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Original Article

Various Skin Manifestations of Mycosis Fungoides: Histopathological Features and Prognosis

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Abstract Mycosis fungoides (MF) is a type of T cell lymphoma, and comprises more than one-half of primary cutaneous T cell lymphomas (CTCL). Many variants of MF have been reported to date, although there are only three descriptions of MF variants in the WHO-EORTC classification published in 2005. Herein, we present four cases of MF, namely classical MF, Worringer-Kolopp disease, bullous MF, and folliculotropic MF. These variants of MF were all typical, although they are quite rare. Their unique clinical manifestations arise from characteristic histopathological changes in the lesions. The location and amount of infiltrating tumor cells in the epidermis seem to be profoundly correlated with the prognosis.

Key words : Mycosis fungoides, Histopathological features, Prognosis

Introduction

Mycosis fungoides (MF) was first described in 1806 by Alibert, a French dermatologist. Subsequently, Bazin described three stages, namely, a patch stage, an infiltrated plaque stage, and a tumor stage, during the course of the disease progression. In 1988, MF was classified as a low-grade non-Hodgkin lymphoma (NHL)¹⁾. MF occupies 0.5–3% of NHL²⁾. The tumor cells in MF are derived from CD4-positive T cells, with a phenotype that deviates toward the T helper 2 type³⁾. Although MF is indolent, its leukemic variant, Sézary syndrome is more aggressive with atypical tumor cells in the peripheral blood⁴⁾ and a poor prognosis. The progression of MF is very slow in the patch stage, and even some spontaneous regression with poikilodermatous changes has even been reported. The etiology of MF remains uncertain, although genetic abnormalities, infection, and environmental factors have been proposed¹⁾.

The previous classification of cutaneous T cell lymphoma (CTCL) was confusing for dermatologists because a description of cutaneous lymphoma was not evident. This problem was solved by the WHO-EORTC classification in 2005⁵⁾ and the new WHO classification in 2008⁶⁾, which rendered a diagnosis of MF practical and available to dermatologists. In the WHO-EORTC classification, three variants are described, namely, folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin^{6/7)}. Besides, there are other MF variants such as hypopigmented MF^{8/9)}, poikilodermic MF, pigmented purpura-like MF^{10/11)}, bullous MF, papular MF^{12/13)}, ichthyosiform MF^{14)–16)}, unilesional MF^{17/18)}, and palmoplantar MF^{19/20)}. Histopathologically, interstitial MF^{21/22)} and lichenoid MF²³⁾ have been also reported. Herein we present a case of classical MF, and three cases of rare but typical variants of MF, namely, Worringer-Kolopp disease, bullous MF and folliculotropic MF. We investigated the histopathological findings in association with the characteristic clinical features and prognosis of each variant.

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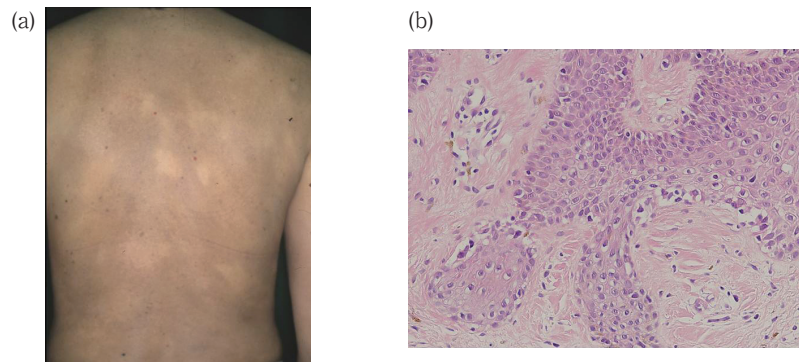


Fig. 1 (a) Multiple brownish macules on the back. (b) Epidermal infiltration of mononuclear cells with halos, and hyperplasia of collagen fibers.

Methods

The subjects were patients who were referred to the Department of Dermatology, Fukuoka University Hospital, from 2002 to 2007. All four patients were diagnosed as MF by biopsies of their skin lesions, H&E staining and immunohistochemical staining were performed on the biopsy specimens.

Case 1 : Classical MF

A 43-year-old woman was referred to our hospital because of the scaly macules, which had appeared on the abdomen 20 years previously, and gradually expanded to cover the entire body. Pale and irregular brownish macules were seen on the trunk (Fig. 1a). Histopathologically, slight acanthosis, parakeratosis, and infiltration of mononuclear cells with large nuclei exhibiting peculiar haloes mainly in the basal layer were found. Increased collagen fibers in the longitudinal direction in the papillary dermis, and a large number of melanophages were observed (Fig. 1b). We diagnosed this case as classical MF. Systemic administration of IFN- γ at 10×10^6 U/day, five times a week, and psoralen plus ultraviolet A (PUVA) therapy were performed. The rash faded gradually. One year later, a skin biopsy from a pigmented patch showed that the atypical cell infiltration had disappeared. The patient has had no relapse for 8 years.

Case 2 : Woringer-Kolopp disease

A 60-year-old man had had an itchy eruption

on the trunk for 30 years. He had been treated as tinea corporis without improvement. An indurated brownish plaque had emerged and expanded on the abdomen at 4 months before he visited our hospital. On examination, a 5-cm-sized indurated brownish plaque with scale and partial atrophy was seen (Fig. 2a). The plaque was surrounded by an erythematous bank. A biopsy taken from the periphery of the plaque showed mild acanthosis, and a number of necrotic keratinocytes were observed in the epidermis. Invasion of large lymphoid mononuclear cells with severe atypia was observed in the basal layer. In addition, small lymphoid cells had infiltrated into the upper dermis (Fig. 2b). The lymphoid cells were positive for CD3, CD4, and CD8 and negative for CD20, CD30, and CD56. In particular, the large cells were positive for CD8 and granzyme B. PUVA-bath therapy with a topical corticosteroid resolved the plaque and left residual pigmentation. No recurrence has been observed for 6 years.

Case3 : Bullous MF

A 65-year-old man had suffered from scaly erythema of the face and the extremities for 13 years. The erythema gradually expanded even though he was treated for psoriasis. A year before his visit to our department, the scaly erythema changed to erosions and fragile blisters. On examination, erythematous plaques with easily bleeding erosions and ulcers in the center were seen in the face, axilla, limbs, and intertrigi-

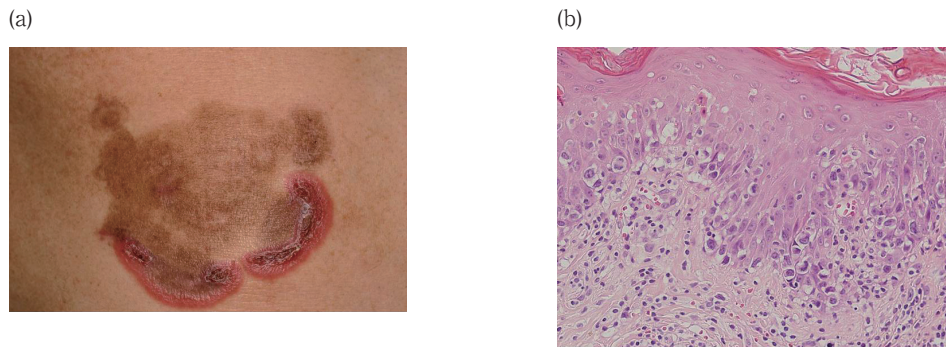


Fig. 2 (a) A 5-cm indurated brownish plaque, surrounded by a slightly erythematous bank on the abdomen. (b) Invasion of large lymphoid mononuclear cells and small lymphoid mononuclear cells was observed showing a pagetoid appearance in the basal layer.

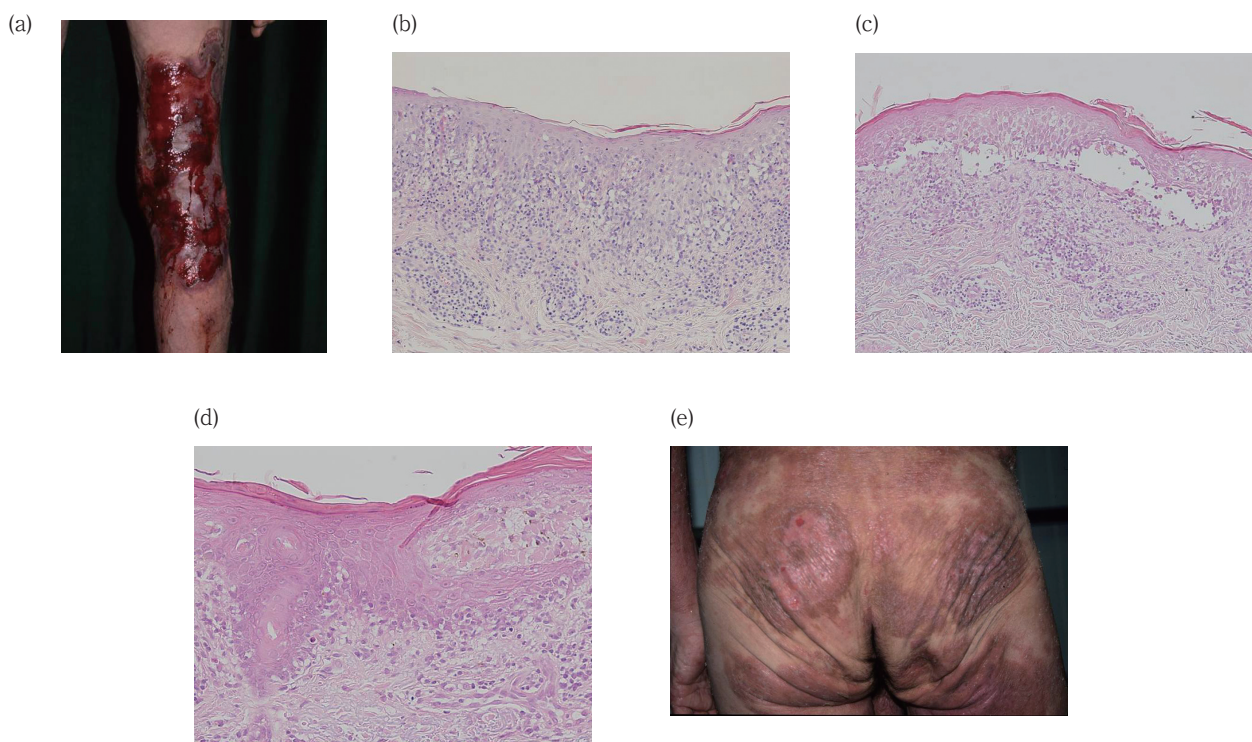


Fig. 3 (a) Ulcer with bleeding on the right lower extremity. (b) Prominent liquefaction degeneration in dermal-epidermal junction, with band-like infiltration of lymphocytes in the upper dermis. (c) Intraepidermal bullae. (d) Sight to moderate degrees of infiltration of atypical lymphocytes into the epidermis in the late period. (e) Poikiloderma is present on the entire body.

nous area (Fig. 3a). Histopathologically, spongiosis with necrotic keratinocytes in the epidermis and prominent liquefaction degeneration in the dermal-epidermal junction were observed. Severe infiltration of lymphocytes in the upper dermis was seen in a band-like manner. Atypia of lymphocytes was not distinct at this point (Fig. 3b). Autoimmune blistering disease, necrolytic migratory erythema and erythema multiforme were raised as differential diagnoses.

However, these possibilities were excluded because there were no significant findings after various examinations, including direct and indirect immunofluorescence studies. Administration of a steroid was not effective. Another biopsy taken at 16 weeks after the first visit showed intradermal and/or subepidermal bullae (Fig. 3c) and epidermotropism of atypical lymphocytes (Fig. 3d). The skin lesions rapidly expanded and became poikilodermic within 6



Fig. 4 (a) Elevated reddish plaque on the right forearm. (b) Perifollicular papule on the right forearm. (c) Aggregation of atypical lymphocytes in the follicular epithelium.

months, and eventually covered the whole body (Fig. 3e). We diagnosed this case as bullous MF at this point. Electron beam irradiation was initiated, but the patient died of sepsis soon afterward. Immunohistochemical staining of the biopsy specimens could not be carried out.

Case 4 : Folliculotropic MF

A 58-year-old woman had had itchy brownish papules on the extremities for 3 years. The papules did not respond to topical treatment. In addition, an elevated reddish plaque emerged on the right forearm at 6 months before her visit to our department. Skin biopsies were performed at both the elevated plaque (Fig. 4a) and one of the follicular papules (Fig. 4b). Atypical lymphocytes showing epidermotropism and Pautrier's microabscesses were observed. In addition, atypical lymphocytes had accumulated as though they were trying to destroy the follicles (Fig. 4c). Immunohistochemically, the infiltrating cells were positive for CD3 and CD4, and negative for CD8, CD20, and CD25. Electron beam irradiation was performed locally with a total of 40Gy (2Gy per day) with intramuscular injections of IFN- γ (1×10^6 U/ day, five times a week, total of 10×10^6 U.). Leukopenia forced us to discontinue the IFN- γ . The reddish plaque finally resulted in pigmentation. The follicular papules in the extremities were ameliorated by PUVA treatment. Although the patient recently developed a new plaque on one of her legs, she has remained alive without systemic complications for 5 years.

Results and Discussion

MF shows great variation in its skin manifestations and clinical courses. The progression of MF is extremely slow. Most patients with MF go through the patch stage and plaque stage, and eventually progress to the tumor stage. The process takes for several decades²⁴. In some cases, the lesions spontaneously disappear, leaving a poikilodermic appearance of the skin, but some MF variants such as folliculotropic MF have been reported to show aggressive courses. MF also shows variety in its histopathologic patterns. Originally, MF was considered to have a CD4-positive T cell origin. However, recent research has revealed that CD8 is also expressed in some MF cases. Although three types of MF variants are described in the WHO-EORTC classification in 2005⁵, this is not sufficient to accommodate all of the rare clinical variants. Therefore, clinicians always need to be reminded of MF for atypical skin lesions.

In this manuscript, typical but rare cases of MF variants are described with a focus on the histopathological findings in association with the clinical course and/or prognosis. In advance, diagnosis for these MF variants was made for H-E stained images and immunohistochemical stainings. TCR gene rearrangement was performed except for case 1, but monoclonality was not detected in other 3 cases.

The first case with classical MF, showed a number of annular brownish macules, and infiltra-

tion of many mononuclear cells in the epidermis histopathologically. As shown in Fig. 1a, the entire body of this patient was covered with mottled pigmented patches. The pigmentation was thought to be caused by destruction of epidermal cells in the basal layer and/or possibly melanocytes, resulting in many infiltrating melanophages infiltration in the upper dermis. The clinical course of this case was favorable with a slow progression. We also experienced a similar patient with same pattern of pigmented patches on the body and a favorable clinical course with PUVA therapy. Therefore, it is speculated that classical MF with pigmented macules in patches has a good prognosis. Histopathologically, atypical lymphoid cell infiltration was not remarkable in the first case, although many melanophages were scattered in the papillary layer of the dermis. Localization of the infiltrating atypical cells in the basal layer only seemed to be related to the slow progression and good prognosis.

The second case was pagetoid reticulosis or Woringer-Kolopp disease^{26)~28)}. This disease was first reported by French physicians, Frederic Woringer and Pierre Kolopp, for a rash that occurred on the arm of a 13 year-old boy. This type of MF is also designated localized or unilateral MF. The responses to various therapeutic modalities such as topical steroid, PUVA and irradiation are extremely good. Our patient was almost completely cured by a combination of topical steroid and PUVA. Histopathologically, pagetoid atypical large lymphoid cells had mainly infiltrated in the basal layer. Small lymphoid mononuclear cells without clear atypicality infiltrated mainly in the upper papillary dermis. Similar to case 1, case 2 also had infiltration of lymphoid cells around the basal layer of the epidermis, although the morphology of the cells was pagetoid. This infiltration pattern seemed to be correlated with the good prognosis. The phenotype of Woringer-Kolopp disease is largely CD8-positive, but not CD4-positive²⁹⁾. Although the reason for this phenotypic deviation is not

known, it may be related to the self-limiting expansion of the lesions.

In case 3, ulcers and erosions appeared on the psoriasis-like plaques from the early period of the disease. Reaching a diagnosis in this case was very difficult because of the unusual clinical manifestations and histopathological findings showing vacuolar degeneration of the dermal-epidermal junction with lymphocytic cell infiltration and numerous necrotic keratinocytes. Several biopsies during the late clinical course finally revealed atypical lymphocytes accompanied by halos with remarkable bullous changes. Therefore, we diagnosed this case as bullous MF. Bullous MF is extremely rare, and only 20 cases have been reported to date^{30)~32)}. Bowman *et al.*³¹⁾ proposed the following diagnostic criteria for bullous MF ; (1) the blister formation regardless of the clinical findings ; (2) characteristic pathological features of MF ; and (3) negative immunofluorescence, and impossibility for other causes of vesicle lesions. Various histopathological types of blisters, which are located in the subcorneal, intraepidermal or subepidermal regions, have been described in the previous reports. This variation makes a clinical diagnosis more difficult. In some cases, the blisters resemble pemphigus vulgaris or bullous pemphigoid. Case 3 showed a poor prognosis with about 15 years of survival after emergence of the skin lesions. The histopathology in the late stage revealed massive epidermal necrosis with atypical lymphoid cell infiltration in addition to the subepidermal or intraepidermal blisters. Therefore, the infiltration pattern of the atypical lymphoid cells in case 3 was quite different from those in case 1 and case 2. Aggressive destruction of the epidermis by infiltrating lymphoid cells seemed to be correlated with the rapid progression and poor prognosis.

Folliculotropic MF is also a rare variant of MF. Neoplastic T lymphocytes display tropism for the follicular epithelium³³⁾. In contrast to the classical MF which mainly affects bathing areas, the most common sites involved in folliculotropic MF

are the head and neck regions (80%) and upper extremities. Muniesa *et al.*³³⁾ reported 20 cases of folliculotropic MF. Infiltrated plaques or tumors were the most common skin manifestations, and cysts, follicular papules, or alopecia were also seen. In general, folliculotropic MF is resistant to PUVA compared with classical MF. However, the papular lesions in our case showed a good response to PUVA. Folliculotropic MF has been reported to show a poorer prognosis than that of classical MF³⁴⁾. In our case, a reddish plaque appeared suddenly after a long indolent course, followed by the development of disseminated brownish papules in the extremities. These unusual phenomena are not found in the course of classical MF, suggesting more aggressive disease progression in folliculotropic MF. Our case remained well without relapse after treatment with irradiation and IFN- γ injection for about 4 years. However, the sudden appearance of a new infiltrated plaque on one of her legs occurred thereafter. So, we need to continue to follow up this patient, carefully. Histopathologically, atypical lymphoid cells showed remarkable epidermotropism with the formation of Pautrier's microabscesses, and characteristically, the lymphoid cells showed massive infiltration into the follicular tissues to cause necrosis of the follicles. However, usual folliculotropic MF showed more aggressive infiltrating pattern of atypical lymphoid cells into the epidermis and/or follicular epithelium. Therefore, we considered that this case was more aggressive rather than typical MF, but the better for typical folliculotropic MF with relation to prognosis.

Conclusions

The clinical features of classical MF and several MF variants are quite different. In addition, the disease progression and prognosis differ between classical MF and the MF variants. In the present study, it is concluded that the histopathological findings, especially the pattern and location

of the infiltrating tumor cells, as well as the state of the epidermal destruction possibly caused by the infiltrating cells are important when we consider the disease progression or prognosis of various types of MF.

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(和文抄録)

菌状息肉症における皮膚病変の多様性と病理組織学的所見, 予後との関連性についての検討

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菌状息肉症 (Mycosis Fungoides : MF) は, 原発性皮膚悪性リンパ腫 (Cutaneous T cell lymphoma : CTCL) の約半数を占める T 細胞系のリンパ腫である。臨床経過として, 紅斑期, 扁平浸潤期を経て腫瘍期に移行するが, その期間は数年から数十年という長い経過をたどり, 中には poikiloderma 様の皮疹を残し, 病変が消退する例もある。MF を含め CTCL のほとんどが, 緩徐に進行する。近年, このような一連の経過をたどり, その腫瘍細胞が異形を呈し CD4 陽性である場合には, MF と診断される傾向が強いように思われる。2005 年に発表された WHO-EORTC 分類では, 3 亜型のみ記載があるが, 実際には多くの亜型が報告されており, その疾患スペクトラムは幅広く多様性がある。今回我々は, 古典型 MF と, 稀ではあるが特徴的な亜型, もしくは近縁疾患と考えた 3 例について, その臨床像と病理組織学的に再考し, また予後との関連についても検討を行った。病理組織学的に表皮内に浸潤するリンパ球の浸潤様式, 異形の程度で予後との関連が見られる可能性が示唆された。