsy and 17 with LN identified on imaging without biopsy).

### Discussion

PROCLIPI is a prototype data collection study for rare cancers. The PROCLIPI database is an easily accessible secure web-based system with predefined datasets to allow prospective collection of international data. This unique database checks the accuracy of information using in-built intelligence, which auto-calculates stage, prevents entry of obscure data and disallows saving of incomplete data. In addition, once a year a Data Monitoring Committee (Appendix S1; see Supporting Information) trawls data for inaccuracies, which are then raised as queries to centres. Legal data-sharing agreements allow anonymized international data share. An associated Federated Biobank registers tissue stored for future translational studies, providing an invaluable resource of detailed clinicopathological/genotypic data linked to pretreatment biobanked samples.

In 3 years, PROCLIPI recruited a cohort of 430 patients suspected as having early-stage MF from 29 centres in 15 countries spanning five continents. This unprecedented collaboration will test parameters recorded against survival to develop a prognostic index powered to identify patients with early-stage MF at higher risk of disease progression.

Diagnosis of early-stage MF is complex.2 Hence, all enrolled patients are subject to a rigorous clinicopathological review. Overall, the central review process was concordant with the diagnosis of early-stage MF in 85.5% of patients, with most ‘passing’ on the initial ‘virtual central review’ process. Forty-one patients had real-time review and the ‘pass rate’ was 46.3%. Failure of central review was due to advanced-stage disease (3.9%) and nondiagnosis (10.6%). Interestingly, despite the strict criteria for passing central review, of those tested for T-cell clonality in skin (performed at individual sites despite the strict criteria for passing central review, of those 46.3% of patients, with most ‘passing’ on the initial ‘virtual central review’ process. Forty-one patients had real-time review and the ‘pass rate’ was 46.3%. Failure of central review was due to advanced-stage disease (3.9%) and nondiagnosis (10.6%). 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In 85-6% of patients, there was a diagnostic delay (median 36 months, not including time for central review) from onset of lesions to diagnosis of early MF in participating centres, highlighting the need for improved diagnostic tests in early-stage MF. Most patients presented with stage I (49-4% stage IA, 42-8% stage IB), but 7-8% presented with nodal enlargement (stage IIA). No difference in delay was noted between stages, suggesting that stages IB–IIA are not late diagnoses of patients with stage 'I' MF. It could be interpreted that a delay does not result in progression of skin involvement (to a higher stage at least). Nonetheless, delay can be stressful for patients and has the potential to lead to inappropriate treatments. Indeed, at worst, misdiagnosis, particularly when followed by inappropriate use of immunosuppressive therapy, may result in a more rapid disease progression.²³

Most (81-6%) presented with classical MF and 17-8% with FMF, ratified at central review. FMF has previously been associated with more aggressive disease and a prognosis more similar to tumour-stage disease.⁷ However, recent publications have shown a subgroup of patients with FMF with early-stage disease with a good prognosis;³⁰–³² these patients will be tracked to determine the prognostic relevance of FMF in early-stage MF.

Distinguishing patches from plaques of MF is subjective but may determine treatment approaches in early-stage disease.³³,³⁴ Benton et al. found the presence of plaques to be an independent factor for poor survival in early-stage disease,¹⁰ but an adverse outcome due to plaque lesions at diagnosis has not been shown in a prospective study. The revised 2007 staging guidelines do not include plaques as a determinant of stage but recommended recording the presence of patch only or patches/plaques ('a' for patches and 'b' for patches/plaques). In total, 46-0% of our cohort presented with patch-only disease and 39-1% with patches/plaques. Plaques were seen in 46-5% with stage IA MF but were more frequent in IB disease (57-7%; P = 0-045).

The majority of patients (97-1%) presented in good health, with an ECOG score of 0. There was a male predominance with male : female ratio of 1:7 : 1; median age of presentation was 57 years (IQR 44–67), with no difference between stages. This is significantly younger than the median age of 64-5 years (IQR 55–74) of the cohort of 1275 patients with advanced-stage MF reported by our group (P < 0-001).¹⁵ This retrospective analysis of advanced-stage MF found age > 60 years, LCT in skin, stage IV and raised LDH all to be independent factors with a worse prognosis,¹² but the significance of these findings in early-stage MF is unknown. In this early cohort LCT was verified at central review in 1-7% of cases. A raised serum LDH was found in 11-1% and was significantly raised in stage IIA MF (43-5%) compared with stage IA (6-7%) and IB (8-9%) MF (P < 0-001).

Blood involvement in early-stage MF is part of the staging for MF and is utilized in the response criteria.³⁵,³⁶ The majority of patients tested had no blood involvement (80 = 79-3%) but B1-level blood involvement was found in 20-7%, occurring in all stages. Lymphopenia was a frequent haematological abnormality in this cohort with early-stage MF (10-3%) and increased to 29-6% in stage IIA disease. It should be noted these tests are carried out at diagnosis, so MF treatment is not the cause. Lymphopenia is associated with immunosuppression, which may reduce the innate immunity ability to keep cancers – or specifically MF – in check. Ciclosporin, a potent suppressor of lymphocytes, is known to precipitate more aggressive MF and is contraindicated.⁶,²³ The significance of blood abnormalities in early-stage MF is unknown and tracking these patients for survival will determine the relevance.

Radiological imaging is not a recommended investigation in early-stage MF unless there is clinical lymphadenopathy or type-B symptoms, but nearly half of patients had an imaging scan (n = 143; 41-1%), although only 23 of 143 patients (16-1%) had enlarged LN.

PROCLIPI has collected a confirmed early-stage MF cohort that will be followed-up for survival to identify prognostic factors that may allow better management and improve survival by identifying patients at risk of MF progression. There is frequent diagnostic delay (median 36 months), highlighting the difficulties in accurate diagnosis, which is confounded by the lack of a singular diagnostic test and currently relies on clinical, pathological and genotypic studies. Tissue samples within the PROCLIPI federated biobank may be used for future translational studies, which may identify biomarkers to aid diagnosis and to identify predictive and prognostic biomarkers and novel targets for therapy. This study design is a prototype that may be useful in other rare diseases.

References


