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REVIEW ARTICLE

‘Could it be mycosis fungoides?’: an approach to diagnosing patch stage mycosis fungoides

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Abstract Mycosis fungoides (MF) is the most common primary cutaneous T cell lymphoma, which is characterised in its early stages by epidermotropism of small to medium-sized T lymphocytes with cerebriform nuclei. Originally described by Alibert in 1806, MF is classically a disease of adults, although children and adolescents can be affected, and it typically has a protracted, indolent course. Routine dermatopathology practice involves many biopsies submitted with a clinical query regarding the possibility of MF. These are not always straightforward, as the histological features can be variable and are not always readily distinguishable from several other clinical differential diagnoses. Whilst modern molecular testing modalities can assist, even these do not always enable a definitive diagnosis of MF in its early stages. We have reviewed the histopathological features of early MF and currently recognised subtypes and the role of immunohistochemistry and emerging molecular techniques in the diagnosis of this condition. We also outline our approach to a biopsy where the question of ‘Could it be MF?’ has been proposed.

Keywords Mycosis fungoides · Dermatopathology · Cutaneous T cell lymphoma

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Introduction

Mycosis fungoides (MF) is a primary cutaneous T cell lymphoma (PCTCL), representing approximately 50 % of all primary cutaneous lymphomas [1]. It is defined histologically by epidermotropism of small- to medium-sized T lymphocytes with cerebriform nuclei. Originally described by Alibert in 1806 [2], MF is typically a disease of adults, although children and adolescents can be affected, and is characterised by a protracted, indolent course. Three clinical phases are recognised, with progression from patches to infiltrated plaques and eventually tumours. However, it is estimated that over 90 % of patients will not progress to tumour stage, and patients with limited disease show a similar survival to the general population [1, 3].

Routine dermatopathology practice involves many biopsies submitted with a clinical query regarding the possibility of MF. These are not always straightforward, as the histological features can be variable and are not always readily distinguishable from several other clinical differential diagnoses. Whilst modern molecular testing modalities can assist, even these do not always enable a definitive diagnosis of MF in its early stages. In this review, we outline our approach to this problem.

Clinical context

MF is divided into three clinical stages (patches, plaques and tumours) which correlate with disease stage and prognosis. Patches are variably sized and erythematous and have a fine scale. The lesions may be hypopigmented (particularly in darker skinned individuals), a yellowish colour may impart a ‘xanthomatous’ appearance and a wrinkled ‘parchment-like’ appearance has also been described. Initial lesions often

develop on the trunk and show a predilection for sun-protected sites (e.g. the buttocks). Classical MF seldom presents initially on the face, genitalia or perianal region [4]. Plaques are slightly elevated or palpably infiltrated lesions with a reddish-brown colour, surface scale and may be focally ulcerated. Tumours may be seen in association with patches or plaques, are often ulcerated and may be quite disfiguring. The 'mushroom-like' appearance of the lesions gave rise to the name [3].

Extracutaneous involvement is rare but may involve the mucosal sites, lymph nodes, spleen, lung and liver. The bone marrow is usually spared [1].

Early MF can be difficult to distinguish clinically from a number of dermatoses and is one of the more common reasons for submission of a biopsy. Amongst the more common clinical differential diagnoses are eczema, psoriasis, superficial fungal infections and drug reactions [4]. The clinical picture may be further confused by other factors such as pruritus, onychodystrophy, acral lesions and erythroderma, all of which can be associated with MF [3]. One characteristic that may be particularly suggestive of MF is the presence of poikiloderma, especially in non-sun-exposed skin. The presence of persistent poikilodermatous patches in these locations is highly suggestive of MF [5]. Plaque stage MF may require distinction from other cutaneous lymphomas which may present with similar clinical lesions. Thus, histological examination often plays a crucial role in establishing the diagnosis.

Histological features of early MF

Patch or plaque stage lesions of MF are characterised by a proliferation of small- to medium-sized lymphocytes, typically seen in a lichenoid- or band-like arrangement within the superficial dermis. A defining feature is the presence of epidermotropism, which may manifest as collections of lymphocytes within the epidermis ('Pautrier's microabscesses', or more correctly 'Darier's nests') or as linear arrays along the base of the epidermis ('basilar epidermotropism') (Fig. 1a, c). The lesional cells display nuclear irregularity, often described as 'cerebriform' nuclei, and there may be pericellular halos (Fig. 1b, d). While spongiosis may be present, the number of lymphocytes within the epidermis should be disproportionate to the amount of spongiosis in typical cases. A useful clue is the presence of lymphocytes within the epidermis which are larger than their counterparts within the dermis [6–11].

For many years, it was considered impossible to render a definitive histological diagnosis of early MF. In 1979, in the first issue of the American Journal of Dermatopathology, Sanchez and Ackerman first outlined histological criteria for early MF, highlighting the importance of distinguishing the epidermal changes of MF from those of spongiotic inflammatory disorders [9]. They suggested that in MF, intraepidermal lymphocytes were more numerous than in spongiotic disorders, tended to cluster and to be juxtaposed and that they extended up to the granular layer and above. While they noted that an increase in the intercellular spaces between keratinocytes was often seen in MF, they argued that spongiotic microvesiculation was not and its presence indicated a spongiotic dermatosis. The presence of papillary dermal oedema was a similar indication of a spongiotic dermatitis. They also suggested that atypical lymphocytes may not be present in the earliest lesions and thus are not a requirement for diagnosis. Rather, these were more often seen in plaque-stage lesions.

In the decades following this seminal paper, a number of other authors have published similar studies, in an attempt to validate and expand the criteria of Sanchez and Ackerman. In 1988, Nickoloff noted the presence of lymphocytes arranged in a linear fashion along the basal layers of the epidermis as an important criterion [8]. King-Ismael and Ackerman subsequently added the presence of lymphocytes within the epidermis which were larger than those in the dermis and the presence of wiry papillary dermal fibrosis associated with a patchy lichenoid lymphocytic infiltrate [12]. Guitart et al. proposed a scoring system in an attempt to standardise the reporting of these lesions [6]. There have been at least two attempts by international panels to develop diagnostic criteria for early MF. In 2000, Santucci et al. [10] published a retrospective review of biopsies from proven cases of early MF. This study found that the presence of medium to large lymphocytes with convoluted nuclei was the most important histological criterion, including their presence as single cells or small groups within the epidermis or as sheets in the dermis. The proceedings of a workshop conducted in 1999 and published in 2005[5] identified the following as major criteria: the presence of lymphocytes with irregular nuclear contours; the presence of lymphocytes within the epidermis which were larger than those seen in inflammatory dermatoses. Other features, such as haloed lymphocytes, disproportionate epidermotropism or a band-like infiltrate, were found to have less discriminatory value in this study. Both of these international attempts to define diagnostic criteria highlighted the importance of larger lymphocytes with nuclear irregularities; however, as Sanchez and Ackermann noted originally, these cells may not be present in the earliest lesions of MF. Thus, despite these and other studies [11, 13, 14], the diagnosis of early-stage MF has remained one of the more difficult problems in routine dermatopathology.

Subtypes

Folliculotropic MF

Folliculotropic MF is a form of the disease that presents with follicular papules and plaques and that may be associated with

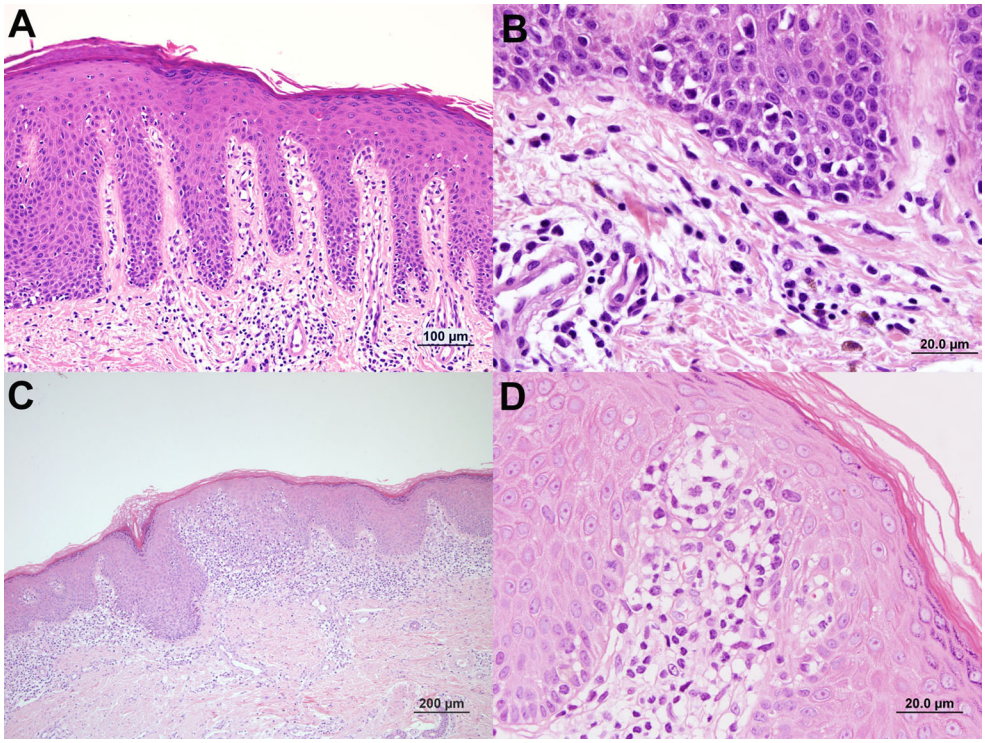

Fig. 1 Typical histological features of early mycosis fungoides. **a** A low power view shows epidermotropic lymphocytes arranged in a linear array along the basal layer of the epidermis. Many of these show a clear surrounding 'halo'. **b** Higher power examination reveals nuclear enlargement and hyperchromasia within the epidermotropic lymphocytes. Occasional atypical lymphocytes are also seen in the underlying dermis, where they can be seen admixed with smaller, non-neoplastic lymphocytes. **c** A low power view of a different case shows a band-like infiltrate of lymphocytes within the upper dermis. Epidermotropic lymphocytes are also present, which in this case form a cluster consistent with a Pautrier's microabscess. **d** A high power view of this case demonstrates the highly convoluted nuclear outlines seen in the epidermotropic lymphocytes

mucin deposition [15, 16]. Destruction of hair follicles leads to generalised or localised alopecia. Eruptions of small infundibular cysts and/or comedones can also be observed, and follicular hyperplasia may result in elevated lesions simulating plaques. The head and neck region is preferentially affected, and leonine facies may result [17].

This variant of MF is characterised by a perifollicular lymphocytic infiltrate and infiltration of the follicular epithelium by neoplastic lymphocytes ('folliculotropism', analogous to 'epidermotropism') (Fig. 2). There is often deposition of mucin within the follicle although the amount of mucin does not necessarily correlate with the number of atypical T cells within the follicular epithelium [17]. Other patterns which have been described include a folliculodestructive granulomatous dermatitis, an eosinophilic folliculitis-like pattern with associated folliculotropism, dilated follicular cysts with folliculotropism and a basaloid folliculolymphoid hyperplasia with folliculotropism [18]. Awareness of these patterns is important as they can be easily misinterpreted as other conditions. Pautrier microabscess formation and involvement of the interfollicular epidermis are uncommon in this variant [17]; however, a relatively recent study found syringotropism in approximately half of the cases studied [19, 20].

Several studies have found folliculotropic MF to have a worse prognosis than classical MF, with higher rates of disease progression and lower disease-specific and overall survival rates. On the other hand, at least one study has documented relatively slow disease progression [21]. Response to skin-directed therapy is poor, presumably due to the location of the neoplastic cells within the deeper follicular epithelium [17, 22, 23].

The relationship between folliculotropic MF and the condition variably termed follicular mucinosis or alopecia mucinosa has been the subject of some debate. Alopecia mucinosa was described in 1957 [24] and is characterised by localised alopecia with the histological finding of mucin deposition within hair follicles. Initially, it was divided into two groups, depending on whether or not there was associated MF. However, subsequent studies showed that this distinction was not reproducible when the proposed criteria were applied strictly [25]. While a number of conditions have been documented to produce mucin deposition within follicles [26], when this occurs without objective evidence of another process, the possibility of folliculotropic MF should at least be considered. Indeed, many authors now regard follicular mucinosis/alopecia mucinosa to be synonymous with folliculotropic MF [19, 25, 27].

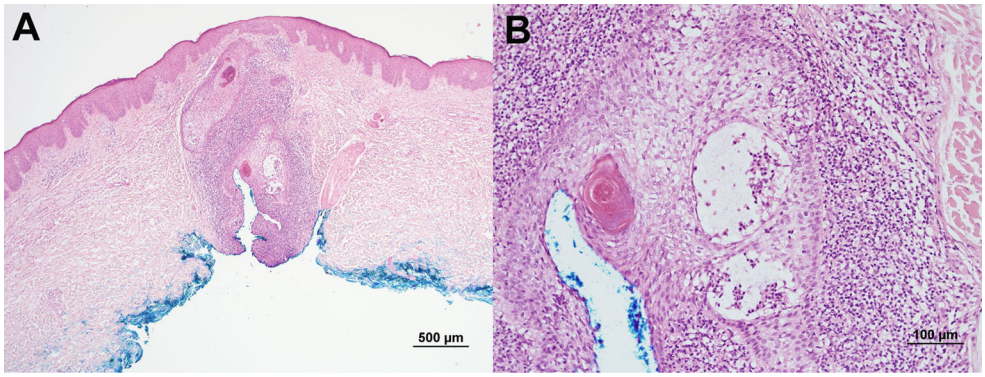

Fig. 2 An example of folliculotropic mycosis fungoides. **a** Low power examination reveals a perifollicular lymphocytic infiltrate. **b** At higher power, numerous folliculotropic lymphocytes can be appreciated, including formation of intra-epithelial collections analogous to Pautrier's microabscesses. The pallor within the follicular epithelium represents mucin deposition.

Syringotropic MF

Related to folliculotropic MF, but rarer, is the variant known as syringotropic MF. The largest series to date of this variant was reported by Pileri et al. [28]. This entity has overlapping clinical features with conventional variants, although solitary lesions seem to be more common and follicular accentuation producing a papular pattern is often seen. Histologically, these lesions are characterised by a dense, often nodular, perieccrine lymphocytic infiltrate. There is prominent syringometaplasia and epitheliotropism, and epidermal involvement is relatively common [28]. Involvement of the hair follicles is also commonly seen, and combined with the findings of Lehman et al. [20], this suggests that both 'adnexotropic' variants of MF are closely related [19].

Pagetoid reticulosis (Woringer-Kolopp type)

The first description of this condition was in 1939, when Woringer and Kolopp presented a case of a 13-year-old boy with lesions of the forearm, for which they could not offer a diagnosis [29, 30]. The term pagetoid reticulosis was subsequently coined by Braun-Falco et al. in 1973, when they described a similar adult case [31]. While a number of cases were subsequently reported, the nature of this condition, and its relationship to MF, remained uncertain for many years. Ioannides et al. were the first to suggest that the condition represented a localised form of MF [32], and subsequent studies supported the notion that it represented a T cell lymphoproliferative disorder [33–35], now considered to be a subtype of MF.

Pagetoid reticulosis presents with one or several, often confluent, scaly, erythematous patches or plaques which are typically located on the extremities. An important criterion for this condition is that the lesions are solitary or at least are localised to one site. The disseminated variant, presenting with generalised lesions of 'pagetoid reticulosis' (Ketron-Goodman disease) would now be classified as other, more aggressive forms of cutaneous T cell lymphoma (e.g. cutaneous aggressive epidermotropic CD8+ lymphoma, cutaneous γ/δ T cell lymphoma or extranodal NK/T cell lymphoma, nasal type) [3].

Histologically, this entity is characterised by marked epidermal hyperplasia and prominent epidermotropism of medium-sized, pleomorphic T lymphocytes. While a dermal inflammatory infiltrate is also present, this is often less striking than the intraepidermal component and is comprised of a relatively mixed population [34]. Neoplastic cells may also infiltrate eccrine structures [3]. The neoplastic cells typically display a cytotoxic phenotype, but this is not invariable [33, 34]. The prognosis of this subtype of MF is good, although the presence of neoplastic cells within eccrine glands may render superficial treatments less effective. Development of conventional MF has been reported [3].

Unilesional MF

Besides the pagetoid reticulosis subtype described above, there are also reports of a solitary or unilesional variant of MF having similar histological features to those seen in classical MF [36–39]. Some authors have suggested that these cases have a better prognosis as a group [36], although large cell transformation has been reported [40]. In addition, many of these lesions may in actuality represent other conditions, such as lichenoid keratosis [3, 37, 41], and thus rigorous exclusion of these possibilities (both histologically and clinically) is warranted before rendering a diagnosis of unilesional MF.

Granulomatous MF

The presence of granulomatous inflammation associated with MF was first reported by Ackerman and Flaxman in 1970 [42]. A granulomatous reaction pattern can be seen at all stages of MF, and while it is most often characterised by

patchy epithelioid granulomas with variable numbers of giant cells, cases with a more diffuse infiltrate of epithelioid histiocytes also occur [43]. A granulomatous reaction to ruptured follicles may also accompany folliculotropic MF [3]. Granulomatous MF may have a worse prognosis than classic MF. Fewer patients respond to superficial therapies, and there are worse progression-free survival rates. These patients are also at risk for developing a second lymphoma [44, 45].

A particularly rare, but striking, form of MF is known as granulomatous slack skin, characterised by areas of lax, pendulous skin containing a neoplastic T cell infiltrate. There is epidermotropism as well as a diffuse lymphohistiocytic infiltrate including giant cells throughout the dermis and subcutis [46, 47]. The initial studies noted prominent elastolysis in association with the granulomatous infiltrate, which was proposed as the mechanism for the lax skin. However, other studies found that elastolysis was not limited to granulomatous slack skin and was more related to the extent of the granulomatous inflammation [45]. In addition, several authors have noted that there is considerable histologic overlap between granulomatous slack skin and granulomatous 'conventional' MF; thus, the diagnosis relies on clinicopathological correlation [3, 43, 45].

Erythrodermic MF

Erythroderma may develop as a complication of MF and may be associated with lymphadenopathy and circulating neoplastic cells. Erythrodermic MF shares the same histological features as conventional MF [3]. There is overlap with Sézary syndrome, which is defined as a mature T cell lymphoma characterised by erythroderma, lymphadenopathy and neoplastic T lymphocytes ('Sézary cells') within the blood [1]. However, the term Sézary syndrome is typically reserved for patients presenting with these features from the outset of their disease. This distinction may require careful correlation with the clinical history in order to detect any evidence of pre-existing MF [3].

Sézary syndrome is associated with a poor prognosis, having a 5-year survival rate of 24 % [48] and is traditionally regarded as the leukaemic variant of MF. Indeed, no reliable histological criteria for distinguishing the two conditions have been identified [49], although some have suggested that epidermotropism is less often seen in patients with primary Sézary syndrome [50]. However, recent evidence has suggested that the conditions may be derived from different T cell subsets, with clonal cells from Sézary syndrome patients having an immunophenotype consistent with central memory cells, while those from MF showed a profile more consistent with resident effector memory cells in skin [51]. In addition, recent molecular analyses have identified differences in the molecular profile between these conditions. With array-based comparative genomic hybridisation (array-CGH) techniques, MF cells were characterised by gains on chromosomes 1 and 7 and losses on chromosome 9. However, cells from patients with Sézary syndrome tended to show gains on chromosomes 8 and 17 and loss on chromosome 10 [52]. These findings suggest that the two conditions may in fact be different diseases and that different treatment regimens may be warranted.

Hypopigmented MF

Lesions of MF may present with a hypopigmented appearance, particularly in patients with darker skin but also in Caucasians (Fig. 3) [53–55]. This is one of the more frequent variants seen in paediatric patients, and while there is typically a good response to therapy, recurrences are common [56]. Histologically, this subtype is indistinguishable from conventional MF, although a large proportion of these cases show a CD8+ phenotype [57].

Other subtypes

Numerous other morphological subtypes of MF have been described, based on either clinical or histological features [3]. These include interstitial MF (showing an interstitial infiltrate of lymphocytes dissecting the collagen bundles), poikilodermatous MF (characterised by an atrophic epidermis), hyperpigmented MF, purpuric MF, papular MF, bullous MF, anetodermic MF, pityriasis et varioliformis acuta (PLEVA)-like MF and even an 'invisible' MF, where the skin appears clinically normal [58]. Despite the wide range of subtypes reported, only folliculotropic MF, pagetoid reticulosis and granulomatous slack skin have been considered distinctive enough to be included in the WHO-EORTC classification as separate entities [48].

Parapsoriasis

The controversial term 'parapsoriasis' was first introduced by Brocq in 1902, to describe a group of dermatoses resembling psoriasis but which lacked some features and showed resistance to therapy [29, 59]. He described three types (parapsoriasis en gouttes, parapsoriasis lichenoides and parapsoriasis en plaques), which he viewed as a group of conditions with features intermediate between cases comprising psoriasis and 'seborrhoea psoriasiformis' and another group comprising lichen planus, pityriasis rubra and MF. Clinically, they were characterised by a long clinical course, absent pruritus, superficiality with possibly some scaling and a resistance to treatment. He described the histological features as a 'round cell' inflammatory infiltrate, dermal and epidermal oedema (i.e. spongiosis), hypogranulosis, hyperkeratosis and parakeratosis [29, 59].

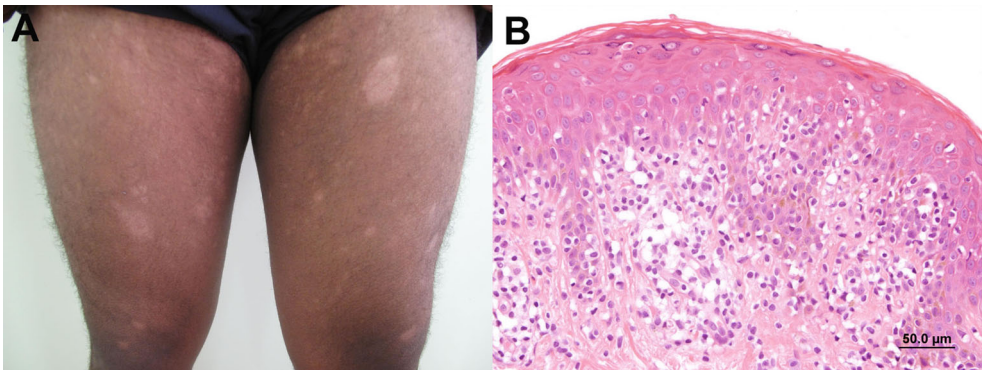

Fig. 3 An example of hypopigmented mycosis fungoides. **a** Clinical appearance, demonstrating multiple hypopigmented macules. **b** Histological section showing numerous epidermotropic lymphocytes. (Clinical photograph courtesy of Dr Prasad Kumarasinghe)

As quoted by Ackerman, Brocq himself acknowledged that 'some cases of mycosis fungoides, for long periods, initially have the aspect of parapsoriasis en plaques' and that the two conditions may be indistinguishable [29, 59]. However, he still regarded them as distinct entities, perhaps due to his perception of a differing prognosis [29], and he argued that the presence of pruritus and dermal infiltration allowed one to separate cases of MF from parapsoriasis.

Over the following decades, the close relationship of parapsoriasis en plaques to MF became apparent. In 1936, Keil noted that parapsoriasis en plaques was complicated by the development of MF 'in so large a percentage of instances as to invite the belief that parapsoriasis in patches and its clinical congeners are probably in most, if not in all cases, the precursors of mycosis fungoides' [29, 60]. In 1953, Degos divided parapsoriasis en plaques into two forms: large plague parapsoriasis and small plaque or digitate parapsoriasis [29, 61]. He felt that transformation to mycosis fungoides occurred only in large plaque parapsoriasis, with small plaque/digitate parapsoriasis representing a 'benign' form. Subsequently, Sanchez and Ackerman declared that large plaque parapsoriasis was simply an expression of MF and should be renamed as such [9]. Other authors of the time argued against this, preferring to interpret large plaque parapsoriasis as a chronic inflammatory condition, with a risk of developing lymphoma due to ongoing antigen stimulation [62–64]. Subsequent studies have revealed that at least a proportion of cases of parapsoriasis have a dominant T cell clone present [65, 66].

To this day, the term parapsoriasis is associated with confusion. The current concept recognises two entities under this term: small plaque parapsoriasis (also known as chronic superficial dermatitis and digitate dermatosis) and large plaque parapsoriasis. A third condition, pityriasis lichenoides, was initially included in the concept of parapsoriasis but is now recognised as a distinct entity [67]. Indeed, the definition of these conditions is imprecise as there are no recognised size criteria for distinguishing a large plaque from a small plaque and there is no classification for a patient having both small and large lesions. Nonetheless, several texts now consider large plaque parapsoriasis to fall within the spectrum of early MF [3, 67] although it is recognised that at this stage, the histological features may be such that a definitive diagnosis is difficult. Small plaque parapsoriasis resembles a mild eczema clinically, and histologically, it shows spongiosis (which may be mild), acanthosis and lymphocytes within the papillary dermis. While a small proportion of these cases have been documented to eventually develop conventional MF [68, 69], the exact relationship between these entities remains a subject of debate.

Immunohistochemistry

The typical immunophentoype of the neoplastic cells in MF (seen in approximately 75 % of cases) is CD2+, CD3+, CD4+, CD5+, CD8−, βF1+, TCRγ− and TIA1−. This profile correlates to α/β T-helper memory T cells [1, 3, 70]. Some variations have been reported, including examples characterised by the following: CD4−, CD8+ and TIA1+ (cytotoxic profile); CD4− and CD8− (double-negative profile); and βF1−, TCRγ+, CD4−, CD8+ and TIA1+ (γ/δ profile). However, no clinical or prognostic differences have been demonstrated for these variations to date (noting that previous examples of these immunoprofiles which showed an aggressive course have since been re-classified as other forms of cutaneous T cell lymphoma, such as CD8+ cytotoxic T cell lymphoma or cutaneous γ/δ T cell lymphoma) [71–74].

Immunohistochemistry is often utilised in the diagnostic workup of biopsies which are suspected of representing MF. Memory T cells with the same profile as neoplastic MF cells are common in any cutaneous inflammatory infiltrate, limiting the usefulness of this immunoprofile per se. However, loss of one or more pan-T markers (CD2, CD3, CD5 or CD7) can be indicative of a neoplastic process. This loss may be seen throughout the totality of the cutaneous infiltrate or may be limited to the lymphocytes within the epidermis (termed 'discordance' by Michie et al. [75]). While loss of any of these markers can be helpful in the diagnosis of MF, the sensitivity is relatively low, estimated as approximately 10 % for a ≥50 %

loss of CD2, CD3 or CD5 expression [75]. The sensitivity may be better for loss of CD7, in the order of 40 % for expression levels of less than 10 % [5, 76]. However, loss of CD7 (as well as other pan-T cell markers) can also be seen rarely in inflammatory conditions [4, 77–80], so the finding should be interpreted with some caution.

Immunohistochemical assessment of the CD4/CD8 ratio has also been touted as a useful diagnostic aide, with the idea being that clonal expansion of a CD4+ T cell population would result in an increase in this ratio [78, 81, 82]. Assessment of this ratio can be made difficult by the fact that CD4 also labels intraepidermal Langerhans cells, which may also be increased in the setting of spongiotic disorders [78], and at least one more recent study has not found this ratio to be of discriminatory value [78, 79].

Newer immunohistochemical markers may emerge from the results of more advanced molecular studies. As an example, Zhang et al. used microarray-based genomic transcriptome profiling to compare early MF with both inflammatory dermatoses and normal skin [83]. They identified a number of transcripts which were upregulated in MF, including TOX (a regulator of early T cell development) and PDCD1 (a pro-apoptosis regulator). The authors were able to demonstrate that immunohistochemistry for TOX labelled T cells strongly in cases of MF, including cells within Pautrier microabscesses [83].

Molecular techniques

The functional diversity required for an effective adaptive immune system is generated by complex rearrangements within antigen receptor genes. This involves alterations of the tertiary gene structure, with recombination of variable, diversity and joining regions within the gene, as well as insertion and deletion of random nucleotides via the action of terminal deoxynucleotidyl transferase (TdT) [84]. Modern molecular techniques attempt to exploit the uniqueness of each rearranged receptor gene to determine whether a population of lymphocytes is clonal or polyclonal. Clonally identical lymphocytes share identical receptor gene rearrangements and yield amplicons of the same size after amplification by PCR, whereas polyclonal lymphocytes yield amplicons having a range of sizes. Monoclonal rearrangements will appear as a discrete band or peak, whilst polyclonal rearrangements appear as a smear or Gaussian curve, depending on the modality used to anlayse the DNA fragments [84].

Clonal T cell receptor (TCR) gene rearrangements can be detected in a large proportion of MF cases, with a sensitivity ranging from 50 % to greater than 70 %, depending on the methodology and the stage of the lesions [85–94]. PCR analysis has been shown to be more sensitive than the Southern blot method used in the older literature [90]. Typically, a PCR analysis would involve the use of a range of primers directed against conserved regions within the receptor genes. The first generation of these tests suffered from a lack of consistency across different groups and platforms, making it difficult to determine the optimum diagnostic approach [84]. In 2003, the BIOMED-2 collaborative study outlined a set of standard PCR primers and methodology, which forms the basis of modern PCR clonality testing [95, 96]. We use this primer set and methodology routinely.

The initial analyses of the BIOMED-2 protocol indicated a sensitivity of approximately 99 % for the detection of clonality in T cell neoplasms [97]. However, this analysis utilised fresh or frozen tissue and did not include primary CTCLs. Goeldel et al. found a sensitivity of 77 % for the diagnosis of CTCL using the BIOMED-2 protocol, with a specificity of 86 % [91]. However, they also used exclusively frozen tissue. Using archived formalin-fixed, paraffin-embedded (FFPE) tissue, Lukowsky et al. were able to demonstrate a sensitivity of 81 % [92], while in a smaller sample of granulomatous CTCL, Pfaltz et al. found a sensitivity of 94 % [93].

PCR analysis is often employed as an adjunct in the diagnosis of early-stage lesions. Perhaps not surprisingly, early patch stage lesions typically show the lowest sensitivities, presumably due to the relative paucity of neoplastic cells within the infiltrate [85, 86, 98]. Cerroni et al. showed that the neoplastic cells are often present within the epidermis in these early lesions and suggested that sensitivities might be increased by microdissection of the epidermis [87]. The presence of monoclonality does not appear to be associated with any prognostic significance [72].

Despite deficits in sensitivity, Alessi et al. were still able to use the technique to reclassify a number of cases as MF when a monoclonal result was combined with the clinical and histological features of the cases [85], demonstrating that the technique is a useful additional test when the results are correlated with the other diagnostic modalities. However, it should be noted that monoclonal TCR gene arrangements have been documented in a range of benign inflammatory dermatoses, including lichen planus, pityriasis lichenoides, lichen sclerosus, granuloma annulare and chronic eczema [93, 98–102]. In addition, other factors can potentially confound the interpretation of the result, including clonal heterogeneity within a lesion, poorly annealing primers or false positives due to limited numbers of lymphocytes within a sample [84].

The specificity of using PCR to detect monoclonal TCR gene rearrangements may be improved by testing two different skin sites, with the requirement that identical clones need to be identified to represent a positive result. Thurner et al. demonstrated a sensitivity of 80 % utilising this method, and they were able to demonstrate identical clones in 85 % of a group of patients who had an indeterminate result on initial histological examination but subsequently went on to develop

MF [103]. In addition, the ability to perform analyses on multiple biopsies may allow for the correct identification of a stable pathological clone in the setting of clonal heterogeneity, which has been documented in 30–48 % of MF cases [104, 105].

Differential diagnosis

The histological diagnosis of early MF can be extremely challenging, due to the protean nature of the disease and its ability to mimic many inflammatory dermatoses, both clinically and histologically [106, 107]. This has led some authors to label it as 'the great imitator' of modern dermatopathology, a designation once applied to syphilis [107]. The difficulties are reflected in interobserver variability studies, which have shown only fair to moderate agreement between pathologists with regard to early MF diagnosis [78].

Despite the broad range of potential differentials, there are a number of conditions which seem to be more commonly considered in routine practice.

a. Spongiotic dermatoses

Spongiotic dermatoses are often under consideration (Fig. 4a, b), especially as the lesions are often suspected to be eczematous clinically (indeed, in our experience, there is often a history of 'eczema' which is refractory to treatment). A degree of spongiosis is often seen in early MF, and marked spongiosis has been documented in a small percentage of cases [7]. The presence of numbers of intraepithelial lymphocytes which are disproportionate to the amount of spongiosis is often quoted as a distinguishing feature [7, 8]; however, clearly, this assessment is subjective. In their original study, Sanchez and Ackerman suggested that spongiotic microvesiculation argued against MF [9]. While immunohistochemical and molecular analyses may help in selected cases, ultimately, the distinction rests on careful clinicopathological correlation [108].

b. Psoriasiform or interface dermatitis

Changes of psoriasiform or interface dermatitis are also well recognised in lesions of MF [13, 109]. Indeed, a psoriasiform lichenoid or a spongiotic psoriasiform lichenoid pattern is typical of the low power appearance of MF [110]. Massone et al. reported changes of interface dermatitis in up to 59 % of cases of their cases of early MF [7]. While this was typically a focal finding, in a small number of cases, the changes involved much of the dermoepidermal junction, and necrotic keratinocytes were also occasionally present. Lichen sclerosus is one example of an interface dermatosis which is recognised as a potential mimic of MF (Fig.4c, d) [108]. With regard to the latter, it is useful to recall that the first biopsy of MF will almost never come from genital skin, which is seldom involved in early MF. Of course, extragenital lichen sclerosus can present a more troubling mimic. In addition, a recently described entity known as annular lichenoid dermatitis of youth (ALDY) may also be a cause of confusion [111]. These patients, as the name suggests, are typically young and present with erythematous macules and annular lesions on the groin and flanks. The clinical appearances are reminiscent of MF, and histologically, the cases are characterised by a band-like inflammatory reaction pattern with lichenoid interface changes. While these histological features can be confused with MF, in ALDY, the lymphocytes are seen predominantly at the tips of rete ridges, where they are often associated with prominent keratinocyte apoptosis [111].

c. Pigmented purpuric dermatoses

Massone et al. [7] also documented the presence of melanophages and extravasated erythrocytes in a small percentage of cases, imparting a resemblance to the group of dermatoses known collectively as pigmented purpuric dermatoses (PPDs). Purpuric lesions occur in MF [112], the histological features of PPDs and MF show significant overlap [110, 113], and clonal rearrangements of T cell receptor genes have been documented in a relatively high proportion of PPD cases [110]. Indeed, there is ongoing debate as to whether a subset of PPD represents a precursor to MF, or simply a mimic [110]. From a practical point of view, restriction of lesions to the lower legs is indicative of a PPD.

d. Pseudolymphomatoid drug reactions

Drug reactions have also been documented to cause a histological reaction similar to MF. These 'pseudolymphomatoid' drug reactions have been associated with a wide range of drugs, including phenytoin [114], carbamazepine [115], captopril, enalapril [116], fluoxetine, amitriptyline [117], antihistamines [118] and imatinib [119], amongst others [120]. Magro et al. have proposed that histological features favouring a pseudolymphomatoid drug reaction include vacuolar degeneration of basal keratinocytes, necrotic keratinocytes, moderate to marked spongiosis and papillary dermal oedema [120]. Again, a thorough clinical history, including details of any medications, is likely to be the most useful criterion.

e. MF subtype mimics

In addition to the conditions listed above, which can be confused with classical MF, the various subtypes have unique differentials of their own, relating to their particular histological characteristics. Folliculotropic MF can be confused with perifolliculitis, an epidermoid cyst in the comedonal forms, or a basal cell carcinoma in the basaloid folliculolymphoid hyperplasia form [18]. Syringotropic MF needs to be distinguished from perniosis or autoimmune forms of hidradenitis [28]. Granulomatous MF can be mistaken for a granulomatous dermatitis [43], and

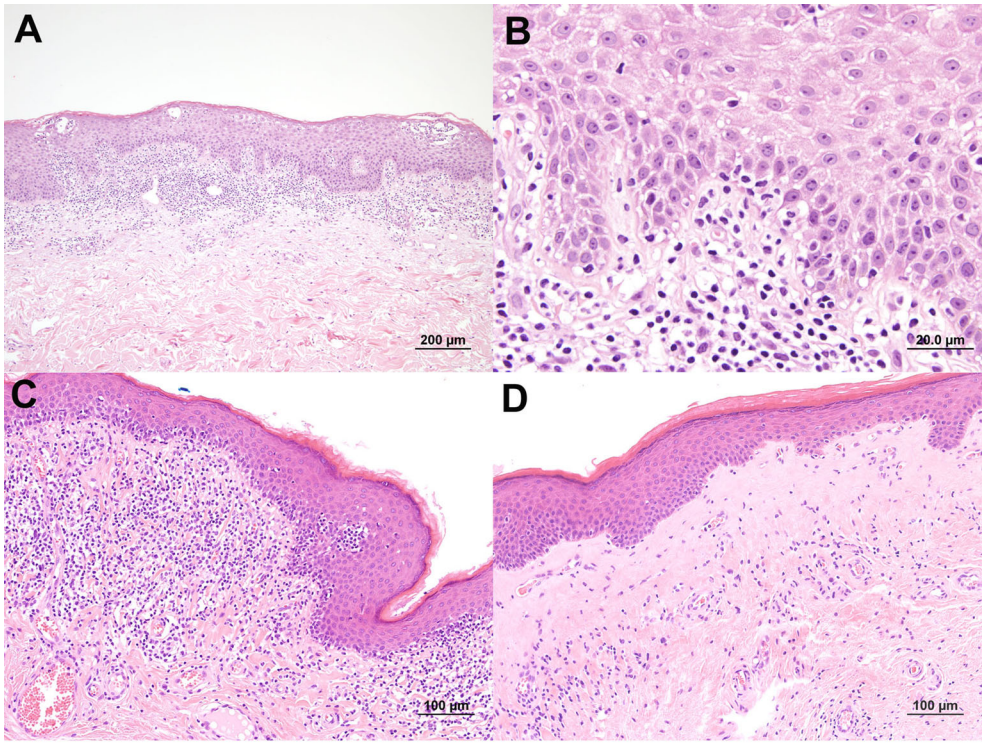

Fig. 4 Two examples of cases showing morphological overlap with inflammatory conditions. **a** A low power view of this specimen from the flank shows spongiosis with a band-like lymphocytic infiltrate within the dermis. There are small vesicles within the epidermis, some of which contain lymphocytes. **b** At higher power, occasional linear arrays of lymphocytes are seen within the basal epidermis, some of which show irregular nuclear contours and a surrounding halo. The background spongiosis is readily apparent in this panel. This patient had an established history of classical mycosis fungoides, with demonstration of identical clonal T cell populations in multiple biopsies, including this sample. This biopsy was interpreted as mycosis fungoides, rather than as spongiotic dermatitis. **c** This medium power view of a specimen of foreskin demonstrates features which could easily be mistaken for mycosis fungoides. There is a band-like infiltrate of lymphocytes with apparent epidermotropism of lymphocytes, including a focal intra-epidermal collection which could be interpreted as a Pautrier's microabscess. **d** However, elsewhere, the features are more typical of lichen sclerosis, which was the diagnosis rendered in this case

hypopigmented MF enters the differential diagnosis of vitiligo [121].

f. Other cutaneous T cell lymphoproliferative disorders

Finally, cases of possible MF need to be distinguished from other forms of cutaneous lymphoma. Epidermotropism may be a feature of extranodal NK/T cell lymphoma (nasal type), primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma and cutaneous γ/δ T cell lymphoma [48], as well as some subtypes of lymphomatoid papulosis (in particular types B and D) [48, 122]. While immunoprofiling of the neoplastic cells may help in the distinction between these entities, the range of immunophenotypes documented for MF may overlap with these other cutaneous lymphoproliferative disorders (see above). Indeed, many cases were likely to have been previously classified as variants of MF. The clinical behaviour of extranodal NK/T cell lymphoma (nasal type), primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma and cutaneous γ/δ T cell lymphoma is much more aggressive than that of MF, and thus, it is critical to identify these conditions in particular. Once again, correlation with the clinical features is most likely to yield a correct diagnosis.

Our algorithmic approach to the diagnosis of early MF

There is no foolproof approach to biopsies where early- or patch-stage MF is a consideration. Nonetheless, we have attempted in the following paragraphs to summarise our general approach to this situation (Fig. 5).

As with all biopsies, the initial step involves assessing the overall histological pattern of the process. As described above, MF is typically characterised by a band-like infiltrate of lymphocytes within the dermis, with 'psoriasiform lichenoid', 'psoriasiform spongiotic lichenoid' and 'atrophic lichenoid' patterns regarded as typical of MF [110]. Assessing the histological pattern also brings to mind potential differential diagnoses, and specific features of those conditions should be sought: Positive recognition of an alternative dermatosis is

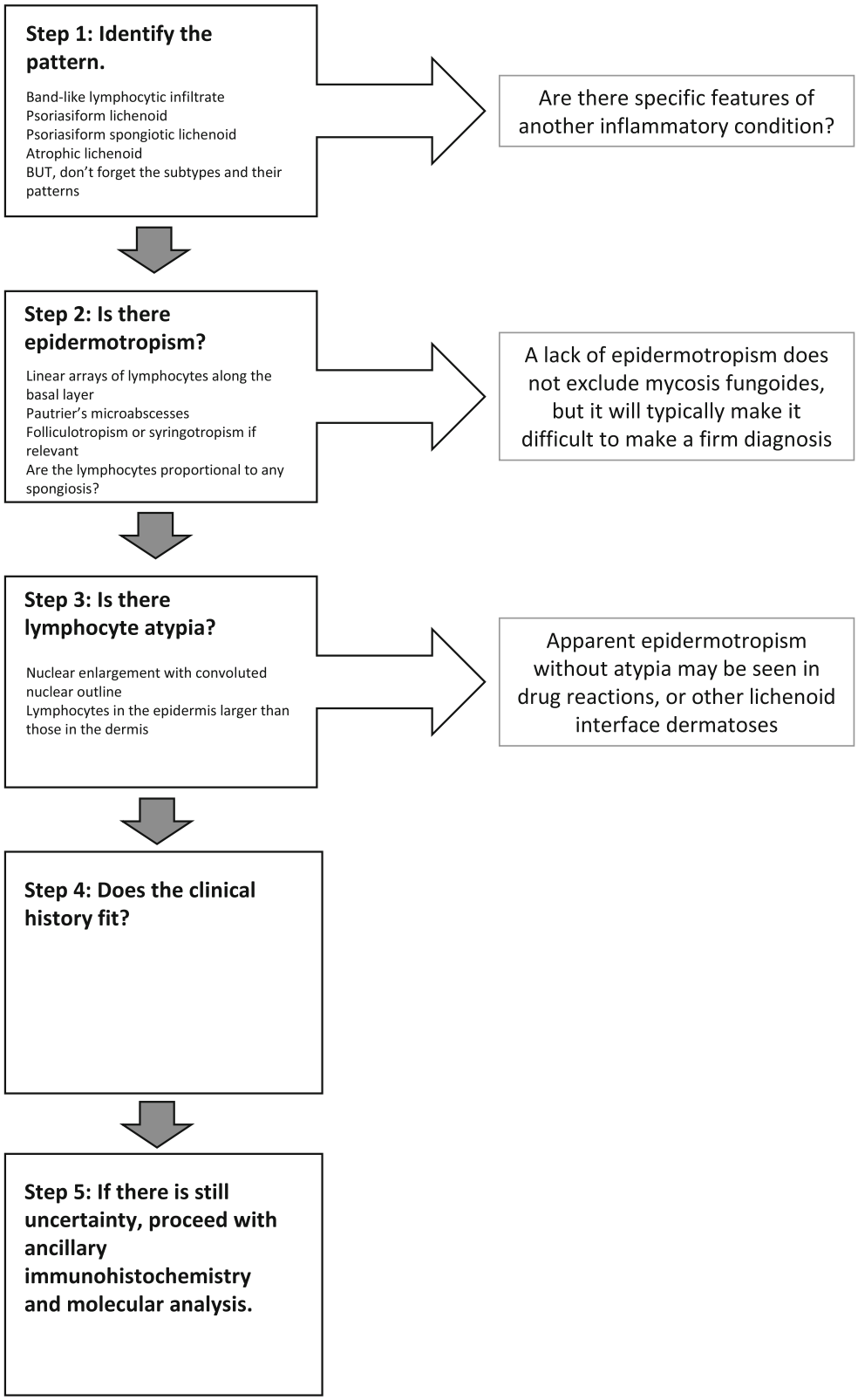

Fig. 5 A flow chart summarising our approach to a biopsy where mycosis fungoides is a diagnostic possibility. Please refer to the text for details

of great value when attempting to 'exclude MF'! Pathologists should also be cognizant of the various subtypes of MF listed above, and of the variant histological patterns, they may present.

Once we have established that the histological pattern may be compatible with MF or one of its variants, we next assess whether epidermotropism is present. While the absence of

epidermotropism does not exclude a diagnosis of MF, it does limit the ability to make a definite histological diagnosis.

Once the presence of epidermotropism is established, we next turn our attention to the presence or absence of the various diagnostic features that are described above. In particular, we look for the presence of clusters of intraepidermal lymphocytes (do they represent Pautrier microabscesses?), haloing of lymphocytes, basilar epidermotropism and fibrosis of the papillary dermis. If there is accompanying spongiosis, we attempt to make a judgement as to whether the number of lymphocytes within the epidermis is disproportionate to the spongiosis. We also pay attention to the cytological details of the epidermotropic lymphocytes, in particular noting whether they have convoluted nuclear membranes and whether they are larger than dermal lymphocytes. In our experience, thin sections (e.g. 2 μm thick) are useful for this assessment, and we routinely request thin sections in cases of possible MF.

At this point in our assessment, we have formed an opinion as to whether MF is a reasonable consideration and how strongly the histological features support this. We then interpret these features in light of the clinical scenario. This will almost always involve direct communication with the referring clinician, either via phone or a clinicopathological conference. If both the clinical and histological features support the diagnosis, we will usually make a diagnosis of MF without any further studies. If the clinical features are not compatible, we would review the case, mindful of potential differential diagnoses. A drug history can be particularly useful in this scenario. If the clinical features are strongly suggestive of MF, it can be virtually impossible to exclude it histologically unless a definitive diagnosis of another condition can be rendered [3].

If there is still uncertainty after careful consideration of the clinical and histological features, we then consider ancillary testing. This would typically involve immunohistochemistry as well as molecular studies for clonal TCR gene rearrangements, particularly testing of lesions from multiple sites and/or at different points in time.

It is important to recognise that patch stage MF is a clinically indolent condition with a protracted course. Currently available treatments do not alter the prognosis. There is significant overlap of treatment modalities between early MF and the inflammatory conditions which enter the differential diagnosis, with the caveat that biologic immunomodulatory agents have been associated with progression of MF in some case reports and should be avoided if MF remains a consideration. In this context, it is appropriate that cases which fall short of a definitive diagnosis be reported descriptively, highlighting the differential diagnostic considerations. In these cases, symptomatic management and clinical follow-up in a multidisciplinary team setting is undertaken. An iterative approach to clinical evaluation and biopsy can resolve many cases satisfactorily. It is preferable to avoid overdiagnosis of MF in such circumstances—it is easy to 'upgrade' a temporising diagnosis such as 'superficial cutaneous T cell infiltrate of uncertain character, please refer to the comment', while a premature diagnosis of MF may be almost impossible to revise.

Conclusion

MF is the most common cutaneous T cell lymphoma, and any pathologist who deals with skin specimens, particularly dermatopathologists or haematopathologists, needs an approach towards a biopsy where early MF is considered. As well as being aware of the key histological criteria for 'classical' MF, pathologists need to be mindful of the many and varied subtypes which can present histological findings showing considerable overlap with other dermatological conditions. A familiarity with the clinical and histological features of these inflammatory considerations is a sine qua non for approaching such a biopsy. Similarly, it is important to actively consider those neoplastic conditions which may mimic MF histologically, particularly lymphomatoid papulosis and the more aggressive forms of cutaneous T cell lymphoma.

While immunohistochemistry and molecular techniques may help, they should not supersede careful and considered correlation with the clinical features, which remains by far the most useful 'adjunct test'. In difficult cases, it is appropriate to reserve definitive diagnosis and follow the patient in a multidisciplinary setting; 'tincture of time' is the second most useful 'adjunct test' in such circumstances. Early MF can be a hard, at times almost impossible, diagnosis. But, delay in diagnosis does not often lead to significant morbidity. The cost of premature overdiagnosis is likely to be much greater.

Compliance with ethical standards

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