Mycosis Fungoides: Facts and Controversies

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ABSTRACT

Mycosis fungoides (MF) is the commonest primary cutaneous T-cell lymphoma. The diagnosis of MF is basically by clinico-pathological correlation with the assistance of ancillary tools like gene rearrangement studies and immunophenotyping studies. There are no histological features that are pathognomonic of MF and inter- and intra-observer variations were well documented. Proper clinical staging using the TNM system is essential in its management. PUVA is a common treatment modality for MF and adequate maintenance PUVA therapy is important to keep the patient free from relapse. Combination therapy, either concomitant or sequential is the logical approach and biological response modifiers are likely to play an important role in the treatment of MF in the future.

Keywords: *Cutaneous T-cell lymphoma, Mycosis fungoides, Sezary syndrome*

INTRODUCTION

Long before fungi were known to cause disease, Alibert in 1806 described a mushroom-like skin neoplastic condition and named it mycosis fungoides (MF) in 1832.[1] MF is the commonest primary cutaneous T-cell lymphoma (CTCL). It is a clonal proliferation of CD4+, CD45Ro+ helper/memory T-cells. MF is an indolent type of CTCL that evolves slowly through skin-limited disease to systemic involvement. It is well known that it can remain in the skin for years to decades without dissemination. For almost two centuries, controversies surrounded this disease and received intense focus and discussions from dermatologists, haematologists, oncologists and pathologists.

DIAGNOSIS

The diagnosis of MF is basically by clinico-pathological correlation with the assistance of ancillary tools like gene rearrangement studies and immuno-phenotyping studies. Diagnosis of early MF is often very difficult. It is reported that the mean and median durations from onset of symptoms to diagnosis of MF were 73.2 months and 48 months respectively.[2]

Clinical features

In its earliest stage, flat patches of erythematous pruritic rash with superficial scales occurring typically in covered area like the buttock, breast or axilla. As the disease progresses, there is an increase in thickness of the lesions leading to the formation of palpable plaques. The plaques may develop from existing patches or may arise de novo. The plaques are usually well-defined, scaly, dusky red to violaceous, or hypopigmented, sometimes annular, serpiginous, indented to bizarre configurations. The plaques can be single or multiple and may coalescence to form larger plaques. Spontaneous resolution may occur leaving post-inflammatory hyperpigmentation. Lesions at different stages of development may overlap and grow on top of one another.

A minority of the patients progress to the tumour stage and is associated with a poor prognosis. There is a predilection to the face and intertriginous areas like the axilla, groin, antecubital fossae, and, in women, the inframammary area. The tumour can be an exophytic nodular growth, an ulcer or a fungating mass and often

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co-exists with patches and plaques of MF lesions. Those arise de novo without concurrent evidence of classic indolent patches and plaques, previously known as MF d'emblee, are now classified as CD30 + or - cutaneous T-cell lymphoma and are considered as separate entities. Erythroderma may develop at any stage with or without other features of Sezary Syndrome (SS) and bears a poor prognosis. Poikiloderma, follicular mucinosis, hypopigmentation, and bullous formation may be present. Bone marrow, liver, gastrointestinal tract, spleen, kidney, stomach, brain, tonsils and oral mucosa and other organs may be involved. The functions of the invaded organs are usually not impaired until the terminal stage.

Histopathology

It was demonstrated that based on histologic findings alone false-negative and false-positive rate were as high as 40% and 44% respectively in the diagnosis of early MF.[3] Less that half of the skin biopsies were diagnostic of MF in the outset and there was also a high portion of cases in which the findings were not diagnostic and were just suspicious or suggestive of MF. It is thus well known that repeated biopsies are necessary to confirm the diagnosis.

There are no pathognomonic features that are diagnostic of MF and there are always subtle patterns and features that bear subjective elements of the observers. Inter- and intra-personal variations were well documented. Ackerman et al suggested that the critical features for histologic diagnosis of early and late patch lesions of MF was the presence of an increased number of mononuclear cells distributed singly or in small collections within an epidermis devoid of spongiotic microvesiculation. Haloed lymphocytes are another important features and atypical lymphocytes are not necessary for the diagnosis of early patch of MF when cytologic changes at this stage are only slight.[4] The diagnostic value of these atypical lymphocytes is debatable in very early MF. In the absence of atypical lymphocytes some dermatopathologists, like Burg et al[5] would be reluctant to render the outright diagnosis of MF, while others like Ackerman et al[4,6] disagreed. In one study, only 6% of early patch MF showed atypical lymphocytes.[3] In fact, it is said that one would be unable to pick up most of the earliest MF if one required the presence of marked cytologic atypia for diagnosis.[7]

Smoller et al[8] in his histopathologic study of 64 MF patients demonstrated that five or more "*haloed lymphocytes*" in a 20x field were the most robust discriminator and strongest indicator of MF ($p<0.0001$). They also noted that the presence of *epidermal lymphocytes that were larger that dermal lymphocytes and Pautrier's microabscesses* were also specific but less sensitive markers of MF. Several other features were also demonstrated to be statistically significant in Smoller's series; namely *basilar epidermotropism, atypical lymphocytes within the epidermis and intraepidermal lymphocytes associated with little spongiosis*.

Moreover, there is an ever-growing list of histologic simulants of MF which range from unusual presentation of common conditions like contact dermatitis to uncommon conditions like pseudolymphoma.[3] In very early MF, there are only scanty malignant T-cells and the picture is dominated by the reactive inflammatory responses elicited.[7] In conclusion, a constellation of these features correlating with clinical features is the key to the diagnosis of MF.

T-cell receptor gene rearrangement studies (TCRGRS)

Normal T cells rearrange the variable, joint and constant regions of their TCR genes during maturation. Such unique surface molecules become the fingerprints of each T cell and its daughter cells. Detection of these clonal populations via identification of their TCR is the foundation of TCRGRS. TCRGRS using either southern blot or polymerase chain reaction (PCR) has been used as an adjunct to the histopathological diagnosis of MF. PCR is more commonly used because it is more sensitive, and does not involve radioactivity and can be performed on unstained sections of archived, formalin-fixed tissues. Amplification of the gamma chain is commonly employed because it contains only a limited number of variable segments. However, even the most comprehensive sets of available primers are not complete and thus cannot detect all possible rearrangements. Using TCRGRS, the average rate of T cells monoclonality is found to be 71-74% (50-83% in different studies) in MF biopsies and are independent of the histological features.[9,10] Furthermore, it was found that up to 13% of non-MF cases also showed monoclonality. Some of these non-MF "clonal

dermatitis" were found to progress to overt CTCL in long term follow up.[9]

Immunophenotyping

Immunophenotypically, MF is a clonal proliferation of CD4+, CD45Ro+ helper/memory T cells and rarely some may express predominantly a suppressor/cytotoxic CD8+ phenotype. There is a frequent loss of CD5 and CD7. Deletion of CD7, an antigen present in normal mature T lymphocytes, is the most sensitive and specific T-cell deletion marker for diagnosis of MF, with a sensitivity ranges from 42% to 88% and specificity ranges from 25% to 98%. Ormsby et al in their study of 17 MF cases demonstrated that CD7 deletion and TCR-γ PCR using formalin-fixed, paraffin-embedded tissue was sensitive (94%) and specific (96%).[11] On the other hand, other authors believed that in the diagnosis of early MF, unlike most lymphoma, attempts to strengthen a diagnosis of early MF using immunohistochemistry are frequently inconclusive and deletion of CD7 was also seen in 40% of non-lymphoma controls.[12]

Peripheral blood involvement, the Sezary cells

The number of circulating Sezary cells to define Sezary syndrome, and the best methods for their identification in the peripheral blood have not been well defined.[1,13] Arbitrarily, 5-20% of the circulating lymphocytes or an absolute count of 1000 cells/mm^3 have been proposed.[14] Sezary cells can be found in all stages of disease and up to 20% of advanced MF.[1]

CLINICAL STAGING

Staging system

Unlike other lymphoma, there has not been a unified staging system for MF. The TNM staging system (Table 1) adopted by Bunn et al[15] in the MF Cooperative Group in 1979 was widely used although not universal.

It is noted that the prognosis of T4 patients is better than that of T3 patients and the prognosis of patients with T2 patch and T2 plaque is significantly different.[16] In view of these, Kashani-Sabet et al[17] has published a modified staging classification in 2001. They split up

Table 1. TNM staging system by Bunn et al[15]

T-Stage			
T0	Clinically and/or histopathologically suspicious lesions		
T1	Limited patches or plaques (<10% body surface area)		
T2	Generalized patches or plaques (>10% body surface area)		
T3	Cutaneous tumour (one or more)		
T4	Erythroderma		
N-Stage			
N0	No clinically abnormal peripheral lymph nodes, pathology *negative* for CTCL		
N1	Clinically abnormal peripheral lymph nodes, pathology *negative* for CTCL		
N2	No clinically abnormal peripheral lymph nodes, pathology *positive* for CTCL		
N3	Clinically abnormal peripheral lymph nodes, pathology *positive* for CTCL		
B-Stage			
B0	<5% of atypical circulating cells		
B1	>5% of atypical circulating cells		
M-Stage			
M0	No visceral organ involvement		
M1	Visceral involvement with pathological confirmation		
Staging			
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T1,2	N1	M0
IIB	T3	N0,1	M0
III	T4	N0,1	M0
IVA	T1-4	N2,3	M0
IVB	T1-4	N0-3	M1

T2 into T2a (patches covering >10% skin surface) and T2b (plaques covering >10% skin surface) and this give a better prognostic stratification.

Staging procedures

A thorough physical examination is mandatory. Sites affected, surface area involved and the type of lesions present should be carefully mapped. Lymphadenopathy and organomegaly should be looked out for.

The following staging investigation procedures are recommended:

- Complete blood count
- Sezary cells / atypical lymphocytes count
- Liver and renal function tests, calcium, phosphate, uric acid, lactate dehydrogenase
- Skin biopsy for histopathology, TCRGRS and immunophenotyping
- Chest radiograph
- Ultrasonogram or CT scan of abdomen / thorax / pelvis

Additional investigations depending on clinical findings:

- Lymph node biopsy
- Bone marrow biopsy
- Liver biopsy

Blind lymph node biopsy is controversial, and is not commonly practiced. It is reasonable to use lymph node and blood involvement as a surrogate marker for extracutaneous involvement and to guide further investigations. In the absence of deranged liver functions or abnormal imaging studies, most centres do not perform routine liver biopsy or bone marrow biopsy.

DIFFERENTIAL DIAGNOSIS

Early MF bears close resemblance to many inflammatory dermatoses. In general, differential diagnosis of MF should include the followings:

- dermatitis,
- psoriasis,
- parapsoriasis,
- superficial fungal infections,
- drug eruptions,
- photodermatoses,
- leprosy,
- capillaritis (especially the lichenoid type),
- various causes of erythroderma,
- primary or secondary cutaneous malignancies for MF tumour,
- various causes of poikiloderma e.g. dermatomyositis or lupus erythematosus,
- vesiculobullous diseases for MF bullosa,
- hypopigmentation disorders for hypopigmented MF.

CLINICAL VARIANTS

Sezary syndrome (SS) is a form of aggressive leukaemia-lymphoma with the triad of erythroderma, generalized lymphadenopathy, and circulating atypical hyperconvoluted mononuclear cells (Sezary cells). SS is rare and constitutes about 5% of all newly diagnosed CTCL.[18] Despite this classic triad, adenopathy is only present in 57% of the SS cases. Intense pruritus is almost invariably present. Hepatomegaly, alopecia, palmo-plantar keratoderma, ectropion and onychodystrophy are each present in about 1/3 of the cases of SS. Pagetoid reticuloid (Woringer-Kolopp disease), granulomatous slack skin, hypopigmented MF, invisible MF, MF bullosa, follicular MF, and suppressor T-cell lymphoma are rare variants of MF. Granulomatous foci were identified in 10% of MF (granulomatous MF) and some may show granuloma annulare-like features.[3] Adnexotropic MF includes variants like syringotropic MF and pilotropic MF have also been described. Purpuric MF is perhaps the most controversial histopathological and clinical variants. It resembles pigmented purpuric dermatosis clinically and histopathologically. It is suggested that lichenoid pigmented purpuric dermatosis, especially in atypical sites, may be biologically related to CTCL.[3]

ASSOCIATIONS WITH OTHER DISEASES

MF has been described in more than 30 cases of HIV infected patients. This is an interesting and unexpected occurrence because the malignant proliferation of CD4+ lymphocytes is the target of HIV destruction. It is not known whether the malignant CD4+ T cells are more susceptible or resistant to HIV destruction. There was one case of spontaneously regressed MF in an HIV infected patient and the balance in that case was towards CD4+ T cells destruction.[19,20] Patients with MF may be more likely to have other

haematopoietic neoplasia, such as leukaemia, B-cell lymphoma, non-Hodgkin's lymphoma and other rare malignancies like Merkel cell tumours and thymoma. About 1% of patients with MF are associated with Hodgkin's lymphoma.[21,22]

PROGNOSIS

The overall disease-related 5- and 10-year survival rates for MF patients are 87-89% and 75% respectively. The corresponding rates for stage Ia are 100% and 97%; and drop to 40% and 20%; 0% and 0% for stage IVa and IVb patients respectively. The long term survival of stage Ia patients is not different from the matched general population.[2,14] Apart from clinical staging, a number of poor prognostic indicators have been suggested:

- Elevated LDH
- Follicular mucinosis
- Old age and male sex
- CD4/CD8 ratio >20
- Sezary cell counts >4000/mm^3 or presence of large Sezary cells
- CD30-negative
- Large cell transformation
- Absence of a complete remission

TREATMENT

The choice of treatment modality of MF is guided by the clinical staging. The age of the patients, symptoms, presence of concurrent diseases, availability of treatment modalities and patient compliance are key factors to tailor the best treatment regime. The choice of treatment for various stages is summarized in Table 2.

Topical corticosteroids

Topical corticosteroids are commonly prescribed first line topical therapy. Topical corticosteroid alone can induce complete remission and partial remission in

Table 2. Treatment strategies for MF[25]

Stage IA: limited patch/plaque
- Generalized topical HN_2
- If not available or intolerant to HN_2 → PUVA or RePUVA or BCNU
- If disease progression or if refractory → total skin electron beam therapy (TSEBT) or PUVA with interferon-α

Stage IB and stage IIA
- Chronic disease → as above, topical HN_2 or PUVA
- Rapidly progressive
  - TSEBT with optional follow-up therapy such as topical HN_2, PUVA, or photopheresis to maintain remission
  - If refractory, add systemic agent such as interferon-α, retinoid, or single agent chemotherapeutic agent (e.g. methotrexate)

Stage IIB
- TSEBT with local radiation to tumours with optional follow-up topical therapies or photopheresis to maintain response
- Sequential topical therapies for refractory lesions as in stage IA
- If disease progression → photopheresis; if no response, systemic chemotherapy

Stage III / Sezary syndrome
- Photopheresis
- Add methotrexate to photopheresis if progressive or no response
- If progressive → palliative PUVA, palliative topical HN_2, interferon-α, systemic chemotherapy, retinoids or experimental agents e.g. monoclonal antibodies or bone marrow transplantation.

Stage IVa
Individualized palliative treatment
- Interferon-α, systemic chemotherapy
- Local radiation to local symptomatic disease
- Photopheresis
- Retinoids, or experimental agents

Stage IVb
Individualized palliative treatment
- systemic chemotherapy
- Interferons, retinoids, or experimental agents

31% and 63% of T1 patients; 25% and 57% of T2 patients respectively.[23] The effect can be enhanced by the use of potent topical steroid under occlusion and the response rate increases to 80-90% for T1 and T2 patients.

Topical mechlorethamine (nitrogen mustard, HN_2) and carmustine (BCNU)

HN_2 and BCNU are not available in Hong Kong. HN_2 is applied three times a week to twice daily. It usually takes three to six months for solution; and six to 12 months for ointment to achieve clearance in early patch and plaque MF patients. With further maintenance therapy, remission in excess of two years has been reported.[24] The response rate is from 50% to 75% in T1 patients and from 25% to 50% in T2 patients. Allergic or irritant dermatitis, urticaria, anaphylactoid reactions and increased risk of skin cancer with prolonged use are possible side effects. BCNU gives similar result as HN_2[25] and can be used in patients allergic to HN_2.

Phototherapy

UVB is effective for stage I patches but may be less effective for plaques because of its limited penetration.[14] The overall complete remission (CR) rate reported in the literature was 65-90%.[25] Herrmann et al's reviewed 244 MF patients treated primarily with PUVA, the CR rates were found to decrease with advanced stages whereas the relapse rates increased (Table 3).[26]

Because of the low CR rates and high relapse rates, it is not recommended to treat advanced MF with PUVA alone. The relapse rate for stage III disease is particularly high probably due to the persistence of circulating Sezary cells in the blood despite clearance of skin lesions. Moreover, as the relapse rates are considerable for all stages, prolonged maintenance PUVA is advocated to keep the patients clinically clear of skin lesions. Maintenance PUVA should be commenced after *complete* skin clearance and kept for at least one year to indefinitely. With maintenance PUVA the mean duration of remission reported was 43-53 months.[14] There is also evidence to suggest that long term survival of early MF patients may be improved with PUVA therapy, and indeed a significant decline in the mortality since the introduction of PUVA as the standard therapy for patch and plaque diseases was seen in Sweden.[27] More than 8% of patients were reported to develop squamous cell carcinoma or basal cell carcinoma after several years of PUVA treatment in Caucasians.[26] However, there was no PUVA-related non-melanoma skin cancer reported in a ten-year local survey.[28]

Total skin electron beam therapy (TSEBT) and Radiotherapy

TSEBT results in 56-96% CR in patients in stage Ia to IIa. If no adjuvant therapy is given, the relapse-free survival rate is 33-52% in 10 years for stage Ia disease and only 16% for stage Ib disease.[14] Hence, adjuvant therapy (topical HN_2 or PUVA) is recommended after completion of TSEBT.[25,29] The acute skin toxicity includes soreness, erythema, swelling, blister formation, impairment of sweating, nail dystrophy and alopecia. Xerosis, hyperpigmentation and telangiectasia are encountered as long term adverse effects. Deep organ toxicity such as myelosuppression does not occur. Low dose superficial X-ray can be used to treat resistant plaques and adjuvant local low dose radiotherapy can be used to treat resistant localized tumours.[25]

Table 3. PUVA therapy results of Herrmann et al's study

	No. of patients	CR rate (%)	Relapse rate after CR (%)
Stage Ia:	60	90	31
Stage Ib:	116	76	56
Stage IIa:	9	78	71
Stage IIb:	27	59	62
Stage III:	18	61	82
Stage IVa:	10	40	25
Stage IVb:	4	0	0
Total	244	74	51

Systemic chemotherapy

This is reserved for those resistant to other therapies and for those who have nodal or visceral involvement. Although 60-80% of patients showed some response albeit short-lived, palliation is the realistic aim. Single-agent chemotherapy with methotrexate, cisplatin, etoposide, doxorubicin, bleomycin, deoxycoformycin (pentostatin), fludarabine, vinblastine, alkylating agents, topoisomerase II inhibitors, oral corticosteroids and other agents have been used. The overall CR rate with various agents was about 30% but the duration of response was usually short, averaging several months.[15,30]

Methotrexate was demonstrated to produce the best results. A consistently higher CR rate of around 60% and remission of 6 to 30 months maintained with low to medium dose of weekly methotrexate had been reported.[30] A 70% 5-year survival rate among 17 methotrexate-treated stage III patients had been reported.[14]

Various combinations of chemotherapeutic agents have been used:-

- **CHOP**: Cyclophosphamide, Hydroxodaunorubicin (Adriamycin), Oncovin (Vincristine), Prednisolone
- **CVP**: Cyclophosphamide, Vincristine, Prednisolone
- **MOPP**: Mechlorethamine, Oncovin (Vincristine), Procarbazine, Prednisolone

Analysis of several studies in this aspect concluded that the response rate was 81%, the complete response rate was 38% and the duration of response ranged from five to 41 months.[15] Although these figures are better than that of single-agent chemotherapy, their efficacies must be balanced against their side effects and toxicity.

Extracorporeal photopheresis

Oral 8-methoxypsoralen is ingested two hours before leukopheresis with isolation of the mononuclear fraction. Approximately 25% of the patients treated with photopheresis show complete remission, half show a partial response and the rest do not. The toxicity is minimal but the procedure is remarkably expensive and labour intensive.[14,31]

Biological response modifiers

Biological response modifiers have received tremendous interest and enthusiasm as they confer advantages over chemotherapeutic agents. They preserve the patients' immune function, augment the patients' anti-tumour inflammatory response and are less toxic than chemotherapeutic agents.[27]

Isotretinoin, etretinate and acitretin have been used to treat MF. It has not been documented that they are potent enough to be given as monotherapy, although an overall response rate as high as 60% had been reported.[25] Combination with PUVA gives similar results as PUVA alone but the number of sessions and UVA dose needed to induce remission appeared lower. Combination with interferon-α (IFN-α) gave variable results and some revealed similar response rate as IFN-α monotherapy while sustained remission was reported in some trials. Targretin (Bexarotene), a novel RXR-selective retinoid analog, has shown promising results both topically and orally in the treatment of early and advanced stage of CTCL.[32]

IFN-α has a direct anti-proliferative and immuno-modulatory effects. Low dose is given at 3 to 18 MU daily to 3 times per week systemically or intra-lesionally. The optimal dose is believed to be 3MU three times weekly. Newer long acting weekly-dosing IFN-α is also available now. The objective response rate is 50-60% and CR rate is about 10-20%, which are comparable to single-agent chemotherapy. Its combination with PUVA has given superior results, with the CR rates increasing to 90-100%.[14,33]

Miscellaneous and investigational agents

Denileukin diftitox (DAB389-IL-2; Ontak) was recently approved by the US FDA to treat CTCL. It is a cytotoxic fusion protein that combines the receptor-binding domain of interleukin-2 with diphteria toxin. Indication for therapy includes stage IIb to IVb, who has failed other modalities. The partial and complete response rates are 20-37% and 10-14% respectively.[34] Monclonal antibodies, with or without conjugation, photodynamic therapy using hypericin,[14] thymopentin,[35] and acyclovir[35] had been tried. The responses remained partial and transient.

Some reports had shown that cyclosporin could give transient response. However, use of cyclosporin in patients with advanced MF, in whom the immunity is already compromised, has been complicated by severe and sometimes fatal infections. It is thus not recommended as a standard treatment for MF.

The experience of bone marrow transplantation for MF is very limited. Both autologous and allogeneic bone marrow transplantation had been tried. Remissions induced were usually not sustained and skin infections in open skin lesions in the presence of prolonged immunosuppression could be risky.

Combination therapy

As no single modality of treatment is definitely superior, combination therapy, either concomitant or sequential is the logical approach, especially in advanced diseases. In general, biological response modifiers with debulking skin directed therapy give better results than skin directed therapy alone. For example, patients with extensive plaques who fail to clear with PUVA alone may go into CR when IFN is added.[27]

The followings are some promising combinations:

- Interferon + PUVA
- Interferon + Photopheresis
- TSEBT + Photopheresis
- TSEBT followed by PUVA maintenance

CONCLUSIONS

It is evident that the diagnosis of early MF/CTCL is difficult to make. Close follow-up with additional biopsies over time will clarify the diagnosis in most cases. TCRGRS and immunophenotyping may provide additional useful information in some cases. However, clinico-pathological correlation remains the gold standard in MF/CTCL. The treatment of MF can be prolonged and the choice should be individualized. Biological response modifiers are likely to be the choice of treatment in the future.

Learning points:

MF can mimic almost any inflammatory skin disorders histologically. There is no single feature that is diagnostic of MF. Proper clinical staging is essential to guide the management of MF patients.

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