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Histopathologic Evaluation of Density and Depth of the Lymphoid Infiltrate in Clinically Defined Patches and Plaques in Early Stage Mycosis Fungoides

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Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) [1]. In most patients, MF runs an indolent clinical course for years to decades, but in approximately 25% of patients, progression to advanced-stage MF is observed [2, 3]. The prognosis of MF depends on the type and extent of skin lesions and the presence of extracutaneous disease. Early-stage MF is characterized by the presence of patches and/or plaques covering less than 10% (stage IA) or 10% or more of the body surface area (stage IB). Several studies reported that patients presenting with both patches and plaques have a higher risk of progression to advanced-stage MF and a worse survival than patients presenting with only patches [3–5]. Therefore, the distinction between patches and plaques is clinically relevant, but it can be difficult due to a lack of standardized and reproducible criteria [6]. In the current classification system, differentiation between patches and plaques is based exclusively on clinical examination. Patches are defined as skin lesions without significant elevation or induration, while plaques are defined as skin lesions with elevation or induration [7]. However, this definition is subjective and prone to considerable inter-observer variability [6]. Previous studies on folliculotropic MF (FMF) found that a clinicopathologic approach, combining clinical and histopathological criteria, can facilitate the distinction between early and advanced plaque-stage disease [8, 9]. At recent meetings, the question was raised whether histopathologic criteria, in particular the extent and depth of the infiltrates, could also facilitate the distinction between patches and plaques in classical MF. The infiltrates in plaques in classical MF are indeed generally denser and deeper than in patches [6, 10]. However, studies investigating whether these differences may contribute to a more reliable distinction between patches and plaques have not been published thus far. In the present study, we investigated the extent and depth of the infiltrate in patches and plaques in classic MF to find out if these histopathological criteria can serve as an adjunct to differentiate between these two types of lesions.

Using a database of scanned HE stained sections obtained from pretreatment biopsies of patients with early-stage classical MF, 100 cases with variable extent and depth of the infiltrates were selected without knowledge of the clinical data. Corresponding clinical records and clinical images of the biopsied lesions were evaluated and, blinded to the histopathologic characteristics, scored as either patch or plaque by three individual dermatologists using ISCL/EORTC criteria described previously [7]. In case of discrepancy (< 5% of lesions) cases were discussed together and consensus was reached. In the total group of 100 cases with early-stage classical MF, 66 lesions were classified as patches and 34 as plaques. In all cases, the diagnosis was confirmed by an expert panel from the Dutch Cutaneous Lymphoma Tumor Group. Based on the extent and depth of the infiltrates, four histopathological categories were distinguished: (1) minimal or mild infiltrate in the upper dermis; (2) moderately dense infiltrate in the upper dermis; (3) thick band-like infiltrate in the upper dermis; (4) infiltrate extending into the deep dermis/subcutis (Figure 1). All scanned HE-stained sections were independently scored into one of these four categories by five dermatopathologists with ample experience in cutaneous lymphoma (TD, PV, AS, PJ, and RW), who were blinded to the clinical data.

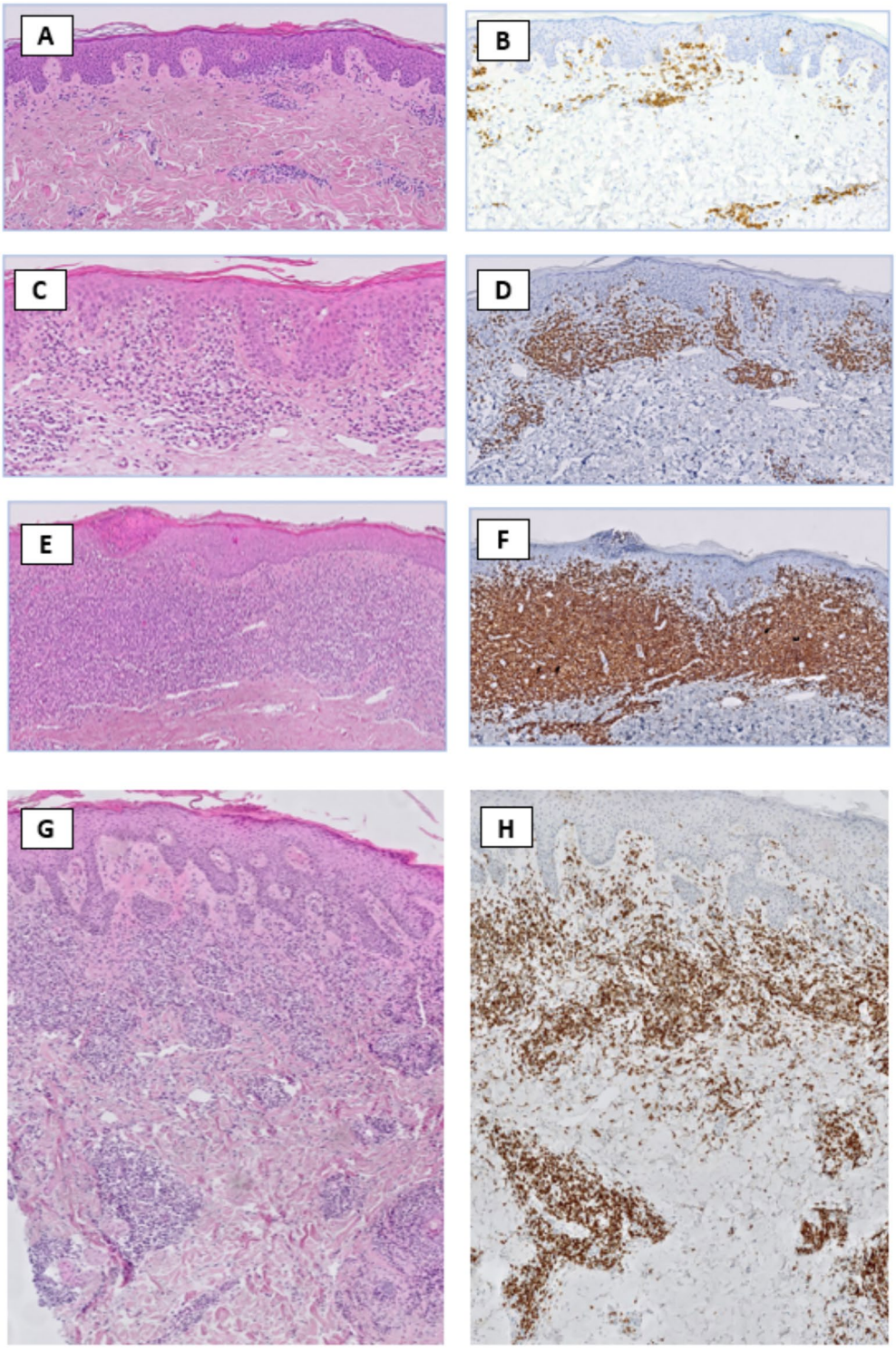

FIGURE 1 | Early-stage mycosis fungoides: Overview of four categories to describe the extent and depth of the infiltrates: (A, B) Histologic sections showing minimal to mild infiltrate in the upper dermis (Category 1; A: H&E, ×100; B: CD3 staining, ×100); (C, D) Histologic sections showing moderately dense infiltrate in the upper dermis (Category 2; C: H&E, x100; D: CD3 staining, ×100); (E, F) Histologic sections showing thick band-like infiltrate in the upper dermis (Category 3; E: H&E, ×100; F: CD3 staining, ×100); (G, H) Histologic sections showing infiltrate extending into deep dermis/subcutis (Category 4; G: H&E, ×100; H: CD3 staining, ×100). CD3 sections (B, D, F, H) were added for better visualization, but were not used for scoring by the panelists.

For HE-stained sections where there was no initial consensus, a pathologist meeting was held and consensus was reached.

The results showed that 17% of cases were classified as category 1, 45% as category 2, 16% as category 3, and 22% as category 4. Correlation between clinical and histopathological scores showed that 15 of 17 (88%) cases in category 1 originated from clinically defined patches and only 2 of 17 (12%) from clinically defined plaques. Also, cases classified as category 2 predominantly arose from patches (30/45; 67%) compared to plaques

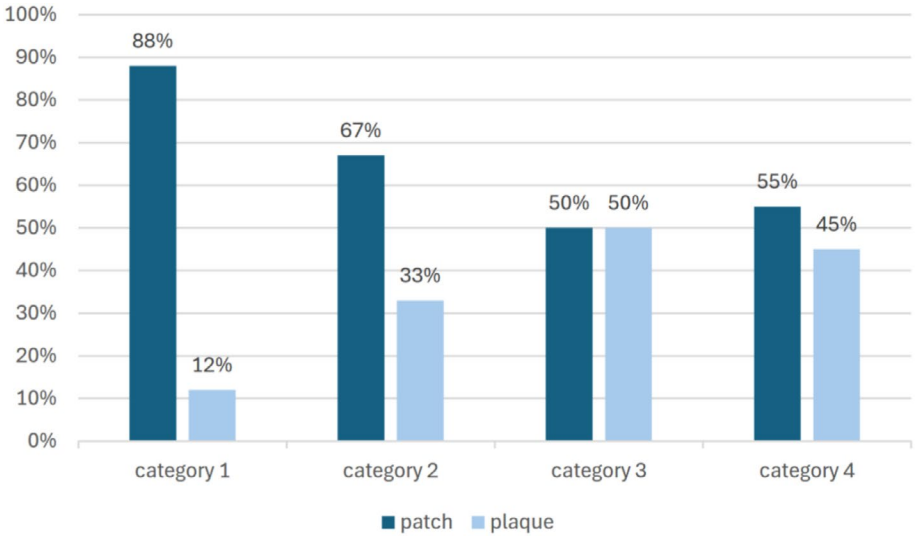

FIGURE 2 | Categories 1–4 with percentages of patches and plaques.

(15/45; 33%). Cases classified as category 3 and, remarkably, also cases classified as category 4 were distributed equally between patches (category 3: 8/16; 50%; category 4: 12/22; 55%) and plaques (category 3: 8/16; 50%; category 4: 10/22; 45%) (Figure 2). These results suggest that lesions with a minimal to mild infiltrate in the upper dermis (category 1) most likely represent a patch (88%). However, the observation that infiltrates extending into the deep dermis/subcutis (category 4) are found not only in plaques but also in patches implies that the extent and depth of the infiltrate cannot be considered reliable criteria in differentiating between patches and plaques.

Notably, our study focused on the total lymphohistiocytic infiltrate, including both tumor and reactive cells. The study of the extent and depth of only neoplastic T-cells would be of more interest but is generally not possible due to a lack of tumor-specific markers.

In a recent survey, cutaneous lymphoma experts indicated that the distinction between thin and thick plaques may be important, since it may have prognostic and therapeutic significance as described in FMF [6, 8, 9]. In the present study, no attempt was made to differentiate between thin and thick plaques, mainly because defining criteria for these lesions are lacking [6]. Whether patches showing infiltration of the deep dermis have an increased risk of disease progression compared with patches with a minimal to mild superficial infiltrate could not be evaluated because of the low number of events in this group.

In summary, a broad panel of cutaneous lymphoma experts emphasized recently the need for well-defined and reproducible histopathological criteria to differentiate between patches and plaques in early-stage MF [6]. However, the results of the present study suggest that assessment of the extent and depth of the total infiltrate solely by histopathology has limited value in differentiating these two types of lesions. Other histopathological criteria, such as the number of blast cells, CD30 expression, or composition of the inflammatory infiltrate may be important as well. Whether histopathology combined with other diagnostic tools as ultrasound, magnetic resonance imaging, or artificial intelligence-based models can contribute to a better definition of plaques and their differentiation from patches requires further studies [7, 11, 12].

Ethics Statement

The study was evaluated by the ethics committee of the Leiden University Medical Center and provided with a waiver of consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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