Mycosis Fungoides

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Mycosis fungoides (MF) is a CD4+ primary cutaneous T-cell lymphoma with a good prognosis. Patients with MF classicly present with pink-to-erythematous patches, well-demarcated plaques, and/or tumors on sun-protected areas, including the flanks, breasts, inner thighs, groin, and buttocks. Cutaneous biopsies of classic MF demonstrate characteristic epidermotropism, "tagging" of atypical T cells along the dermoepidermal junction, and Pautrier microabscesses. There are a number of subtypes of MF with varied presentations, including folliculotropic MF, pagetoid reticulosis, granulomatous slack skin, poikilodermatous MF, and hypopigmented MF. This chapter will discuss the clinical presentation, prognosis, treatment, histopathology, immunohistochemistry, and molecular biology of several of the subtypes of MF. It closes with five clinical cases, each representing a different subtype of MF.

5.1 Clinical

5.1.1 Clinical Presentation

Mycosis fungoides (MF) is a rare, indolent, CD4+ T-cell lymphoma [1]. In the United States, MF is the most common of the cutaneous lymphomas, comprising 54–65% of all cutaneous T-cell lymphomas (CTCLs) and 40–50% of cutaneous lymphomas overall [2–3]. It is critical to note that the terms MF and CTCL are *not* synonymous, even though they are often used as such. MF is a *subtype* of CTCL, and although MF is the most common CTCL, there are at least 10 other types.

Patients with MF have a median age of 57 [1], but pediatric cases have been reported [4]. There is a trend of increasing risk of disease progression with increasing age [5]. Men are affected twice as often as women [1, 5]. Rates

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of CTCL in general (including MF) are highest in African Americans, followed by non-Hispanic Caucasians, and last by Asians and Hispanics, at ten cases, eight cases, five cases, and five cases per million person years per ethnic group, respectively [2].

MF classicly progresses through patch, plaque, and tumor stages, although patients may manifest multiple stages at any given time. Patients with patch stage MF typically present with a history of years of having salmon-colored, slightly scaling patches long misdiagnosed as psoriasis or eczema (Figs. 5.1 and 5.2) [6]. Over the course of years, the lesions may evolve into the indurated, irregularly shaped plaques of plaque stage MF (Fig. 5.2c, d). These are distributed asymmetrically in a bathing suit or photo-protected distribution, including the breasts, inner arms, flanks, buttocks, and upper thighs [1, 6, 7]. Colors of the lesions can vary from reddish-brown to violaceous to orange [6]. There may be accompanying epidermal atrophy resulting in "cigarette paper" wrinkling (Fig. 5.2a). Other lesions may be poikilodermatous with a delicate reticulate pattern of erythema, hyperpigmentation, hypopigmentation, and telangiectasias (Fig. 5.2f) [6]. The final step in progression is the tumor stage, in which nodules or tumors of neoplastic cells are present. Ulceration may or may not be present (Fig. 5.3) [6–8].

Although rare, it is possible for MF to undergo large-cell transformation (LCT) (Fig. 5.4); transformed MF impacts 4.7 % of MF patients and follows a very aggressive clinical course [1, 9]. Visceral or lymph node involvement can occur late in the disease. Patients can also develop erythroderma reminiscent of Sézary syndrome but lack the blood involvement that defines Sézary syndrome [1]. Of note, lymphadenopathy may occur secondary to either dermatopathic change or nodal involvement of the lymphoma [1, 10, 11].

In the past some considered large-plaque and small-plaque parapsoriasis to be part of the MF family. These terms have largely fallen out of favor. Large-plaque parapsoriasis, increasingly considered patch-stage MF, has lesions greater than 6 cm and typically presents in the same bathing suit distribution as MF. Poikiloderma and atrophy are often present. The entity previously termed large-plaque parapsoriasis evolves into MF in 7.5–14 % of patients, and the majority of clinicians are moving toward terming this entity patch stage MF or in nondiagnostic cases an evolving T-cell dyscrasia [7].

The lesions of small-plaque parapsoriasis (also called digitate dermatosis) are 2–6 cm long with 10–20 digitate or fingerlike extensions and typically occur on the trunk. These lesions lack poikilodermatous changes or atrophy, and biopsies show nonspecific inflammatory changes. Small-plaque parapsoriasis has little to no potential to evolve into MF, and it is no longer considered part of the MF spectrum by many clinicians [7].

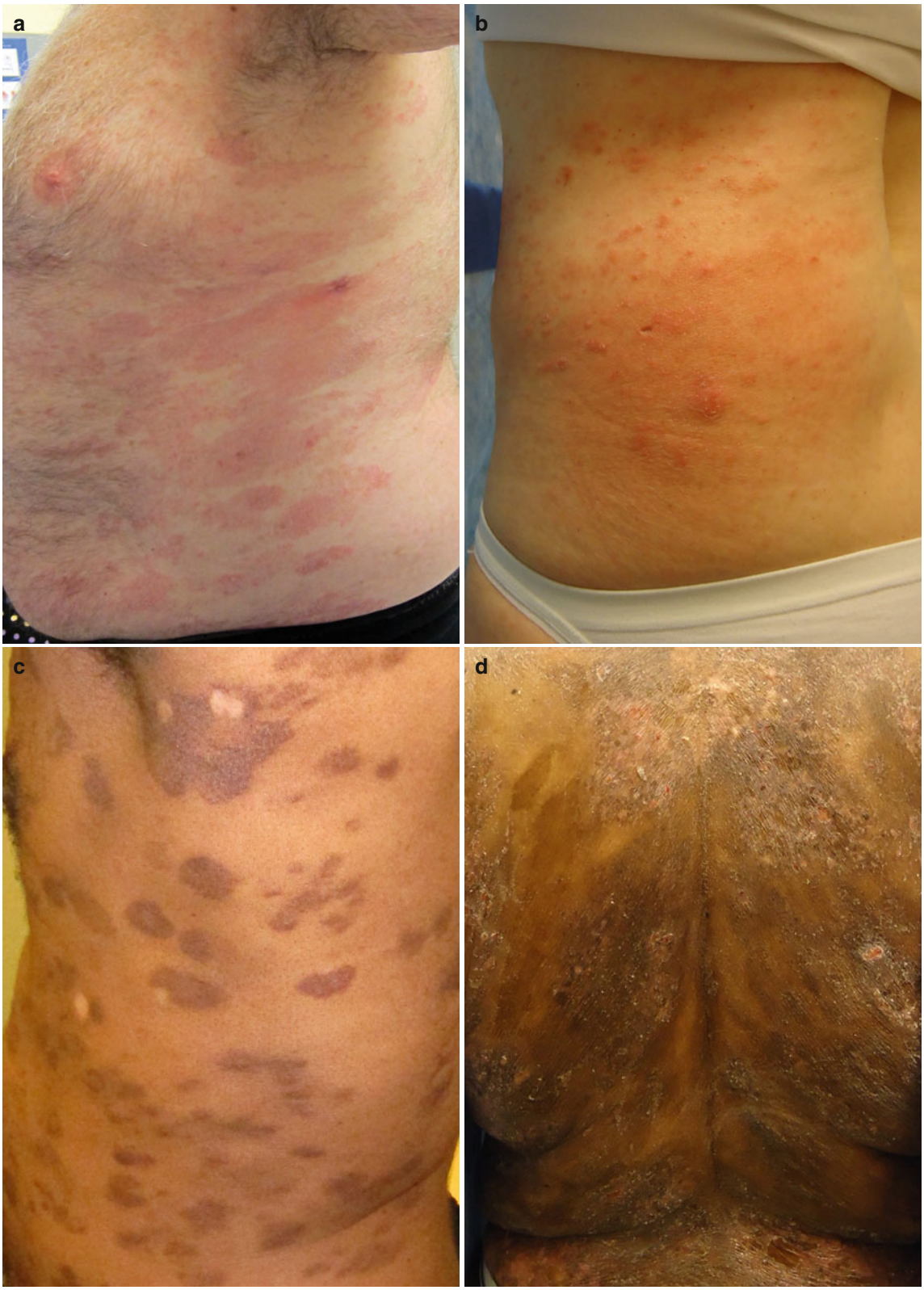

Fig. 5.1 Patch and plaque stage mycosis fungoides (MF), clinical photographs. (**a**) Large, pink-to-red, scaly patches and thin plaques on the flank and axilla of a 56-year-old man with patch/plaque MF. Similar lesions are present on the back, buttocks, and thighs (*patient featured in clinical case* 5.1). (**b**) Numerous pink, minimally scaly macules, papules, and patches on the flank of a 57-year-old woman with patch/plaque MF currently undergoing treatment with nitrogen mustard. (**c**) Scaly brown patches and plaques on the flank of a 57-year-old man with patch/plaque MF. (**d**) Innumerable hypopigmented and hyperpigmented patches and thin plaques with overlying scale and areas of xerosis, on the back of a 41-year-old woman with CD8+ MF. Similar patches and plaques are present over nearly 100 % of body surface area

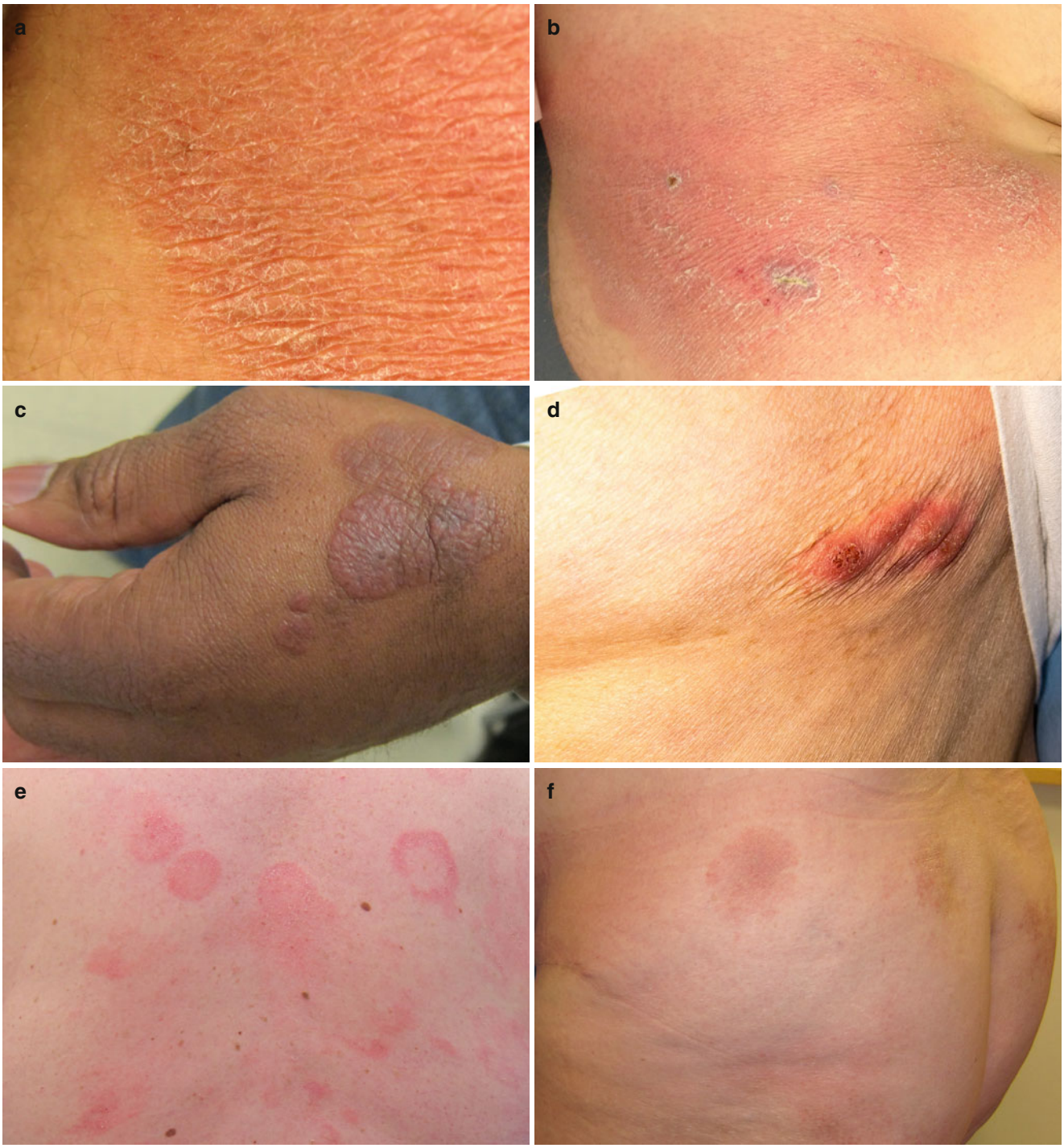

Fig. 5.2 Patch and plaque stage MF, clinical photographs. (**a**) Epidermal atrophy accompanying the atypical T-cell infiltrate results in a "cigarette paper" appearance. (**b**) Erythematous patch with areas of erosion and scale, on the anterolateral thigh of a 40-year-old man. (**c**) Indurated pink-brown plaques on the hand of a 54-year-old man. (**d**) Erythematous, indurated plaque on the chest wall of a 90-year-old man. (**e**), Numerous 1–3 cm pink annular patches and plaques on the back of a 61-year-old man. (**f**) On the buttocks of a 66-year-old woman are several annular patches with areas of atrophy, hypopigmentation, hyperpigmentation, and telangiectasias, lending a poikilodermatous appearance

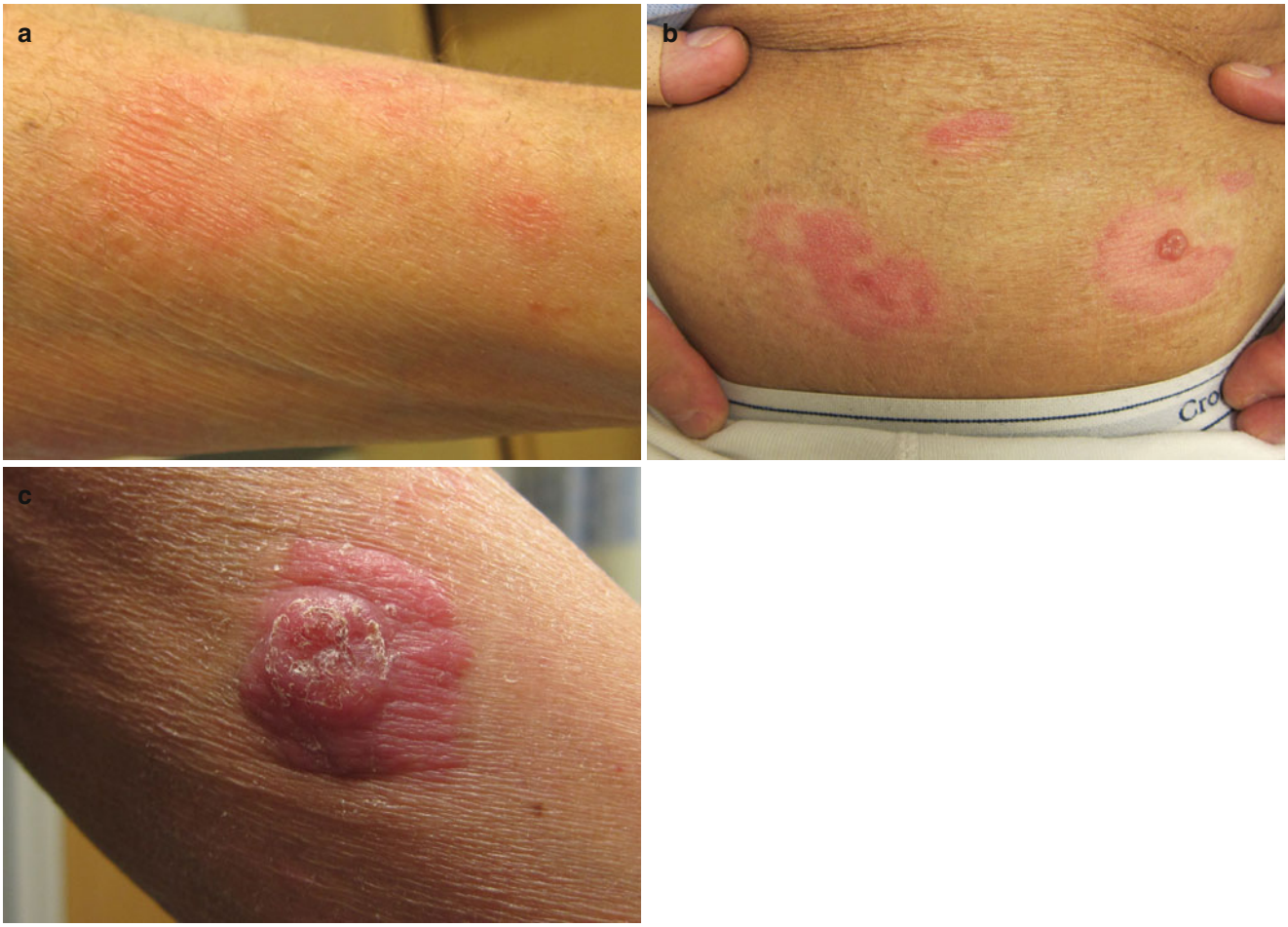

Fig. 5.3 Patch–plaque–tumor progression in MF, clinical photographs. A 64-year-old man with concurrent patches, plaques, and tumors of MF. (**a**) Scattered, pink, scaly patches on the arm. (**b**) Thin, bright pink to erythematous plaques on the lower abdomen. (**c**) Thick plaque with an overlying 3-cm tumor on the upper arm

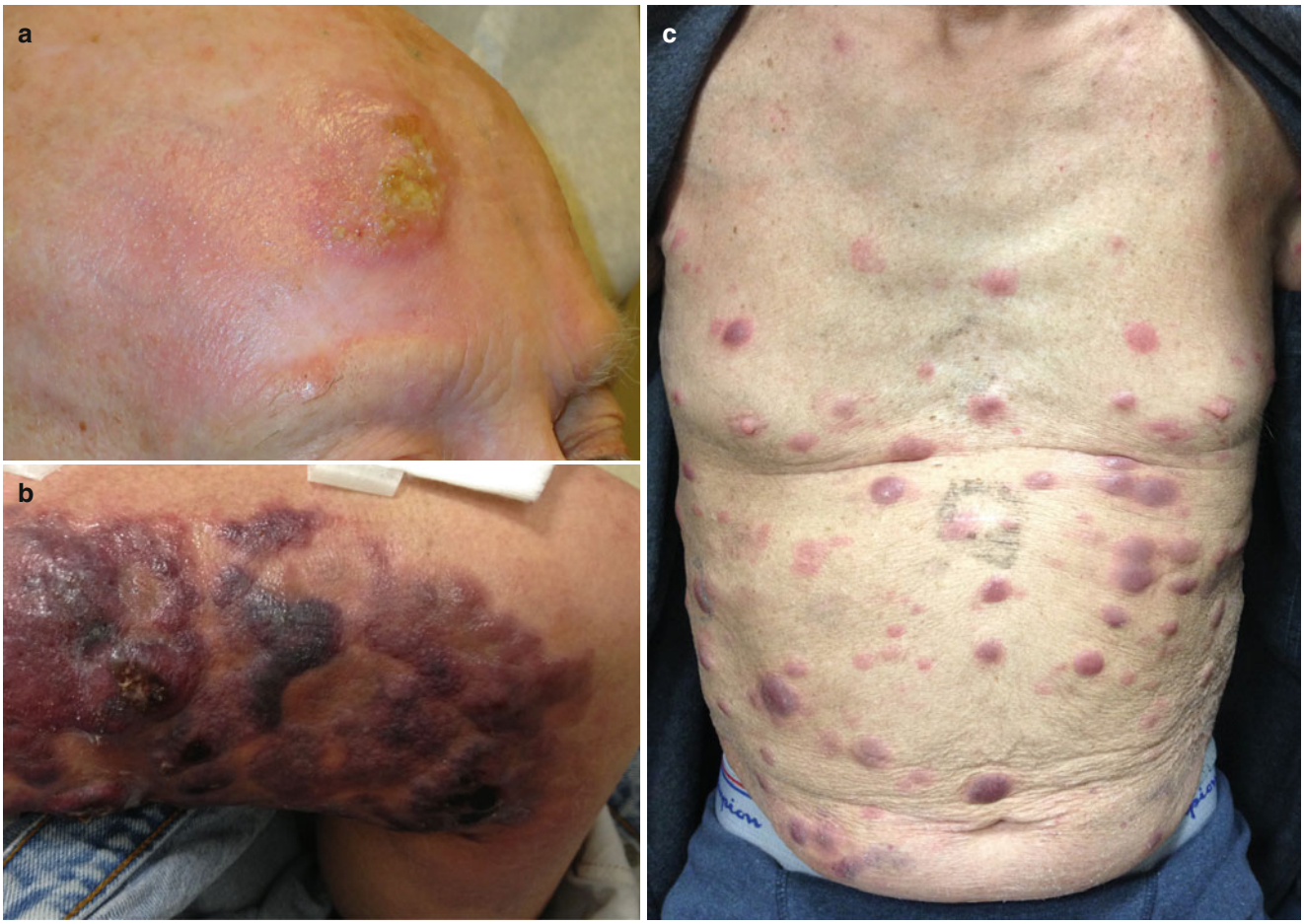

Fig. 5.4 MF with large cell transformation (LCT), clinical photographs. A 70-year-old man with MF with LCT (*patient featured in clinical case* 5.2). (**a**) Smooth, dome-shaped, skin-colored papule in the right eyebrow and 3 cm nodule with overlying crust on right forehead. (**b**) Innumerable 2–5 cm violaceous-to-black nodules coalescing into plaques on the left inner thigh. (**c**) Numerous 2–3 cm violaceous nodules scattered across the abdomen and chest

5.1.2 Prognosis and Treatment

MF generally has an excellent prognosis, with an overall 5-year disease-specific survival of almost 95 % [2]. African American patients have a slightly worse prognosis than other ethnic groups, with a 5-year mean survival of 85 % [2]. Staging guidelines for MF were revised in 2007 (Table 5.1) [12]. Although the majority of patients present with stage IA or IB disease, a higher clinical stage at diagnosis correlates with a shorter estimated survival time (Table 5.2) [10].

Large-cell transformation (LCT) has a particularly poor prognosis, with mean survival ranging from 2 to 36 months and a 5-year overall survival rate of 33 % [13]. Patients with CD30+ LCT fare somewhat better than those with CD30– transformation [13].

Negative prognostic factors of MF include increasing age, LCT, the presence of dermatopathic lymphadenopathy, and increased LDH [10]. Patients with more advanced disease at diagnosis are more likely to experience further disease progression [5]. Positive prognostic indicators include poikilodermatous or hypopigmented subtypes [10].

Although a wide array of treatment options is available, treatment is rarely curative. In early stage disease, initial therapy is typically skin directed; options include topical steroids, nitrogen mustard, topical retinoids, phototherapy, and radiation therapy. More advanced stage disease often requires systemic therapies such as bexarotene, interferon alpha, extracorporeal photopheresis, targeted therapies, single or multiagent chemotherapy, and finally bone marrow transplant [14–16]. Treatment regimens vary from patient to patient, depending on clinical presentation and subtype of MF.

Table 5.1 Staging criteria in mycosis fungoides (MF)

Stage	Skin	Nodal	Visceral	Blood	TNMB
I					
IA	**Limited patches, papules, and/or plaques on <10 % BSA (T1)**	No involvement (N_0)	No involvement (M_0)	No significant involvement (B_0) *or* Low tumor blood burden (B_1)	$T_1N_0M_0B_{0-1}$
IB	**Generalized patches, papules, and/or plaques on ≥10 % BSA (T2)**	No involvement (N_0)	No involvement (M_0)	No significant involvement (B_0) *or* Low tumor blood burden (B_1)	$T_2N_0M_0B_{0-1}$
II					
IIA	Any extent of patches or plaques (T_{1-2})	**Clinically evident dermatopathic lymphadenopathy (N1) or Early involvement by MF (N2)**	No involvement (M_0)	No significant involvement (B_0) *or* Low tumor blood burden (B_1)	$T_2N_{1-2}M_0B_{0-1}$
IIB	**One or more tumors (≥1.5 cm diameter (T3)**	Up to early lymph node involvement (N_{0-2})	No involvement (M_0)	No significant involvement (B_0) *or* Low tumor blood burden (B_1)	$T_3N_{0-2}M_0B_{0-1}$
III					
IIIA	**Erythema ≥80 % BSA (T_4)**	Up to early lymph node involvement (N_{0-2})	No involvement (M_0)	**No significant involvement (B0)**	$T_4N_{0-2}M_0B_0$
IIIB	**Erythema ≥80 % BSA (T_4)**	Up to early lymph node involvement (N_{0-2})	No involvement (M_0)	**Low tumor blood burden (B1)**	$T_4N_{0-2}M_0B_1$
IV					
IVA1	Any degree of involvement (T_{1-4})	Up to early lymph node involvement (N_{0-2})	No involvement (M_0)	**High tumor blood burden, >1,000 Sézary cells with positive TCR Clone (B2)**	$T_{1-4}N_{0-2}M_0B_2$
IVA2	Any degree of involvement (T_{1-4})	**Partial or complete nodal effacement by MF (N3)**	No involvement (M_0)	Any degree of involvement (B_{0-2})	$T_{1-4}N_3M_0B_{0-2}$
IVB	Any degree of involvement (T_{1-4})	Any degree of involvement (N_{0-3})	**Visceral involvement (M1)**	Any degree of involvement (B_{0-2})	$T_{1-4}N_{0-3}M_1B_{0-2}$

Data from Olsen et al. [12]
Key elements of the clinical or pathologic presentation differentiating each stage are in boldface
BSA body surface area, *MF* myosis fungoides

Table 5.2 Incidence of types of MF and disease specific survival (DSS)

	% of cases of MF	5-year DSS %
Classic MF	63.2	95
Folliculotropic MF	12.6	77
Poikilodermatous MF	11.2	92
MF with LyP	4.9	98
MF with LCT	4.7	65
Hypopigmented MF	3.4	98

Adapted from Agar et al. [10]

5.2 Pathology

5.2.1 Histopathology

The histopathology of classic MF differs based on the stage of the lesion (patch, plaque, tumor, or LCT). The other variants of MF also have different histopathologic characteristics.

5.2.1.1 Patch Stage

Cutaneous biopsies of early MF are characterized by a superficial bandlike or lichenoid infiltrate of atypical T-cells with marked epidermotropism (Fig. 5.5) [1]. The neoplastic T cells are small to medium and have cerebriform, hyperconvoluted nuclei with conspicuous peripheral chromatin margination [1]. The atypical cells are generally arrayed along the basal layer of the epidermis either linearly or singly; the pattern of single atypical cells along the basal layer is referred to as tagging of the dermo-epidermal junction (Fig. 5.6). The atypical lymphocytes also percolate through the epidermis and may form intraepidermal aggregates, termed "Pautrier microabscesses," usually without surrounding epidermal spongiosis (Fig. 5.7). The superficial papillary dermis may display a delicate fibrosis that leads to artifactual halo-like clearing around the dermal atypical lymphocytes. Eosinophils, histiocytes, and non-neoplastic lymphocytes may also be present.

Additional findings may include a normal to slightly acanthotic epidermis, epidermal atrophy, mild hyperkeratosis, or focal parakeratosis. Basal cell hydropic change and individual necrotic keratinocytes are very occasionally present. Red cell extravasation and pigment incontinence are common. Overall, the presence of epidermotropism, Pautrier microabscesses, and tagging are the most characteristic findings [1, 11]. Epidermotropism is most common in patch and plague stage MF and may be absent in tumor stage disease (Table 5.3).

Table 5.3 Helpful characteristics in the pathologic diagnosis of mycosis fungoides

Helpful biopsy findings in patch/plaque MF
Atypical lymphocytes with cerebriform nuclei
Lymphocytes tagging along the dermoepidermal junction forming a "string of pearls"–type configuration of lymphocytes
Pautrier microabscesses
Cerebriform cells within the epidermis, epidermotropism
Enlarged lymphocytes with surrounding halos
Epidermal lymphocytes larger than dermal lymphocytes
Lichenoid infiltrate associated with wiry bundles of collagen in the papillary dermis
Helpful biopsy findings in tumor MF
Dense diffuse/nodular dermal infiltrate of atypical cerebriform cells
<25 % Large cells
Epidermotropism, when present
Ulceration
Prominent mitotic activity, often atypical
Helpful biopsy findings in MF with large-cell transformation
>25 % Large cells
Epidermotropism, when present
Prominent mitotic activity, often atypical
CD30+ tumor cells (found in 1/3 of cases)

5.2.1.2 Plaque Stage

Biopsies of plaque stage MF demonstrate more pronounced epidermal involvement by the neoplastic T cells, including prominent epidermotropism, tagging, and Pautrier microabscesses [1, 11]. The neoplastic infiltrate is typically superficial and bandlike, although the atypical T cells are usually present singly or in clusters in the epidermis. In rare cases they can replace nearly the entire epidermis. There may be overlying mild acanthosis, compact hyperkeratosis, or patchy parakeratosis, although significant epidermal hyperplasia or scale crust is not usually seen. Other possible findings include pigment incontinence, edema, fibrosis of the papillary dermis, and proliferation of postcapillary venules. Eosinophils, plasma cells, macrophages, and dendritic cells may rarely be present [17].

5.2.1.3 Tumor Stage

Tumor stage MF is characterized by a dense, diffuse, or nodular dermal infiltrate composed of sheets of atypical T cells, in some cases extending into the subcutis [1, 17]. Ulceration is common. Epidermotropism may be present or absent [1]. In tumor stage MF cells can range in size from small to large

[1]. By definition large cells must make up less than 25 % of the infiltrate; a higher proportion would be considered LCT. Mitotic figures are readily apparent and often atypical.

5.2.1.4 Large-Cell Transformation

When LCT of MF occurs, it is characterized by the presence of more than 25 % large T cells in the dermal infiltrate on cutaneous biopsy [1]. The large cells may have prominent vesicular or hyperchromatic nuclei with conspicuous nucleoli; nuclear pleomorphism is common. Large cells not only have large nuclei but also may have apparent cytoplasm. There is typically prominent mitotic activity, and atypical mitoses are not uncommon. In one third of cases the transformed cells will be positive for CD30; the remaining two thirds are CD30-negative (Fig. 5.8) [9].

During any stage of the disease patients may develop dermatopathic lymphadenopathy, which is manifested histopathologically as lymph nodes with paracortical hyperplasia comprised of interdigitating dendritic cells, histiocytes, melanophages, and small reactive T cells; dermatopathic lymphadenopathy does not represent lymphomatous involvement of the node [1].

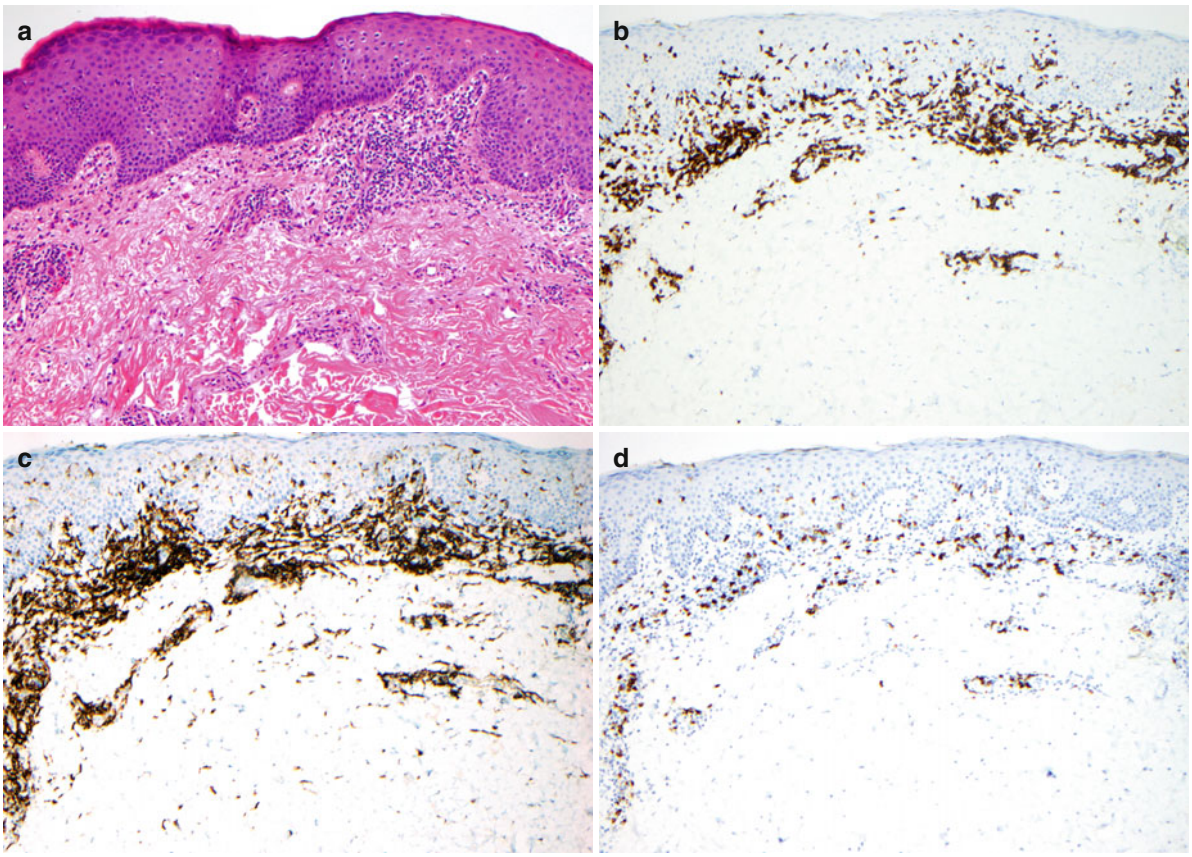

Fig. 5.5 Classic MF, histopathology and immunohistochemistry (*patient featured in clinical case* 5.1). (**a**) An epidermotropic infiltrate of atypical T cells with tagging of neoplastic cells along the dermal–epidermal junction (DEJ) (H&E, 10×). (**b**) Many of the lymphocytes cells express CD3 (CD3, 10×). (**c**) Numerous CD4+ T cells infiltrate the epidermis and superficial dermis, with tagging along the DEJ; some of these cells lack expression of CD3 (CD4, 10×). (**d**) Scattered CD8+ cytotoxic T cells are present in the lymphocytic infiltrate (CD8, 10×)

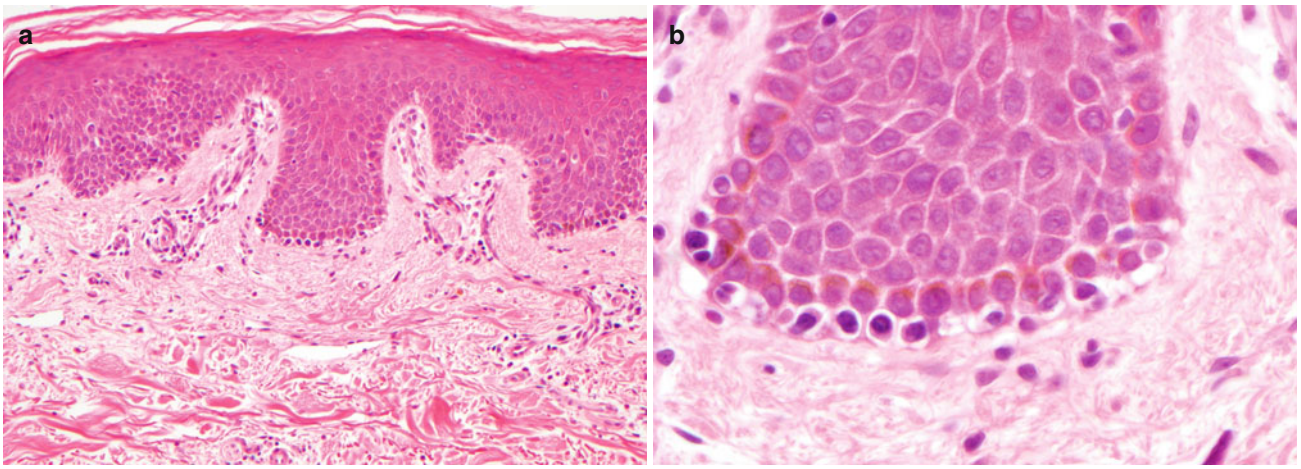

Fig. 5.6 Tagging of the DEJ and the string-of-pearls sign in MF. (**a**) Atypical lymphocytes are present along the DEJ and in the epidermis. When the cells are present singly, it is called "tagging" (H&E, 10×). (**b**) When atypical cells are present along the DEJ in series they resemble beads on a string, yielding the so-called "string-of-pearls" sign (H&E, 60×)

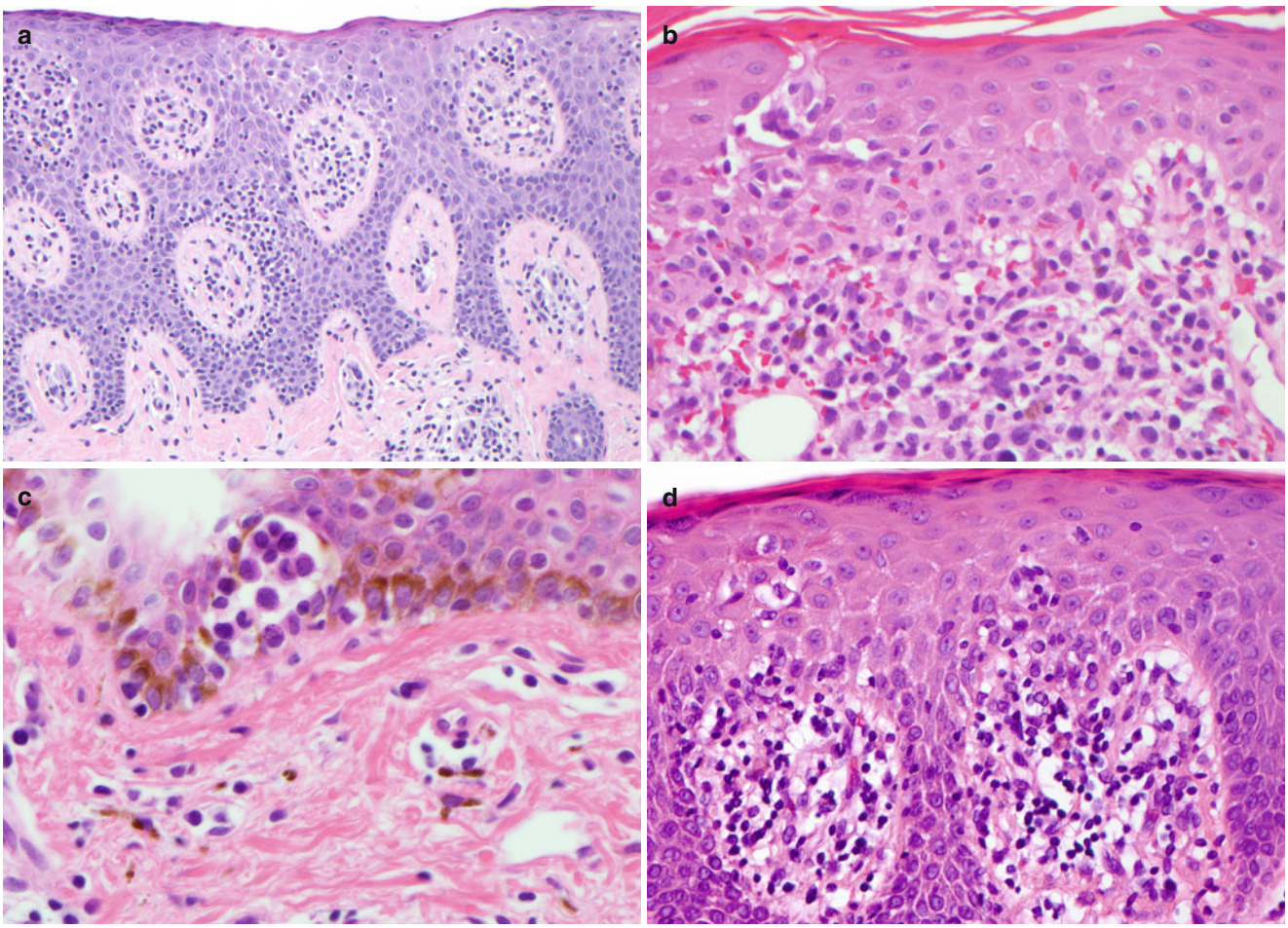

Fig. 5.7 Several examples of Pautrier's microabscesses. (**a**) Numerous Pautrier's microabscesses in the epidermis of a biopsy of a patient with patch/plaque stage MF (H&E, 10×). (**b**) A Pautrier's microabscess in the epidermis of a patient with patch/plaque stage MF (H&E, 20×). (**c**) A Pautrier's microabscess in the epidermis of a patient with exfoliative MF (H&E, 40×). (**d**) Two Pautrier's microabscesses in the epidermis of a patient with patch/plaque stage MF (H&E, 40×)

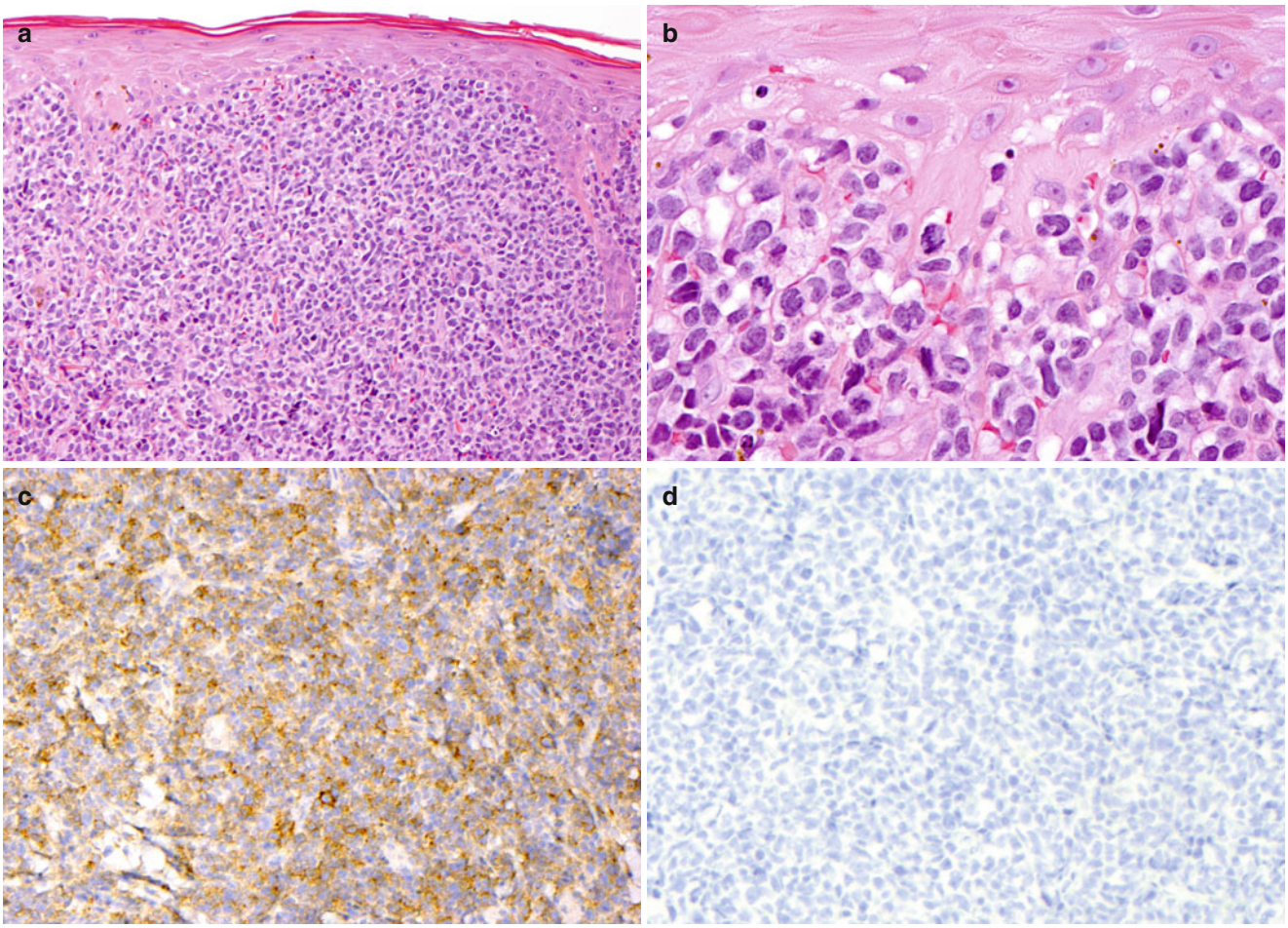

Fig. 5.8 Large-cell transformation of MF (*patient featured in clinical case* 5.2). (**a**) A dense, diffuse dermal infiltrate of sheets of neoplastic T cells, >25 % of which are large. Epidermotropism is retained in this example (H&E, 4×). (**b**) The neoplastic T cells are very large with irregularly shaped, crenellated, heterochromatic nuclei. Blastic cells have prominent nucleoli (H&E, 60×). (**c**) The majority of the large atypical cells express CD30 (CD30, 20×). (**d**) The large atypical cells are Alk negative, (Alk, 20×)

5.2.2 Immunophenotype and Molecular Findings

The neoplastic CD4+ T cells of MF often stain positively for CD2, CD3, CD4, CD5, TCRbeta, and CD45RO. In the vast majority of cases of MF, the neoplastic T cells are CD4+ CD8−; only rarely is MF composed of CD8+ CD4− T cells [1]. Neoplastic cells may show loss of pan–T-cell antigens including CD2 and CD5, a helpful diagnostic finding (*see* Fig. 5.3b–d) [1, 11]. CD7 is lost in one third of cases. However, because CD7 is frequently lost in reactive cutaneous T-cell infiltrates, it is not a useful marker of neoplastic T cells in the skin [1]. CD25 is rarely present [17]. As the disease progresses, loss of CD2, CD3, and CD5 becomes more common (Table 5.4) [17].

Cells typically express CLA, a cell surface antigen involved in homing of lymphocytes to the skin. Cytotoxic granules are rarely seen early in disease progression but may be present in neoplastic cells of advanced lesions [1].

Clonal rearrangement of the TCR is nearly always detected [1]. A concomitant loss of TCR diversity in the blood may contribute to deficiencies in immunity [11]. Of note, the presence of the same TCR clone in multiple biopsies is correlated with a worse prognosis [18].

The genetics underlying MF are poorly understood [19]. Complex karyotypes are usually present, including recurrent loss of 1p, 17p, 10q, 13a, and 19 and gains of 4q, 17q, and 18 [19–25]. Constitutive activation of STAT3, CDKN2A/p16^{INK4a}, and PTEN has also been implicated in disease progression [1, 24]. There is some evidence that

microsatellite instability may play a role in the underlying pathobiology of MF [26].

Table 5.4 Common immunohistochemical findings in MF

Positive markers	Negative markers
CD2[a]	CD8
CD3[a]	CD7 (1/3 cases)
CD5[a]	CD25
CD7 (2/3 cases)	CD56
TCR-beta	TCR-gamma
CD45RO	

Although these are generally true, there are always exceptions. Notable exceptions include hypopigmented MF, which is often CD8+
[a]Often lost with disease progression

5.3 Subtypes of MF

Numerous subtypes of MF have been described. These include classic, erythrodermic, follicular, syringotropic, bullous, granulomatous, poikilodermatous, hypopigmented, hyperpigmented, unilesional (Pagetoid reticulosis), palmoplantar, hyperkeratotic, vegetating, ichthyosiform, pigmented purpura-like, and pustular, among others [17]. Notably, the only subtypes of MF explicitly mentioned in the WHO guidelines are folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin [1]. Here, we will discuss the clinical presentation and histopathology of those three entities as well as hypopigmented, poikilodermatous, syringotropic, and granulomatous variants of MF (Table 5.5).

Table 5.5 Summary of clinical presentations and pathology of selected subtypes of MF

	Clinical presentation	Pathology
Classic	Patch-plaque-tumor progression	Epidermotropic infiltrate of neoplastic cells with "tagging" of the dermoepidermal junction and Pautrier microabscesses. Typically CD4+
Folliculotropic	Grouped follicular papules on the head and neck, alopecia, erythematous patches and plaques, and severe pruritus	Dense, perifollicular neoplastic infiltrate of neoplastic cells. Mucinous degeneration of hair follicles (follicular mucinosis)
Pagetoid Reticulosis	Single patch or plaque, <5 % BSA	Same as classic MF. May be CD4+ CD8− or CD4− CD8+. Often CD30+
Granulomatous slack skin	Bulky hanging skin folds in axillae and groin	Diffuse or band-like dense granulomatous infiltrate with cerebriform cells. Multinucleate giant cells with 20–30 nuclei, phagocytosed lymphocytes, and/or degenerated elastic fibers. Subtle/absent epidermotropism
Hypopigmented	Hypopigmented, slightly pruritic, scaly patches with irregular borders	Same as classic MF. Often CD4-CD8+
Syringotropic	Red-brown patches, slightly infiltrated scaly plaques, small skin colored to erythematous papules, alopecia, and anhidrosis	Dense perieccrine infiltrate of small cerebriform cells, hyperplasia of eccrine apparatus
Poikilodermatous	Patches of alternating hyperpigmentation, hypopigmentation, atrophy, and telangiectasias	Same as plaque or patch stage MF
Granulomatous	Patches and plaques, some with skin atrophy	Diffuse or nodular perivascular or periadnexal lymphocytic infiltrate. Granulomas present in a sarcoid-like pattern

BSA body surface area

5.3.1 Folliculotropic MF

Folliculotropic MF (also called pilotropic or folliculocentric MF) accounts for approximately 13 % of cases of MF [10]. Most often presenting as grouped follicular papules on the head and neck (Figs. 5.9 and 5.10) [1, 17], folliculotopic MF may be accompanied by alopecia, acneiform lesions, mucinorrhea, comedo-like plugs, epidermal cysts, follicular hyperkeratosis, erythematous patches and plaques, and severe pruritus [17, 27, 28]. This form of MF is four to five times more common in men than in women [17]. Folliculotropic MF has a worse prognosis than classic MF, with a 5-year disease-specific survival of 70–80 % (*see* Table 5.2) [1, 10, 29].

Cutaneous biopsy of folliculotropic MF demonstrates a dense, perifollicular and intrafollicular neoplastic infiltrate of small-to-medium CD4+ cerebriform T cells with sparing of the epidermis and interfollicular dermis (Fig. 5.11) [1, 27]. The majority of cases demonstrate mucinous degeneration of hair follicles (follicular mucinosis) (Fig. 5.12), but this is not necessary for diagnosis [1, 27]. Mucinous degeneration can range in severity from focal mucin to complete destruction of the hair follicle and formation of mucin lakes. The mucin stains positively as hyaluronic acid with colloidal iron (Fig. 5.12b), alcian blue, or toluidine blue stains [17]. Pautrier microabscesses may be present in the follicular epithelium [17]. Because infiltration of eccrine ducts may also occur, some consider folliculotropic MF and syringotropic MF to be forms of the overarching entity of adnexotropic MF [17].

5.3.2 Pagetoid Reticulosis

Pagetoid reticulosis is an exceedingly rare form of MF characterized by a single patch or plaque. These lesions usually occur on acral sites but may occasionally be present in a bathing-suit distribution. By definition, the lesions of pagetoid reticulosis cover less than 5 % of body surface area [1, 17]. Pagetoid reticulosis is indolent; extracutaneous spread has never been reported [1]. Of note, most consider pagetoid reticulosis to be synonymous with unilesional MF, whereas others consider these to be distinct entities [30].

The patches and plaques of pagetoid reticulosis are composed of a prominent epidermotropic intraepidermal proliferation of medium-to-large, hyperchromatic, cerebriform T cells, usually with more "pagetoid" distribution of the epi-

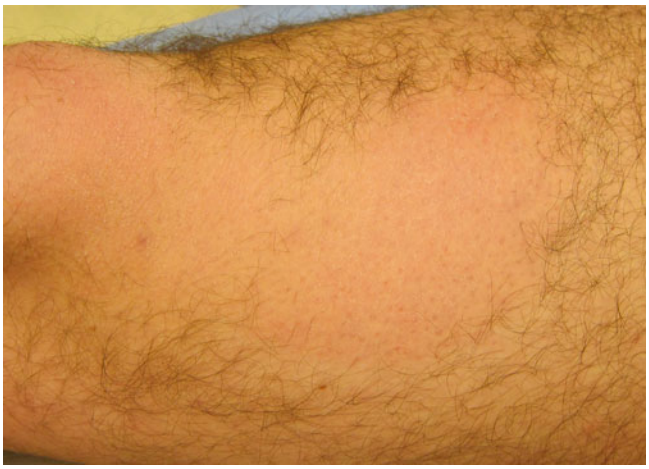

Fig. 5.9 Folliculotropic MF, clinical images. Area of alopecia and faint erythema on the anterior thigh of a 25-year-old man with folliculotropic MF

dermotropic cells than is seen in classic MF (Fig. 5.13). However, usually the pagetoid reticulosis is histopathologically indistinguishable from classic MF and requires clinicopathologic correlation for the diagnosis [1, 17]. The tumor cells may have helper (CD4+ CD8−) or cytotoxic (CD8+ CD4−) immunophenotypes and are often CD30+ [1].

Pagetoid reticulosis was once considered to have two subtypes: Woringer-Kolopp (localized pagetoid reticulosis) and Ketron-Goodman disease (disseminated pagetoid reticulosis) [1, 30, 31]. These are now believed to be distinct disease entities. Woringer-Kolopp is now considered synonymous with pagetoid reticulosis, while Ketron-Goodman is now thought to be more similar to the deadly CD8+ aggressive epidermotropic T-cell lymphoma (CD8+ AECTCL). Because pagetoid reticulosis and CD8+ AECTCL have such different prognoses and presentations, the terms Woringer-Kolopp and Ketron-Goodman are avoided in order to minimize

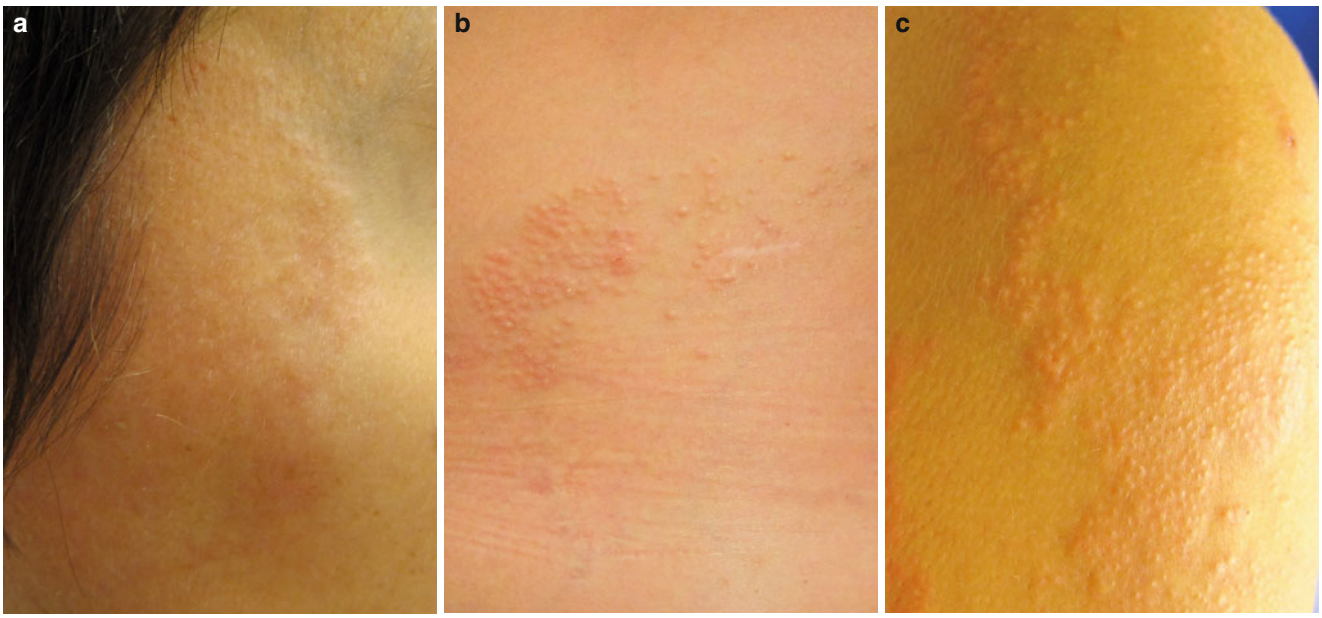

Fig. 5.10 Folliculotropic MF, clinical photographs (*patient featured in clinical case* 5.3). (**a**) An indurated, lightly erythematous, well-demarcated, pruritic plaque on the temple of a 32-year-old woman with folliculotropic MF. (**b**) Grouped follicular erythematous papules on the right flank. (**c**) Innumerable follicularly based papules on an edematous, erythematous plaque on the patient's shoulder and lateral arm

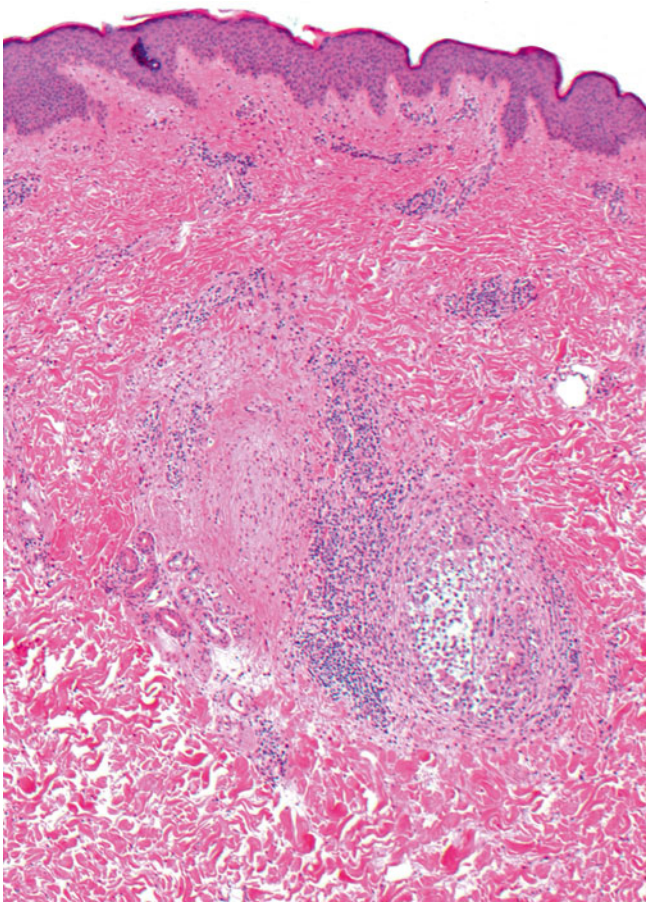

Fig. 5.11 Folliculotropic MF (*patient featured in clinical case* 5.3). Although there is extensive infiltration of the hair follicle by neoplastic T cells, the epidermis and surrounding dermis are largely spared

confusion [1] and are included here only because of their historical significance.

5.3.3 Granulomatous Slack Skin

Granulomatous slack skin (GSS) is an extremely rare but indolent variant of MF [1]. Fewer than 50 cases have been reported in the literature [32]. GSS typically presents with the slow growth of distinctive bulky skin folds in intertriginous areas (Fig. 5.14) [1, 17, 32]. These tend to be particularly prominent in the axillae and groin and may be accompanied by poikilodermatous patches or plaques. Patients often have a longstanding history of the patch and plaque stage of MF [32].

The infiltrate of GSS is composed of a diffuse or band-like dense granulomatous infiltrate of small-to-medium cerebriform T cells, numerous histiocytes, and multinucleate giant cells [1, 17, 32]. The T cells are clonal, express CD3 and CD4, and lack CD8 [1, 32]. The multinucleate giant cells may have as many as 20–30 nuclei and may contain phagocytosed lymphocytes and/or degenerated elastic fibers [17]. Epidermotropism may be subtle or absent. All affected areas will demonstrate loss of elastin, but elastophagocytosis may be subtle [32]. The elastic lamina of large cutaneous vessels is occasionally involved [33].

Of note, although GSS is characterized by a granulomatous infiltrate, it is distinct from granulomatous variants of MF. These two entities cannot be distinguished on the basis of histopathology alone and clinical correlation is necessary (see Sect. 5.3.7) [32].

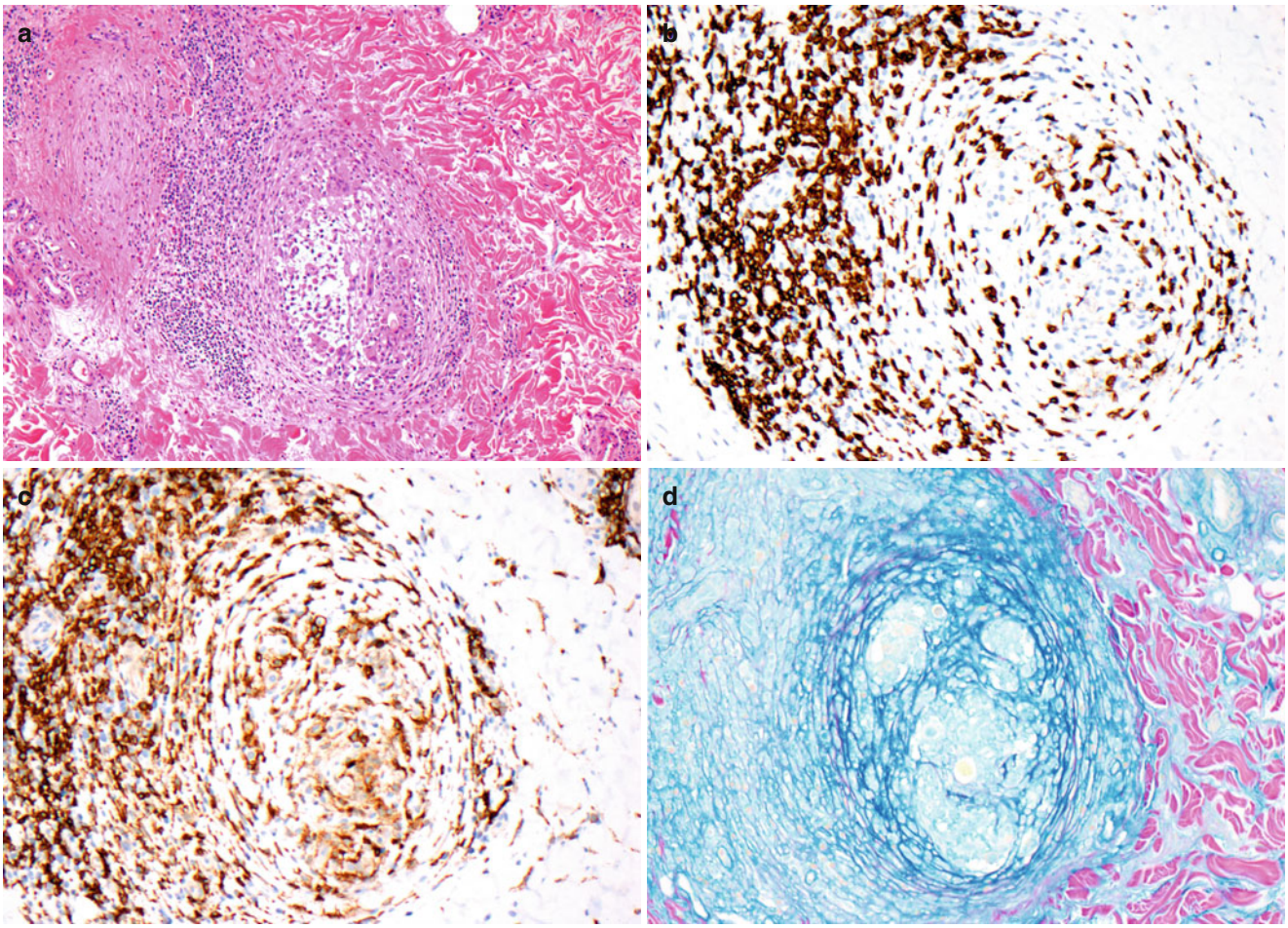

Fig. 5.12 Folliculotropic MF (*patient featured in clinical case* 5.3). (**a**) Dense, perifollicular neoplastic infiltrate of lymphocytes with destruction of the hair follicle (H&E, 10×). (**b**) The invading atypical lymphocytes are CD3+ T cells (CD3, 10×). (**c**) The neoplastic T cells express CD4 (CD4, 10×). (**d**) Colloidal iron stain reveals large amounts of mucin in the hair follicle epithelium with destruction of the hair follicle (colloidal iron, 10×)

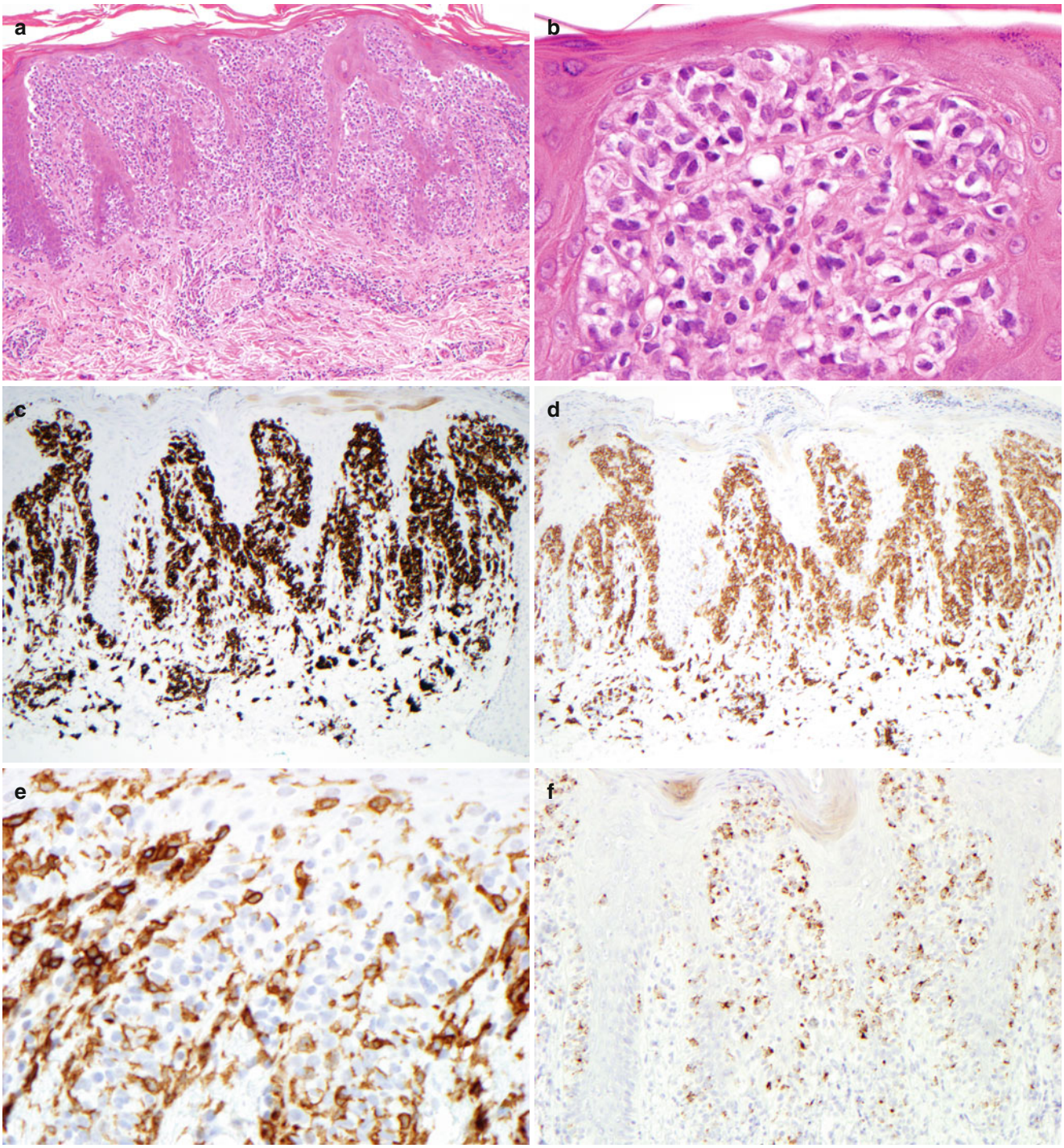

Fig. 5.13 Pagetoid reticulosis (PR). (**a**) Dense lymphoid infiltrate occupies the superficial dermis, directly abutting the epidermis without intervening Grenz zone (H&E 10×). (**b**) The lymphoid cells show minimal cytological atypia (H&E, 40×). (**c**) The infiltrate is composed of CD3+ T cells (CD3, 10×). (**d**) The majority of the lymphoid cells of the infiltrate stain strongly for CD8, indicating a cytotoxic phenotype (CD8, 10×). (**e**) Although some lymphoid cells stain positively for CD4, the majority of the CD4+ cells are histiocytes (CD4, 20×). (**f**) Consistent with a cytotoxic phenotype, many of the lymphoid cells in the infiltrate express granzyme B (Granzyme B, 20×)

5.3.4 Hypopigmented MF

Hypopigmented MF is rare and accounts for just 3 % of patients with MF [10]. Patients typically present with hypopigmented, asymptomatic, slightly pruritic, scaly patches with irregular borders (Fig. 5.15) [17]. Some patients may also have classic patches, plaques, and tumors of MF [34]. Hypopigmented MF has the same indolent nature and excellent prognosis as classic MF [17].

Patients with hypopigmented MF typically have darker skin, but this form of MF has been observed in lighter pigmented or Caucasian patients. Hypopigmented MF may be underreported in Caucasian patients because the loss of pigmentation may be less obvious. Of note, patients with less pigmented skin are more likely to have coincident classic MF lesions [17, 34]. In contrast to other forms of MF, hypopigmented MF often impacts children; nearly 20 % of reported cases are in children [34].

Although the histopathology of the infiltrate is the same as that of classic MF, the T cells of hypopigmented MF are often CD8+ [34]. Hypopigmentation is likely secondary to changes in melanin production rather than to loss of melanocytes. With treatment, perifollicular repigmentation may occur [17, 34].

Of note, there are reports of cases of *hyper*pigmented MF composed of hyperpigmented patches and plaques and also characterized by a CD8+ phenotype [35].

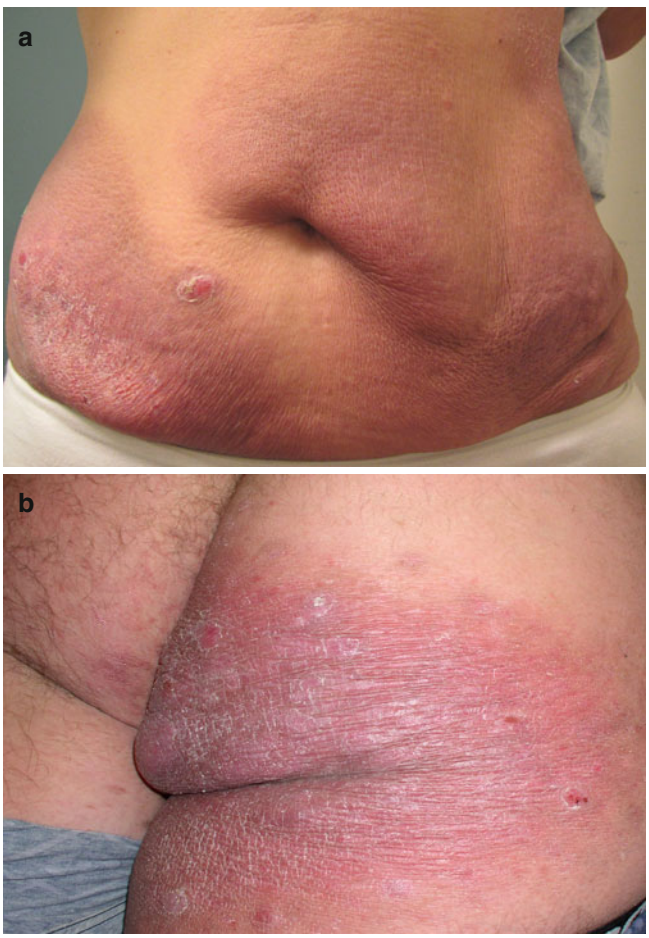

Fig. 5.14 Granulomatous slack skin (GSS). (**a**) Thickened, erythematous-to-violaceous, pendulous plaques of skin with areas of scale and erosion on the abdomen of a young woman. (**b**) Lichenified thickened plaque with erythema, scale, and erosions on the buttock of an 18-year-old man (*patient featured in clinical case* 5.4)

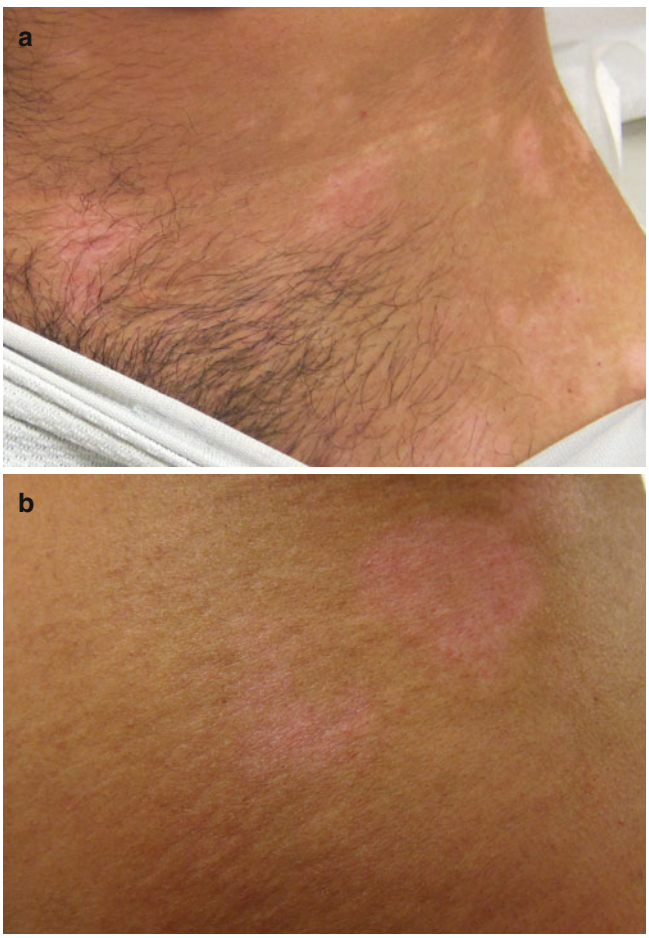

Fig. 5.15 Hypopigmented MF (*patient featured in clinical case* 5.5). (**a**) Numerous, irregularly shaped, hypopigmented-to-erythematous patches on the suprapubic region and upper thigh of a young man. Some patches are atrophic. Areas of hypopigmentation stop abruptly above the waistband, consistent with the classic "bathing suit" distribution of MF. (**b**) Three and 5 cm, pink, hypopigmented patches on the patient's buttock

5.3.5 Syringotropic MF

Syringotropic MF is a rare form of adnexotropic MF, formerly known as "syringotropic MF with alopecia" or "syringotropic cutaneous T-cell lymphoma." It is characterized by red-brown patches, slightly infiltrated scaly plaques, or small skin-colored to erythematous papules (Fig. 5.16) [17, 36]. Alopecia and anhidrosis are common, occurring in up to 70 and 30 % of cases, respectively. There is no location predilection. Patients are almost exclusively male, and many patients carry a previous diagnosis of conventional or classic MF [17, 36]. Nearly 50 % of cases present with solitary or localized lesions [36].

Histopathologically, syringotropic MF is characterized by a dense perieccrine infiltrate of small cerebriform cells with hyperplasia of the secretory portions of the eccrine apparatus (Figs. 5.17 and 5.18) [17, 29]. Conventional histopathologic characteristics of MF, including epidermotropism, are seen in the majority of patients with syringotropic MF (Fig. 5.17a) [36]. Hair follicles may be involved, but unlike in follicular MF, follicular mucinosis is absent [17].

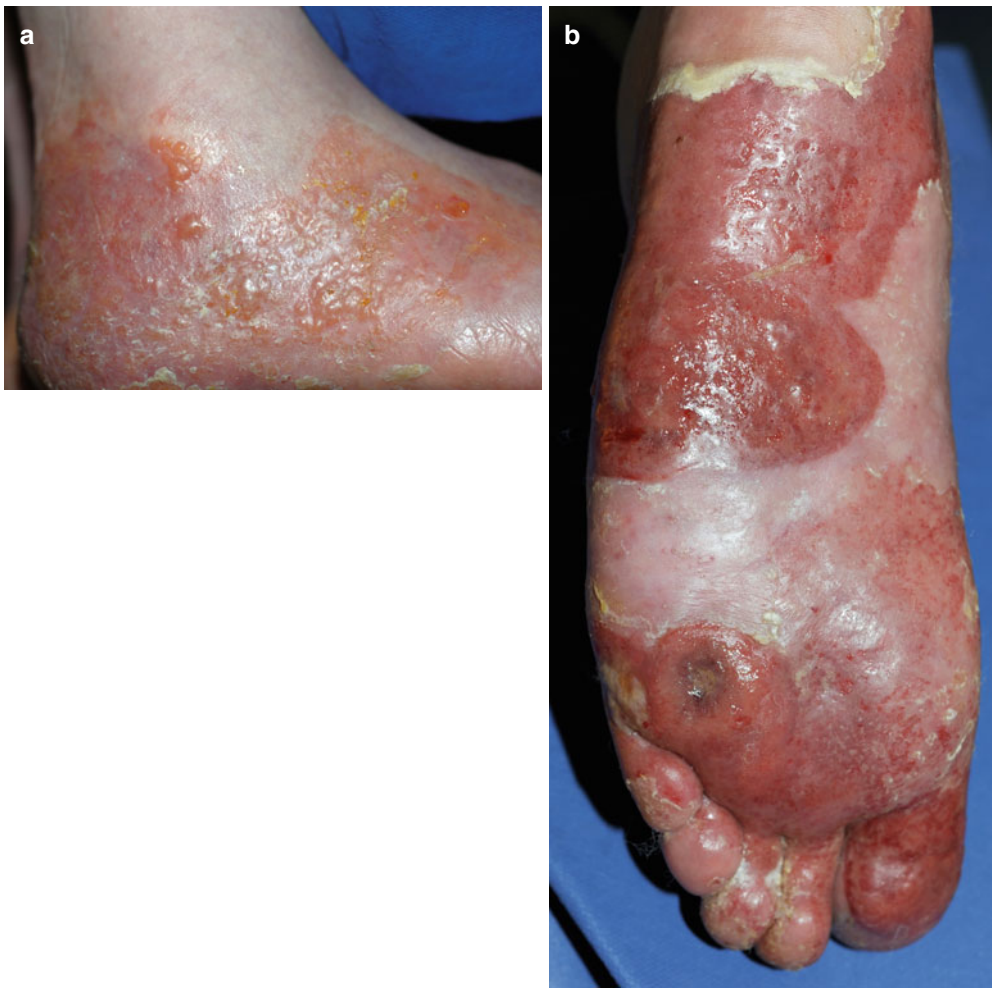

Fig. 5.16 Syringotropic MF (*patient featured in clinical case* 5.6). (**a**) On the lateral aspect of the foot of a 68-year-old man is a pink plaque studded with innumerable flaccid orange vesicles, some with erosion. (**b**) The patient's plantar foot with striking eroded plaques and erythema (Courtesy of Dr. Richard A. Johnson, Massachusetts General Hospital, Boston, MA)

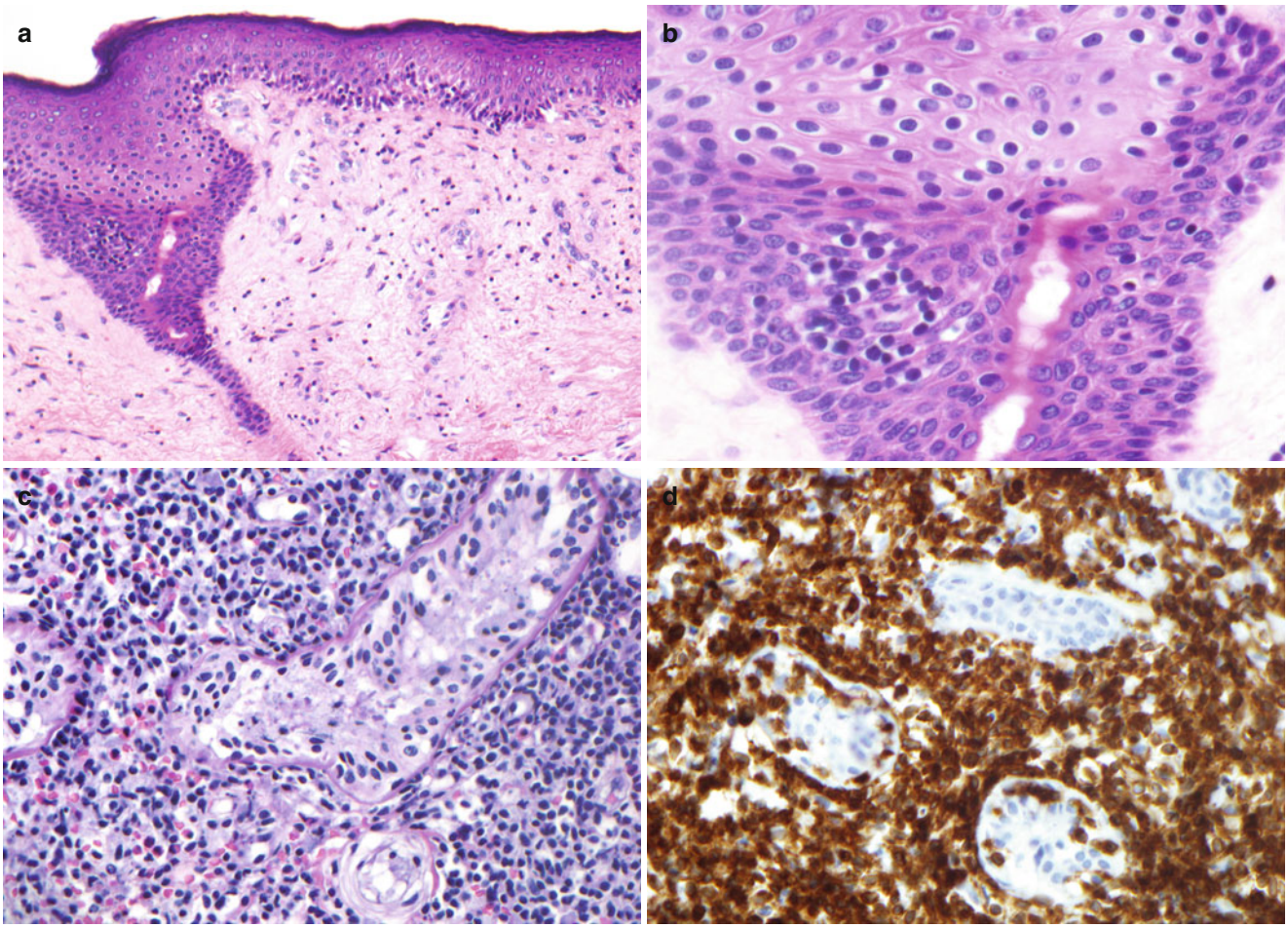

Fig. 5.17 Syringotropic MF (*patient featured in clinical case* 5.6). (**a**) Atypical lymphocytes tag the dermal-epidermal junction and invade the epithelium of the eccrine pore and duct. Eccrine duct hyperplasia is present (H&E, 20×). (**b**) The atypical lymphocytes have irregularly shaped heterochromatic nuclei (H&E, 60×). (**c**) Deeper in the dermis there is a dense perieccrine lymphocytic infiltrate (H&E, 40×). (**d**) Neoplastic CD3+ T cells are present in the eccrine gland apparatus (CD3, 40×)

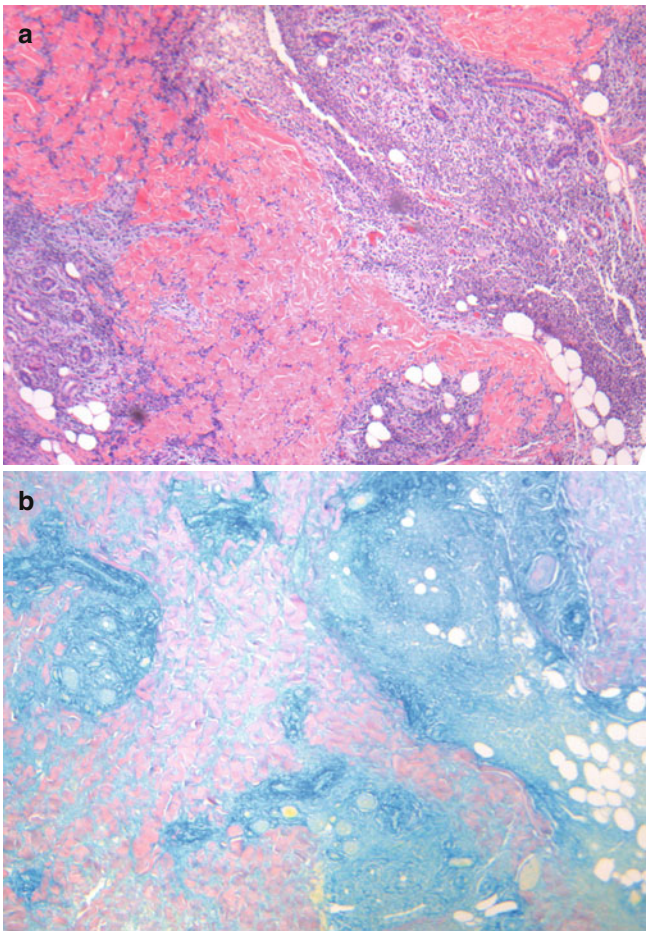

Fig. 5.18 Syringotropic MF (*patient featured in clinical case* 5.6). (**a**) Atypical lymphocytes overrun the eccrine apparatus (H&E, 4×). (**b**) Mucin is present in the dermis and eccrine apparatus (colloidal iron, 4×)

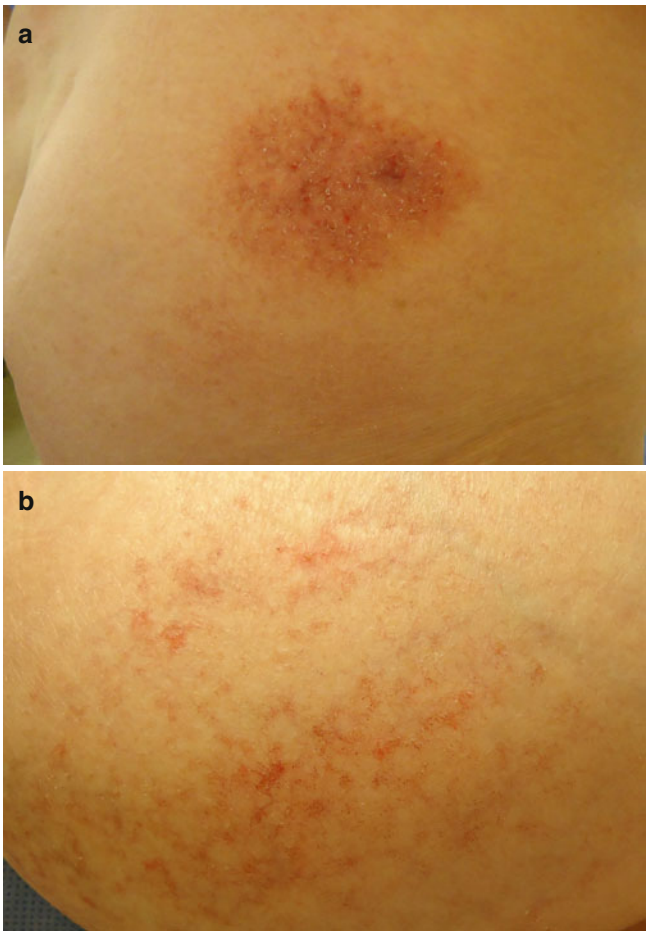

Fig. 5.19 Poikilodermatous (MF). (**a**) A 5 cm poikilodermatous patch with hyperpigmentation, hypopigmentation, and telangiectasias on the buttock of a 75-year-old woman. (**b**) Patches of delicate reticulate erythema are present on the lateral aspect of the same patient's breast

5.3.6 Poikilodermatous MF

Poikilodermatous MF impacts approximately 11 % of patients with MF and is clinically characterized by lesions with alternating hyperpigmentation, hypopigmentation, atrophy, and telangiectasias (Fig. 5.19) [17]. Areas of poikiloderma often develop slowly at the site of other classic MF patches or in areas of chronic friction. Presentation with isolated poikiloderma is possible [17].

Poikilodermatous MF is histopathologically identical to longstanding plaque or patch stage MF [17]. Additional findings include atrophy of the epidermis with flattening or loss of the rete, moderate vacuolization of the basal layer keratinocytes at the dermoepidermal junction, pigment loss, numerous papillary dermal melanophages, telangiectatic vessels, and superficial dermal scarring [17].

5.3.7 Granulomatous MF

Granulomatous MF (GMF) is a rare variant of MF that is often difficult to differentiate from benign granulomatous dermatitis or GSS. Patients typically present with patches and plaques of classic MF, some with atrophy of the skin.

This form of MF is characterized by a diffuse or nodular perivascular or periadnexal lymphocytic, dermal to subcutaneous infiltrate with extensive granuloma formation, numerous histiocytic giant cells, and minimal epidermotropism. Granulomas are typically present in a sarcoid-like pattern. In one study, 80 % of cases were CD4+ CD8−, with the remainder having a CD8+ phenotype. Clonal TCR is present in nearly all cases. Clinical correlation is needed to differentiate granulomatous MF from GSS; patients with granulomatous MF do not develop the pendulous skin folds characteristic of GSS [32, 37]. Patients with GMF have a worse prognosis than those with classic or folliculotropic MF, with a 5-year survival of 66 % [32].

5.4 Differential Diagnosis

5.4.1 Diagnostic Considerations

The differential diagnosis of MF is extremely broad, particularly given the variety of clinical and histopathologic appearances of its many subtypes (*see* Fig. 5.4). In this section, the differential diagnoses are described separately for distinct subtypes of MF. As in all of clinical medicine, diagnosis necessitates a synthesis of clinical presentation and pathophysiology. Important clinical considerations include the clinical evolution of the disease, lesion morphology, and the distribution of lesions [7]. Histopathology, immunohistochemistry, and molecular studies are invaluable in diagnosing MF [7, 38]. Loss of CD2 and/or CD5 supports a diagnosis of MF.

5.4.2 Differential Diagnosis of Classic (Patch/Plaque/Tumor Stage) MF

The differential diagnosis for classic MF alone is quite broad, given the variation in clinical appearance and histopathology at different stages of the disease.

5.4.2.1 Psoriasis

Psoriasis is the most common clinical mimic of classic MF, given that both present with chronic, recurrent, sharply marginated, erythematous patches and plaques. However, in contrast to the lesions of MF, those of psoriasis classically demonstrate silvery-white scales and are located in a symmetric distribution on extensor surfaces [11, 39]. Erythrodermic psoriasis may also mimic MF. Patients with psoriasis may also develop psoriatic arthritis, which is absent in MF. In contrast to MF, psoriasis manifests with hyperkeratosis and parakeratosis, loss of the epidermal granular cell layer, epidermal acanthosis, elongation of the rete, numerous epidermal keratinocytic mitoses, neutrophilic exocytosis with the intraepidermal spongiform pustule of Kojog beneath the stratum corneum, Munro microabscesses within the stratum corneum, thinning of the suprapapillary epidermis, and vascular dilation [40]. While neutrophils may be present in the epidermis and stratum corneum in psoriasis, usually the mononuclear cells, including lymphocytes, are predominantly located in the dermis [40], and neither tagging of the dermoepidermal junction nor Pautrier microabscesses is present. While exocytosis may be seen, epidermotropism is not [41]. Of note, clonal rearrangements can be present in psoriasis [38]. Psoriasis is also an important consideration in the differential diagnosis for pagetoid reticulosis.

5.4.2.2 Atopic Dermatitis

This chronic inflammatory dermatitis often manifests with lichenified patches and is a common mimicker of patch stage/early MF. Atopic erythroderma may also mimic MF. In contrast to MF, the histopathology of chronic atopic dermatitis is characterized by spongiosis, lymphocytic exocytosis, parakeratosis over areas of spongiosis, and a mixed perivascular infiltrate of lymphocytes, histiocytes, and occasionally neutrophils and eosinophils. There may be considerable overlap with the histology of early MF. However, MF typically lacks spongiosis, and the immune infiltrate is primarily lymphocytic; additionally, the cerebriform cytology of lymphocytes in MF and the appearance of tagging and epidermotropism allow for the diagnosis.

5.4.2.3 Hypersensitivity Reactions to Ingested Antigens Such as Drugs

This reactive process is another common mimicker of early MF. There may be considerable overlap between some drug reactions and MF; indeed, MF-like drug hypersensitivity may be histologically indistinguishable from MF. Findings that favor a diagnosis of a hypersensitivity reaction include intraepidermal Langerhans cell microabscesses, keratinocyte dyskeratosis, and the presence of papillary dermal pigment-laden macrophages and eosinophils. Immunohistochemical staining may also be helpful in this differential diagnosis: in cases with a dominant intraepidermal population of cytologically banal CD8+ lymphocytes and a dermal infiltrate of CD4+ T cells, a diagnosis of hypersensitivity is favored. An intraepidermal and dermal infiltrate of purely CD4+ atypical cells favors a diagnosis of MF but may also be observed in MF-like hypersensitivity reactions. TCR rearrangement studies are not helpful because they may be clonal in both MF and hypersensitivity reactions [42].

5.4.2.4 T-Cell Dyscrasia

It often takes many years before a diagnosis of MF can be definitively established. In the interim, many patients are seen with idiopathic chronic dermatoses that relapse after topical treatment and have no known triggering event. Biopsies of these cutaneous lesions lack overtly malignant cytology, do not show loss of T-cell antigens, and do not show a constellation of histologic features that allow for a definitive diagnosis of MF. In retrospect these changes may histopathologically represent early MF, and a clonal TCR rearrangement may or may not be present. Although some of these lesions may ultimately evolve into cutaneous T-cell

lymphoma, they are not predictive of this outcome [43]. Differentiating T-cell dyscrasias from overt malignancy can be exceedingly difficult and may require numerous biopsies over time.

5.4.2.5 Adult T-Cell Leukemia/Lymphoma (ATLL)

The histopathology of this HTLV-1-induced T-cell lymphoma can be nearly indistinguishable from that of MF. Common characteristics include epidermotropism and Pautrier microabscesses [44]. ATLL and MF can be differentiated on the basis of HTLV-1 positivity: ATLL is caused by HTLV-1, and the neoplastic cells (circulating and cutaneous) always demonstrate proviral integration, while MF has no known association with HTLV-1. Of note it is possible for patients with MF to be concomitant carriers of HTLV-1, especially in HTLV-1 endemic areas; direct PCR testing of skin lesions for proviral integration is necessary to correctly diagnose these patients [45, 46]. Immunohistochemistry may also be helpful—the cells of MF rarely express CD25, while those of ATLL are often positive for CD25 [17, 47]. Clinical presentation can also be invaluable in differentiating these lymphomas: while MF is indolent and progresses through classic patch, plaque, and tumor stages, acute ATLL is rapid, systemic, and aggressive. The chronic and smoldering forms of ATLL may be more difficult to distinguish from those of MF [46].

5.4.2.6 Lymphomatoid Papulosis (LyP), Type B

This form of LyP is commonly considered to be histopathologically "MF-like." LyP type B also presents with marked epidermotropism, and lesions of tumor stage MF can be very similar clinically to the larger ulcerated nodules of LyP. The clinical presentation often distinguishes these entities, with MF showing an evolution from patch, plaque, to tumor stage versus the self-resolving papules of LyP. Differentiating LyP and MF can be complicated by the fact that patients with LyP are at increased risk of developing secondary lymphoid malignancies, including MF [48]. Although the papules of LyP regress spontaneously, the tumors of MF are persistent.

5.4.2.7 Sézary Syndrome

Although it is an uncommon occurrence, patients with MF may present with widespread erythroderma, clinically similar to that of Sézary syndrome. However, patients with erythrodermic MF typically have preceding clinical features that are classic for MF (e.g., patch-plaque-tumor progression) and lack of significant circulating atypical lymphocytes, whereas in Sézary syndrome patients have erythroderma, lymphadenopathy, and clonality and one or more of the following (1) loss of one or more pan–T-cell antigens, (2) Sezary cells greater than 1,000 cells/μL, or (3) CD4:CD8 ratio greater than 10:1 [17]. The skin biopsy in erythrodermic MF demonstrates more prominent parakeratosis, acanthosis, papillary dermal fibrosis, telangiectasia, and mitotic figures and has a more prominent atypical dermal infiltrate with more striking epidermotropism than is typically found in Sézary syndrome [17].

5.4.3 Differential Diagnosis of Adnexotropic (Folliculotropic and Syringotropic) MF

Given the unique presentation of the adnexotropic forms of MF, it is not surprising that the differential diagnosis for these malignancies differs significantly from that of classic MF. Folliculotropic MF can mimic an array of follicularly-based inflammatory conditions clinically and histopathologically.

5.4.3.1 Follicular Mucinosis (FM)

This nonspecific reactive epithelial condition can be extraordinarily difficult to distinguish from follicular MF given significant clinical and histopathologic overlap [49]. To further complicate the diagnosis, monoclonal populations of T cells may be present in either follicular MF or FM [1, 49], and FM may precede development of follicular MF [49]. Patients with FM are typically young and have areas of alopecia histologically characterized by abundant mucin in hair follicles, hair follicle epithelial destruction, and marked lymphohistiocytic intrafollicular infiltrate [36, 38]. Follicular mucinosis may occur in a number of skin conditions, ranging from inflammatory to infectious to neoplastic [49]. While FM has a benign course and can go into complete remission, follicular MF has a moderate to poor prognosis. Abundant mucin may or may not be present in the follicular epithelium in follicular MF, and biopsies show a dense perifollicular and intrafollicular infiltrate of neoplastic cerebriform T cells [1, 27].

5.4.3.2 Alopecia Areata (AA)

This common form of nonscarring alopecia is a key element in the clinical differential diagnosis for follicular MF and a common misdiagnosis [38]. AA is a lymphocyte-mediated autoimmune condition that presents with round or oval smooth patches of alopecia with a surrounding rim of "exclamation-mark" hairs. Follicular MF often occurs with destruction of hair follicles and loss of hair in circumscribed areas. These can be differentiated on histology: AA shows a classic peribulbar lymphohistiocytic infiltrate ("swarm of bees"), miniaturization of hair follicles, and pigment incontinence [50] but lacks the follicular mucin and atypical neoplastic T-cell infiltrate of follicular MF.

5.4.4 Differential Diagnosis of Granulomatous Slack Skin (GSS)

Because of the unique clinical appearance of GSS, the differential diagnosis is limited. The primary disease that must

be distinguished on histopathology is granulomatous MF (see Sect. 5.3.3).

5.4.5 Differential Diagnosis of Granulomatous MF

The differential diagnosis for granulomatous MF includes entities that present with granuloma formation within the skin, including sarcoidosis, granuloma annulare, and other benign granulomatous dermatitis such as drug rash and bug bites. The presence of an aberrant T-cell immunophenotype with pan–T-cell antigen loss and cutaneous lesions characteristic of MF help to support the diagnosis of granulomatous MF.

5.4.6 Differential Diagnosis of Hypopigmented MF

The primary clinical considerations in the differential diagnosis for hypo- or hyperpigmented MF are conditions that cause local alteration in skin pigmentation, including vitiligo, pityriasis versicolor, pityriasis alba, and leprosy.

5.4.6.1 Vitiligo

This autoimmune skin condition is characterized by depigmented areas secondary to complete destruction and the absence of melanocytes. Although the depigmented areas may look similar to those of hypopigmented MF, clinically vitiligo usually lacks poikiloderma, scaling, or pruritus [7]. Unlike in vitiligo, hypopigmentation in MF is caused by abnormal function of melanocytes; they can still be seen on histologic examination [17, 34]. Additional clinical clues are that vitiligo may demonstrate koebnerization and enhancement of the lesion on Wood's lamp examination, characteristics absent in MF [51]. In vitiligo, immunohistochemical stains reveal an absence of intraepidermal melanocytes and no basal layer keratinocytic pigmentation on Fontana stain.

5.4.6.2 Tinea Versicolor

This benign, chronic, noninflammatory, superficial colonization of the stratum corneum by *Malassezia* spp. yeasts presents with hypo- or hyperpigmented macules and patches on the face, arms, and trunk with fine scaling. Delicate hyphal forms and numerous yeast ("spaghetti and meatballs") are readily identified on potassium hydroxide preparation (KOH) or periodic acid–Schiff (PAS) stain [52].

5.4.6.3 Pityriasis Alba (PA)

This chronic dermatosis of childhood presents with white or pink irregular, scaly, well-demarcated patches that occur on the face in 50 % of cases [53]. While both PA and hypopigmented MF are seen in children [34], these conditions can be differentiated on the basis of clinical presentation and histology. PA and MF have very different distributions. Biopsies of pityriasis alba show irregular pigmentation of the basal layer, follicular plugging, follicular spongiosis, and atrophic sebaceous glands [54]. The atypical lymphoid infiltrate and epidermotropism of MF are not seen in PA.

5.4.7 Differential Diagnosis of Poikilodermatous MF

Poikilodermatous MF has a variegated appearance and must be distinguished from a number of other conditions that clinically manifest as acquired poikiloderma [38, 55]. These include the connective tissue disease and iatrogenic conditions such as overuse of topical steroids and radiation dermatitis.

5.4.7.1 Dermatomyositis

The late phase of this connective tissue disease may present with poikiloderma of sun-exposed skin such as on the neck or central upper back (including the classic shawl sign). Histopathologically there is epidermal atrophy, interface dermatitis, increased dermal mucin (identified on colloidal iron or alcian blue stain), telangiectasia, and a sparse inflammatory infiltrate without the atypical T-cell infiltrate and epidermotropism of MF [55].

5.4.7.2 Overuse of Topical Steroids

Overuse of topical steroids can cause thinning of the skin and telangiectasias, leading to a poikilodermatous appearance. Although clinical history will typically yield the correct diagnosis, this may be complicated by the fact that MF is frequently treated with topical steroids. A skin biopsy will not show the atypical T-cell infiltrate and epidermotropism of MF.

5.4.7.3 Radiation Dermatitis

Although iatrogenic exposure to radiation may result in poikilodermatous changes in the skin, this is usually readily differentiated from MF on the basis of clinical history.

5.4.8 Differential Diagnosis of Pigmented Purpuric Variant of MF

This heterogeneous group of dermatoses manifests with petechiae and bronze discoloration of the skin, most often on the lower legs, and can be difficult to distinguish from the rare pigmented purpuric variant of MF. PPD can be subdivided into a number of conditions, including Schamberg disease, Majocchi purpura, Gougerot-Blum purpura, lichen aureus, and eczematid purpura of Doucas and Kapetanakis. Histopathologically, pigmentary purpura is characterized by the presence of papillary dermal pigment-laden macrophages,

erythrocyte extravasation, endothelial cell swelling of small superficial dermal vessels, and a lymphoid infiltrate with variable numbers of histiocytes that may be lichenoid or perivascular. It may also be associated with epidermal changes, including spongiosis and parakeratosis. Differentiation from the pigmented purpuric variant of MF may be difficult given that approximately half of cases of PPD are associated with a clonal rearrangement of the TCR [56]. Cellular atypia may be also be present [56].

5.5 Clinical Cases

Case 5.1 Patch/Plaque MF

A 56-year old man with a history of eczematous dermatitis since childhood, previously managed with topical steroids, presented with pruritic, diffuse, light pink scaly patches covering 30–40 % of his body surface area, including the chest, abdomen, axillae, medial upper arms, upper thighs, and buttocks (see Fig. 5.1a). He reported that these plaques worsened in the winter. In the past the plaques had improved with sun exposure, but recently his symptoms had persisted despite sun exposure. Physical examination revealed numerous scaly pruritic patches and thin plaques in a photoprotected distribution.

A biopsy performed 7 years prior had shown a superficial perivascular and papillary dermal lymphocytic infiltrate with minimal cytologic atypica, consistent with mild chronic eczematous dermatitis or an evolving T-cell dyscrasia.

A new biopsy of one of the plaques was performed and revealed a lichenoid lymphocytic infiltrate with tagging of the dermoepidermal junction, significant epidermotropism, and notable cytologic atypia. The intraepidermal lymphocytes were almost exclusively CD3+ CD4+ T cells with loss of CD2 (*see* Fig. 5.5). A CT scan and a complete blood count were performed and showed no evidence of systemic disease. The patient was diagnosed with stage 1B MF.

Total clearing of truncal MF patches was achieved with narrow band ultraviolet-B (NBUVB) phototherapy and topical triamcinolone.

Comment This case of classic patch/plaque stage MF illustrates several important points about disease progression in MF. First, many patients may carry a diagnosis of eczema or chronic dermatitis for decades before they are diagnosed with MF. Second, initial biopsies may be nonspecific, and patients may require multiple biopsies to finally receive a diagnosis. Third, this disease occurs in a bathing suit distribution (in this case the chest, abdomen, axillae, medial upper arms, upper thighs, and buttocks) and is often ameliorated by sunlight.

Case 5.2 MF with LCT

A 70-year-old man presented with a 1-year history of right eyelid swelling and a 3-week history of a new 3-cm indurated plaque by his right eye. Biopsy of the right eye lesion revealed a dense infiltrate of large lymphoid cells expressing CD3, CD4, CD5, and TCR gamma and lacking CD30; the patient was diagnosed with cutaneous T-cell lymphoma, not otherwise specified (CTCL-NOS) and treated with surgical debulking and radiation.

After treatment, he remained disease-free for 4 years. However, he then developed a new nodule in his right eyebrow (*see* Fig. 5.4a) as well as pink scaly patches and smooth dome-shaped papules on his bilateral thighs; the papules on his left thigh progressively enlarged to become violaceous-to-black nodules coalescing into plaques (*see* Fig. 5.4b). This was accompanied by the rapid development of numerous violaceous nodules on the abdomen and chest (*see* Fig 5.4c). Several biopsies were performed. Biopsy of the eyebrow revealed a dense dermal infiltrate with numerous CD30+ large cells and focal folliculotropism, accompanied by atypical CD3+ T cells with irregular nuclei and moderately abundant cytoplasm. Polymerase chain reaction (PCR) revealed a clonal T-cell receptor (TCR). Biopsy of the thigh lesions showed a diffuse dermal infiltrate with epidermal sparing, composed of medium to large lymphoid cells with moderate pale cytoplasm, oval to irregular nuclei, vesicular chromatin, frequent mitoses, and focal necrosis. The atypical cells expressed CD3, CD4, CD5, and CD7. The neoplastic cells lacked expression of CD8, CD30, ALK1, and CD20, consistent with the characteristics a T-cell lymphoma, particularly MF (*see* Fig. 5.8). In spite of the marked variation in the pattern of lymphoid infiltrate and the immunohistochemical staining patterns of the neoplastic cells between the leg and eyebrow lesions, they both showed the same clonal TCR gene rearrangement, suggesting that both represented the same disease process.

Serial CT scans demonstrated no metastatic disease, while flow cytometry revealed the development of a circulating population of neoplastic cells with the same TCR gene rearrangement as those in the skin. The patient was ultimately diagnosed with MF with CD30+ LCT with a small circulating component.

Despite treatment with radiation, methotrexate, targeted therapies, and chemotherapy, the patient's disease continued to progress. Nine years after initial presentation, he died of complications of his MF with LCT.

Comment This case of MF with CD30+ LCT underscores the aggressiveness and poor prognosis associated with LCT. It also highlights the utility of clonality studies in determining if separate lesions are part of the same disease process.

Case 5.3 Folliculotropic MF

A 31-year-old female with an 8-year history of diffuse plaques and pruritus presented with worsening pruritus and increasing plaque thickness and size. Physical examination showed a well-demarcated light pink thin plaque on the right cheek as well as countless diffuse flesh-colored 1-mm follicular papules coalescing into arcuate plaques with alopecia centrally on her arms, back, abdomen, and buttocks (*see* Fig. 5.10). There was no evidence of tumors, nodules, or patches.

Previous biopsy performed 8 years prior revealed mucinous degeneration of the follicular epithelium with a moderately dense superficial and deep perivascular, periadnexal, and perifollicular lymphohistiocytic infiltrate of CD3+ CD5+ CD2+ T cells. Clonal rearrangement of the TCR and immunoglobulin heavy chains was absent. These findings were thus consistent with follicular mucinosis but insufficient for a diagnosis of MF. A repeat biopsy yielded similar results, again insufficient for a diagnosis of MF.

Because of progressive disease despite use of retinoids and phototherapy, a biopsy of her flank was performed and revealed a perivascular and periadnexal atypical lymphoid infiltrate with hair follicle infiltration (pilotropism), disruption of the follicles, and follicular mucin. Significant epidermotropism and Pautrier microabscesses were noted. Immunohistochemical studies revealed the lymphocytes infiltrating the hair follicle to be CD3+ CD4+ T cells with partial loss of CD7 and intact expression of CD2 and CD5. The patient was diagnosed with follicular MF.

She is currently controlled with combination therapy, including bexarotene, PUVA, methotrexate, and intermittent radiation therapy.

Comment This case of follicular MF highlights the variability clinical and histopathologic presentations of MF; one of the major features of this type of MF, which is absent in other types, is the accumulation of mucin within the hair follicles. As with case 5.1, this case demonstrates that it often takes years and multiple biopsies to finally achieve a diagnosis. This patient's clinical course also exhibits the fact that follicular MF may be preceded by follicular mucinosis. Finally, follicular MF can be more recalcitrant to therapy than patch-plaque stage MF.

Case 5.4 Granulomatous Slack Skin (GSS)

An 18-year-old man presented with an 8-year history of pruritus and eczematous-appearing plaques on the forearms and buttocks. In spite of the administration of topical corticosteroids and tacrolimus, over the last year he had developed tender, draining cystic nodules within the eczematous plaque on his buttock, without evidence of any infectious etiology. Physical examination was notable for a confluent, slightly hyperpigmented, reddish-brownish plaque comprised of multiple raised and slightly boggy papules with some overlying scale on the lateral arm. On the lateral aspect of the right buttock a slightly atrophic, shiny red plaque with overlying fine scale was seen. On the medial aspect of the buttock there was a dense infiltrative, violaceous, confluent plaque and an outpouching of pendulous, infiltrated skin with underlying induration (*see* Fig. 5.14b).

A skin biopsy of the right buttock revealed a dense superficial and deep dermal granulomatous infiltrate of atypical lymphoid cells with focal epidermotropism, prominent folliculotropism, and perivascular and periadnexal extension. The infiltrate was composed of small-to-medium sized cells with ovoid to irregular nuclei, variably condensed chromatin, distinct nucleoli, and moderate pale eosinophilic cytoplasm. These cells stained positively for CD3, CD4, and CD5, with some loss of CD7 and focal CD25 positivity. Elastophagocytosis was not seen. A clonal TCR rearrangement was present. Flow cytometry, CBC, and LDH were all within normal limits, and a CT scan of his chest, abdomen, and pelvis revealed no evidence of internal disease. In combination with the clinical presentation, this was consistent with a diagnosis of GSS.

The patient was subsequently treated with PUVA and electron beam therapy in combination with bexarotene and mupirocin, which improved the cutaneous disease.

Comment GSS is a rare variant of MF with an indolent course; this patient had disease for almost a decade without evidence of extracutaneous involvement. As in this patient, the pendulous skin folds tend to occur in the gluteal, inguinal, and axillary regions. As showcased here, diagnosis of GSS necessitates a combination of clinical information and histopathology.

Case 5.5 Hypopigmented MF

A 28-year-old man presented with a 3-year history of progressive, minimally pruritic hypopigmented patches on his hips, trunk, inguinal region, buttocks, inner thighs, and left axilla (*see* Fig. 5.15). He reported a 23-year history of similar hypopigmented macules and patches in a bathing-suit distribution. He noted that he had previously been treated with PUVA for 4 years, with complete resolution of all lesions; however, 4 years after cessation of treatment, asymptomatic truncal lesions with increased erythema began to reappear. Physical examination was notable for scaly, hypopigmented patches and plaques with faint erythema covering 6–8 % of his body surface area.

A punch biopsy of the plaque on his thigh revealed a superficial dermal lymphoid infiltrate composed of small- to medium-sized CD8+ T-cells with epidermotropism and tagging along the dermoepidermal junction. In combination with his clinical presentation, this was consistent with a diagnosis of hypopigmented MF.

Comment Hypopigmented MF is a rare entity usually found in children. In addition, the T cells of hypopigmented MF often have a CD8+ phenotype.

Case 5.6 Syringotropic MF

A 68-year-old man with CLL presented with a 5-year history of painful, debilitating, pruritic bilateral foot dermatitis, previously diagnosed as dyshidrotic eczema or allergic contact dermatitis. He had seen more than ten dermatologists and underwent patch testing four to five times. Despite treatment with topical steroids, lotrisone, griseofulvin, NBUVB, PUVA, and topical tacrolimus, the blistering had become so severe that he was unable to walk. Clinical examination showed large, oozing, painful, malodorous erosions with areas of crusting and innumerable small pustules and vesicles covering the soles of his feet (*see* Fig. 5.16). His nails were dystrophic with anonychia of the left great toe.

An initial biopsy was consistent with dyshidrotic eczema with severe hypersensitivity reaction. However, repeat biopsy showed dense predominantly dermal lymphocytic infiltrate with extension into adipose tissue and skeletal muscle, and focal epidermo- and syringotropism (*see* Fig. 5.17). The atypical neoplastic cells were small to intermediate with irregular nuclei and condensed chromatin. The atypical lymphoid infiltrate is comprised predominantly of T cells showing reactivity for CD3, CD5, and CD4 with loss of CD7; approximately 20 % of cells were positive for CD30, but all were ALK-negative. A PET scan revealed mildly 18-fluoro-deoxyglucose (FDG)-avid left external iliac and inguinal lymph nodes. The patient was diagnosed with syringotrophic MF, worrisome for early LCT.

The patient received two fractions of electron beam therapy to the left foot and had complete resolution of his disease. Two years later he is without recurrence and has been able to resume his normal activities.

Comment This case demonstrates the remarkable efficacy of radiation therapy seen in many cases of localized MF. While other treatments had been ineffective, radiation therapy resolved this patient's disease within two treatments.

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