Mycosis Fungoides: a review

Dear Editor,

Thank you very much for your response. Please also extend my sincere thanks to the reviewers for their thoughtful and constructive feedback. We have found the comments very helpful in improving the manuscript and have revised the text accordingly.

Below, I have addressed each of the points raised in the feedback, along with a description of the corresponding improvements in the manuscript. These have also been marked in red within the body of text.

I look forward to hearing from you again,

Kind regards.

Round one of comments

Reviewer 2

Comment	Action
In the abstract, please delete the sentence about rare phenotypic variants	Thank you for this comment. This has been deleted.
Please discuss the relationship between MF and Sézary syndrome (which is not so obvious as one could expect)	Thank you for this suggestion. This has been added on page 6 using the 2019 BAD guidelines.
Regarding the diagnosis I am personally a strong supporter of MULTIPLE biopsies. Please also discuss shave vs ellipse vs punch biopsy techniques. Which recommended?	Thank you for this helpful comment. This has been emphasised in the diagnosis section.
This is a CLINICAL journal. I would love seeing two additional tables: i. other clinicopathological variants of MF; ii. the main ddx and the respective clues	Thank you for this suggestion. Table 1 now describes other clinicopathological variants of MF, and Table 2 now presents the main ddx and the respective clues.
Regarding diagnosis, in my eye clonality studies mostly matter if the same clone is documented on different samples (please quote the problem of clonal dermatitis)	Thank you for this helpful comment. A paragraph outlining this issue has been added under the diagnosis heading.

Reviewer 3

Comment	Action
It is better to describe it as a skin malignancy	Thank you for this comment. This has been revised on page 3
Spelling of Folliculotropic	Thank you for highlighting this mistake. This has been corrected on figure 4
TNM staging table	Thank you for highlighting the incorrect reference. This has been corrected in the staging section, and on Table 3.
Histological grade number	Thank you for this comment. The NCI grades have now also been added.
B0b mistype	Thank you, this has now been corrected.

Mycosis Fungoides: a review

Round two of comments

Comment	Action
Please note that the first and the last paras of the Sézary syndrome subheading are redundant.	Thank you for this comment, these paragraphs have been removed.
A wider list of clinicopathological variants may include the following:	Thank you for these further variants. This has now been added to table 1 for a more complete list of clinicopathological variants
I have only one comment highlighted (page 9, line 17) in the attached revised version of the manuscript.	Thank you for this comment. This sentence has been adapted.

Mycosis Fungoides: a review

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Conflicts of interest
KM is a deputy editor of Clinical Experimental Dermatology
NJL is a trustee of the British Association of Dermatologists charity, which owns CED.

Journal:
Clinical Experimental Dermatology

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Table count: 7
Figure count: 9

Abstract
Mycosis fungoides (MF) is the commonest subtype of cutaneous lymphoma, characterised by the infiltration of malignant T cell clones into the skin. It accounts for approximately 60% of all cutaneous T-cell lymphoma (CTCL) diagnoses. MF has three distinct stages - patch, plaque and tumour - presenting most commonly on the buttocks, trunk and breast. The presentation often mimics common inflammatory dermatoses such as eczema and psoriasis. Despite numerous theories, the aetiology of MF remains mostly unknown.

Since its first description in 1806, diagnosis has remained a challenge and requires careful clinicopathological correlation. Patients may require multiple skin biopsies, especially in patch stage, to identify the characteristic epidermotropic infiltrates of small to medium-sized lymphocytes. ~~Yet, rare phenotypic variants can occur~~. First-line management involves skin-directed therapies (SDT) such as topical corticosteroids, and phototherapy. If this is unsuccessful, systemic medications such as interferon alpha, oral bexarotene, methotrexate and novel antibody therapies are trialled. MF can also respond to localised radiotherapy, total skin electron beam therapy and haematopoietic stem cell transplant. Despite being primarily a cutaneous lymphoma, MF can progress to involve other organs.

This review provides a comprehensive overview of the epidemiology, clinical features, diagnosis and management of mycosis fungoides.

Mycosis Fungoides: a review

Introduction

Mycosis fungoides (MF) is a rare cutaneous malignancy, described as a 'classic type of cutaneous T-cell lymphoma'. It is the most prevalent CTCL subtype, accounting for 60% of CTCL cases in Europe.[8] Consequently, more is understood about the clinical and histological characteristics of MF than other, rarer subtypes of CTCL.

From the first description MF in 1806[9] to the present day, the diagnosis of MF and other CTCL subtypes remains a challenge. This is due its rarity, and the complex, varied clinical presentations, which may look similar to common dermatoses such as eczema or psoriasis.

Epidemiology

There are limited epidemiological data available for MF. Incidence and epidemiology are challenging to report due to the complex integration of clinical, molecular and histological characteristics required for diagnosis and classification. This is further complicated by its low prevalence and the delay in diagnosis which is reported to be approximately 3-4 years. [10]

In England, the incidence of MF is not routinely reported, however the grouped classification of CTCL are reported by the National Disease Registration Service (NDRS), 'Get Data Out' (GDO) programme. The crude incidence rate (CIR) of CTCL was 0.7 per 100,000 person years (PY) in 2019.[11]

Internationally, the proportion of all CTCL diagnoses that are MF ranged from 29.1-56.6%. [12, 13] In a short report in 2016, Public Health England identified 1659 CTCL diagnosis' from 2009-2013.[14] 920 of these were MF, accounting for 55.5% of all CTCL cases. However, this is likely an underestimate as 28% of cases were categorized as 'not otherwise specified',[14] of which a large proportion are likely to be MF cases.

For most countries, the CIR of MF has increased slightly over the past two decades, ranging from 0.5-1.6PY in 2019 in the Netherlands and France respectively. [12, 15] The annual percentage change (APC) over the last two decades ranged from 1.3–2.4%. [13, 15] Recent data from England showed that the CIR remained stable between 2013-2019.[11]

In England, MF is approximately 1.7x more common in men. 60.7% of patients were under 70 years old at the time of diagnosis, and 39.3% were aged 70+.[11] Rarely, MF can present in children accounting for approximately 4-5% of the total MF cases. [16]

Clinical presentation

In 2018, the World Health Organisation (WHO) classified three distinct subtypes in addition to classic MF: folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin.[8] Although flat, erythematous, scaly patches, plaques, and sometimes large nodules are common to all subtypes (see figures 1-3), each has certain distinct clinicopathologic features, clinical behaviours and prognosis'.

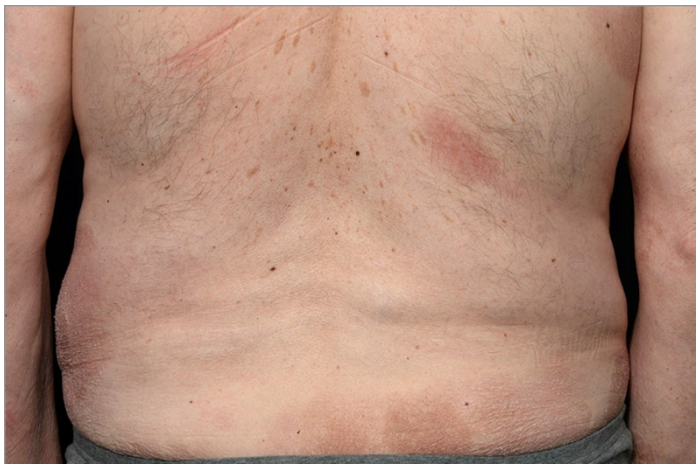

Figure 1a
Mycosis fungoides patches widespread across the back. Confirmed histologically with skin biopsy analysis.

Image courtesy of Norfolk and Norwich University Hospital. Reproduced with full consent.

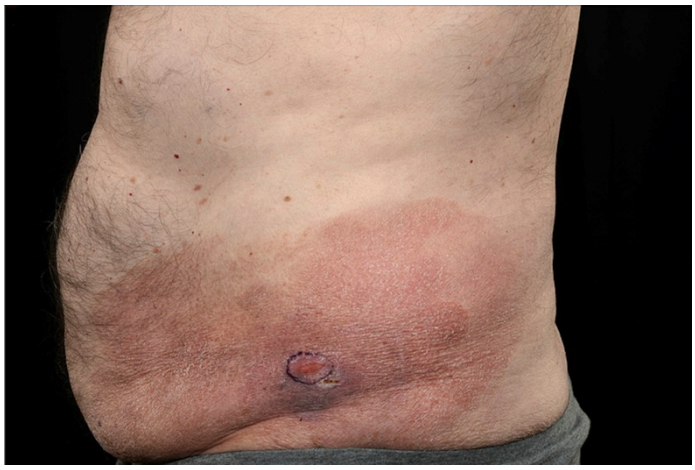

Figure 1b
Mycosis fungoides patches and plaques across the left side of the trunk. Confirmed histologically with skin biopsy analysis.

Image courtesy of Norfolk and Norwich University Hospital. Reproduced with full consent.

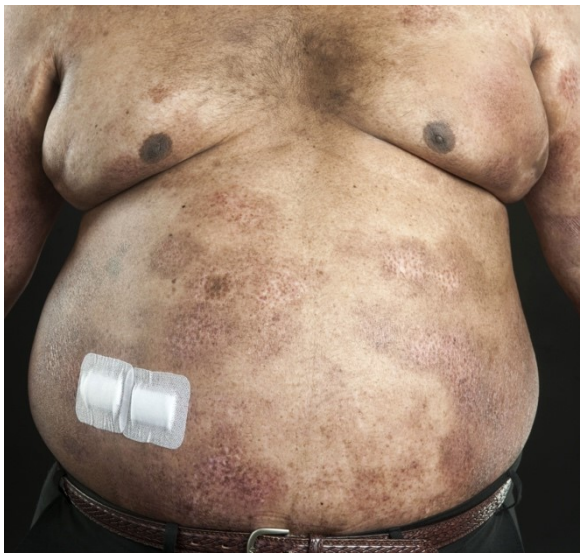

Figure 2
Mycosis fungoides stage IB on the trunk, with atrophic and poikilodermatous patches in skin of colour.

Image courtesy of University Hospitals of Leicester. Reproduced with full consent.

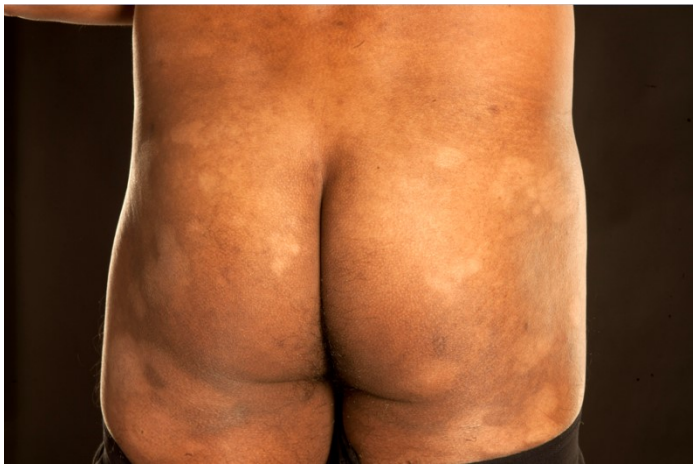

Figure 3
Mycosis fungoides stage IA on the buttocks, with hypopigmented patches in skin of colour.

Image courtesy of University Hospitals of Leicester. Reproduced with full consent.

Classic Alibert-Bazin subtype

This subtype is the most prevalent, accounting for 88.6% of diagnoses.[17] Its course is characterised by initial, non-infiltrating patches, with erythema, scaling and atrophy of the overlying skin. Although the disease course is relatively indolent, it can progress to more infiltrating plaques, that are well circumscribed, with an asymmetrical and 'serpiginous' border.[2, 18] Often years after first presentation, tumours can appear over the pre-existing plaques or even areas of previously healthy skin. Classic MF may also progress to erythroderma

Folliculotropic subtype

Folliculotropic MF (FMF) is the most common, non-classic variant of MF in adults, accounting for 11.4% of diagnosis.[17] The hair follicle is a region of 'immune privilege', and disruption of this is seen in FMF.[19]

FMF typically presents with grouped papules in the head and neck area (see figure 4), with pruritus being the most common symptom.[8] Early stages of FMF can present with patches or thin plaques with follicular accentuation (bumps around the hair follicles), comedones and milder pruritis.[20] Patients with a higher disease burden may present with infiltrated plaques, intense pruritus, and cicatricial alopecia.

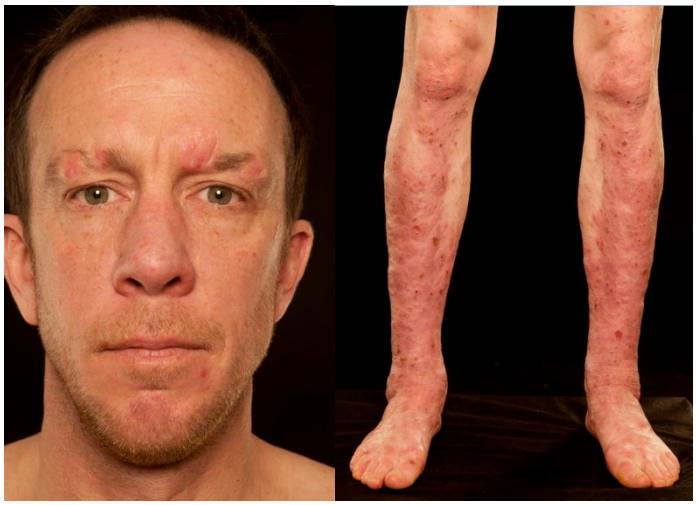

Figure 4
Folliculotropic MF, stage IB.
Thick erythematous plaques seen on both legs, and associated alopecia of the eyebrows.

Image courtesy of University Hospitals of Leicester. Reproduced with full consent.

Pagetoid reticulosis and granulomatous slack skin subtypes

Both of these subtypes have an indolent course, and are rare – each accounting for less than 1% of MF diagnoses'.[17]

Pagetoid reticulosis presents with localised, psoriasiform and hyperkeratotic lesions affecting the extremities (see figure 5)– most commonly the hands.[21]

Granulomatous slack skin initially presents as infiltrated papules and plaques on the skin folds, which develop marked skin laxity. There is an increased risk of a second haematological malignancy.[22]

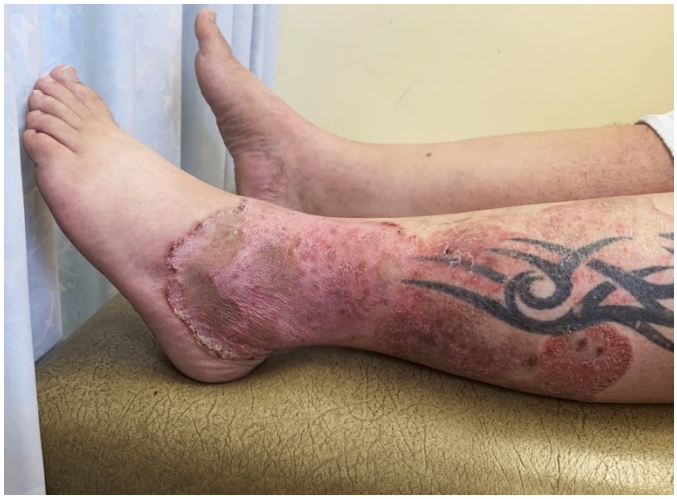

Figure 5
Pagetoid reticulosis on the left lower leg, presenting with a solitary, hyperkeratotic plaque, with an annular border.

Image courtesy of University Hospitals of Leicester. Reproduced with full consent.

In a summary of the presenting symptoms of 1502 patients with both MF and Sézary syndrome, 71.4% of patients presented with patches, 36.5% had plaques and 13.5% had tumours. 16.6% of patients had erythroderma. [2]

Commonly affected sites include buttocks, trunk and breast. Systemic symptoms such as night sweats and weight loss are rare.[8] The morphology of the presenting rash can look similar to benign inflammatory dermatoses such as eczema and psoriasis. Extracutaneous dissemination to blood, lymph nodes or viscera is rare, but has a worse prognosis.

The rarer clinicopathological variants of MF are summarised in table 1.

Sézary syndrome
Sézary syndrome is characterised by the triad of erythroderma (often with severe pruritis), generalised lymphadenopathy and the presence of malignant T-cell clones (Sézary cells) in the skin, lymph nodes and peripheral blood.[23] Furthermore, according to the WHO 2018 classification, one or more of the following are required: an absolute Sézary cell count of > 1000 cells μ/L, a CD4 : CD8 ratio > 10, or loss of one or more T-cell antigens on flow cytometry with T-cell clonality.[8]

Sézary syndrome is classified separately from MF. Although MF can present with erythroderma, the primary distinction is the high level of aberrant clonal T cells circulating in peripheral blood, which significantly impacts prognosis and treatment strategies.

Aetiology/ Pathogenesis
Although the development of novel laboratory techniques such as molecular genetics and cell surface phenotyping have greatly enhanced understanding of MF pathogenesis, the aetiology is still not fully understood.

Recent transcriptomic studies using next generation sequencing technology have uncovered the genomic and epigenetic landscape of CTCL.[24] This has resulted in the discovery of a complex array of mutations causing MF to progress, including the identification of over 50 driver mutations.[16]

Particularly, mutations relevant to T-cell regulation and proliferation, immune surveillance, and JAK-STAT signalling have been defined. Additionally, alterations in the tumour microenvironment (e.g. immunosuppression) have been linked to tumour progression.[24]

Several potential bacterial, viral and fungal causes have been also studied. This includes occupational exposures such as benzene and trichloroethylene,[18] as well as the possibility of a UV signature.[25] However, these results are inconclusive and the trigger remains unknown.

Diagnosis

MF diagnosis can be challenging and requires careful clinicopathological correlation. A comprehensive history should focus on the location and progression of the skin lesions, signs of systemic involvement and response to treatments. [26] A full systemic examination should look for lymphadenopathy and organomegaly, alongside a full work up (see figure 6). Table 2 describes the main differential diagnoses for MF, and the respective diagnostic clues.

Diagnosis often requires multiple skin biopsies for analysis (see figure 7). [6, 27, 28] At least two, 6mm punch biopsies of the most representative lesions are recommended to increase biopsy yield.[28] If lesions are highly variable, multiple biopsies should be taken from several lesions. [28] Deeper punch biopsies are preferred where there is suspicion of folliculotropic involvement.[28] Topical corticosteroids should not be used at least 2 weeks prior to biopsy. Repeat biopsy is required if results are inconclusive and clinical suspicion persists.[6, 26] Further biopsies are required if there is persistent dermatitis after patch test and allergen avoidance or if the morphology of the lesions change such as nodular lesions develop. [26]

Work up for suspected MF:

- Full blood count to consider the neutrophil to lymphocyte ratio (NLR)
  - In early stage MF (grade IA-IB-IIA) the median NLR was 1.88, and high grade MF (grade IIB-IIIA-IIIB) median NLR was 2.64. [3]
- Blood film
- T cell subset analysis analysing for T-cell clones
- Liver function tests
- Lactate Dehydrogenase (LDH)
- Flow cytometry – providing measures of abnormal T cells.
- Screening for HIV, Hepatitis B and C and Human T-lymphotropic virus -1. [6]
- Imaging – Baseline investigations include Chest X-ray, Positron Emission Tomography-Computed Tomography (PET-CT) or Computed Tomography (CT) chest, abdomen and pelvis
- Ultrasound of lymph nodes and biopsy if lymphadenopathy found on examination or imaging
- Bone marrow biopsy from the pelvis is indicated if there is suspicion for systemic involvement, observing for T-cell clones.

Figure 6 – List of investigations a patient requires when MF is suspected.

Skin biopsy analysis in suspected MF:

- Histological analysis with immunohistochemistry most commonly shows predominance of CD4+ T-cells. There is often loss of expression of T cell markers – including CD7 and CD2, with fewer CD8+ cells, although, CD8+ phenotypic variants can rarely occur. [4, 5]
- Clonality studies via Polymerase Chain Reaction (PCR), or next generation sequencing are also commonly used in diagnosis and assessment of relapse and progression. [7]

Figure 7 – List of analysis required to aid the diagnose MF from a skin biopsy.

The presence of clonality, however, does not always imply malignancy. Clonal rearrangement may also be present in benign conditions such as lichen planus, pityriasis lichenoides et varioliformis acuta, pityriasis lichenoides chronica, and lichen sclerosus, as part of the reactive inflammatory process.[29] Therefore, demonstrating consistency of the same T-cell clone in multiple lesions, or over time, strengthens the certainty of an MF diagnosis.[29]

So, reliable diagnosis of MF requires the involvement of a multidisciplinary team (MDT), which may include dermatology, haematology, oncology, radiology and histopathology specialists. This allows for both confirmation of the diagnosis and discussion of clinical management options. [6] Specialist tertiary referral centres, or supra-MDTs involving specialist centres can be consulted where there is diagnostic and management uncertainty.

Staging

MF follows the Tumour, Node, Metastasis, Blood (TMNB) classification (Table 3). This was revised by the international Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC).[30]

The well-known three stages of MF were first characterised in 1876, by French physician Pierre-Antoine-Ernest Bazin.[8, 31] These stages are described, alongside the corresponding histopathological findings in Table 4.

Treatment

As MF often has a chronic benign course, full clearance of cutaneous features may not be realistic to achieve. It is important to control symptoms. There is limited evidence of the ability of treatment to prevent progression or impact on MF survival. The following amalgamates both the most recent British Association of Dermatologists,[6] and European Journal of Cancer guidelines.[32]

Skin directed therapies (SDT)

Many of the topical therapies are unlicenced for use in MF but have good clinical efficacy for patches and thin plaques (see Table 5). SDT can be used in combination with systemic options in more advanced stages.

Phototherapy is used in early stage MF, uncontrolled by topical treatments. Psoralen-ultraviolet A can be used in conjunction with both interferon-alpha and retinoids, to reduce

the cumulative UVA dose. Narrowband ultraviolet B has also been shown to be effective for treatment of early MF, especially for patients with thin plaques or patches.[33]

Systemic therapies

When treatment is more advanced, or resistant to topical therapies, systemic therapies should be considered (see Table 6). These cases should be discussed at specialist MDTs.

Biological therapies and retinoids have higher response rates in early disease, whereas there is no evidence that antibody therapies or chemotherapy should be used in early MF. Overall, results from chemotherapy are disappointing in comparison with other lymphomas.

Novel targeted antibody therapies, including Alemtuzumab and Mogamulizumab have both proven efficacious in the management of MF. [34, 35] Alemtuzumab is a humanised recombinant IgG1 monoclonal antibody, against CD52. Mogamulizumab is a humanised IgG1 monoclonal antibody, directed against C-C chemokine receptor 4 (CCR4). CCR4 is involved in cell trafficking of lymphocytes to skin and is consistently expressed on MF tumour cells. In 2021, Mogamulizumab became the first targeted monoclonal antibody recommended as an option for use in MF, for patients with stage IIB or above who have not responded to two other systemic agents.[36]

Localised radiotherapy

MF can respond very well to localised radiotherapy for patients with all stages of disease, and can be used simultaneously with other SDT. [6]

Experienced clinicians should calculate the dose-fractionation regimen, considering the size of the treatment area, treatment site and potential risk of damage to nearby organs.

Palliative, low-dose radiotherapy is very effective for plaques and tumours, however curative radiotherapy can be considered for solitary patches or plaques. [6]

Total skin electron beam therapy

Total skin electron beam therapy (TSEB) is a type of radiotherapy that is delivered to the entire skin surface. It uses low-energy electrons produced by a linear accelerator to penetrate the first 1-2cm of the skin, sparing the internal organs.[37] It is a highly effective treatment for MF, with excellent complete response rates for all stages. TSEB should be considered as a second-line treatment for stage IB MF that does not respond to topical therapies, or has relapsed.[6] It can be used first-line in patients with extensive cutaneous disease.

Haematopoietic stem cell transplant

Autologous haematopoietic stem cell transplant (HSCT) appears to be associated with short term remission and should not be considered for advanced stages of MF. However, allogenic HSCT can lead to a longer lasting remission. [6]

The future of MF management

There are many emerging therapies for MF, however there is a need for 'well defined RCTs with appropriate clinical end points'. [6] This is challenging, mainly due to the relative rarity of the disease.
These include:

- Extracorporeal photopheresis – often used in specialist centres for Sézary syndrome or stage IIIB MF (erythrodermic with low-blood disease burden)
- Toxin therapies (e.g. Denileukin diftitox)
- Histone deacetylase inhibitors – FDA approved and commonly used in the USA, but not available in the UK.
- Other systemic therapies (e.g. Pralatrexate)

Prognosis

Relative to other subtypes, MF has an indolent course, low risk of metastasis, and relatively good survival prognosis (see Table 7). The well-established factors impacting MF prognosis are detailed in figure 8.

The main factors associated with a poor prognosis in MF: [1, 2]

- Presence of extracutaneous disease
- Age >60 and male gender
- Presence of large cell transformation
- High LDH
- Folliculotropic subtype of MF
- Tumour distribution at diagnosis

Figure 8 - List of the factors identified to have an impact on MF prognosis.

Conclusion

Mycosis fungoides presents unique challenges in both diagnosis and management. The clinical similarities to other benign inflammatory dermatoses highlight the need for careful clinical examination, and histopathological correlation. Whilst skin directed therapies have proven effective in managing the majority of early MF cases, an individualised approach is often needed due to the variability in disease progression. Continued effort into research, early diagnosis and individualised treatment pathways are essential to improving the quality of life of patients with mycosis fungoides

Learning points

- Mycosis fungoides is the most common subtype of cutaneous lymphoma, characterised by epidermotropic infiltrates of small to medium-sized lymphocytes

- The aetiology of mycosis fungoides remains largely unknown. However, transcriptomic studies and next generation sequencing technology have identified a complex array of mutations causing MF to progress, including the identification of over 50 driver mutations

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- Diagnosis is often delayed, as it mimics common inflammatory dermatoses such as eczema and psoriasis. Diagnosis may require multiple, repeat skin biopsies for analysis.

- Histological analysis with immunohistochemistry often shows predominance of CD4+ T-cells. Often, there is loss of expression of T cell markers – including CD7 and CD2, with fewer CD8+ cells. CD8+ phenotypic variants can rarely occur.

- First-line management involves skin-directed therapies (SDT) such as topical corticosteroids, and phototherapy. If this is unsuccessful, systemic medications such as interferon alpha, oral bexarotene, methotrexate and novel antibody therapies are trialled. Additionally, MF can respond to localised radiotherapy, total skin electron beam therapy and haematopoietic stem cell transplant.

CPD Questions

Learning objective
To consolidate understanding of the epidemiology, presentation, aetiology, diagnosis, and management of mycosis fungoides.

1. Which of the following statements regarding mycosis fungoides is correct?
    a. Mycosis fungoides is more common in patients under 70 years old.
    b. Mycosis fungoides presents most commonly on the buttocks, trunk and breast.
    c. The work up for suspected mycosis fungoides only consists of a clinical history, examination and one skin biopsy
    d. Skin directed therapies have poor clinical efficacy in resolving patches and thin plaques of mycosis fungoides.
    e. Men with mycosis fungoides typically have a better prognosis than women.

2. According to the 'Get Data Out' – haematological malignancies dataset, what was the crude incidence rate of mycosis fungoides in England in 2019?
    a. 0.3 per 100,000 person years
    b. 0.5 per 100,000 person years
    c. 0.7 per 100,000 person years
    d. 0.9 per 100,000 person years
    e. 1.1 per 100,000 person years

3. In 2018 the World Health Organisation (WHO) classified three distinct subtypes in addition to classic MF. Which of these is not involved in that classification
    a. Folliculotropic mycosis fungoides
    b. Pagetoid reticulosis
    c. Granulomatous slack skin
    d. Sézary syndrome
    e. They are all included in this classification

4. What potency of topical corticosteroids are recommended for early-stage mycosis fungoides
    a. Mild
    b. Moderately potent
    c. Potent
    d. Very potent
    e. Topical corticosteroids are not recommended for early-stage mycosis fungoides

5. In 2021, Mogamulizumab became the first targeted monoclonal antibody recommended as an option for use in mycosis fungoides, for patients with stage IIB or above who have not responded to two other systemic agents. What is the mechanism of action?
    a. A humanised IgG1 monoclonal antibody, directed against C-C chemokine receptor 4
    b. A humanised recombinant IgG1 monoclonal antibody, against CD52.
    c. Low-energy electrons produced by a linear accelerator to penetrate the first 1-2cm of the skin
    d. Stabilizing the lysosomes in neutrophils, preventing degranulation, and the resulting inflammatory response.
    e. It uses low-energy electrons produced by a linear accelerator to penetrate the first 1-2cm of the skin

Answers

1. b
2. c
3. d
4. d
5. a

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Table 1
Other clinicopathological variants of mycosis fungoides.

Clinicopathological variant	Clinical features	Histological features
Mycosis fungoides with eruptive infundibular cysts	Localised or wide-spread follicular eruption, alongside infundibular cysts and comedones.[38] Due to their size and inflammatory appearance, the lesions may emulate tumour-stage MF lesions[38]	Typical features of an infundibular cyst, surrounded by a dense infiltrate of atypical lymphocytes within the cyst wall. [38]
Syringotropic mycosis fungoides	Erythematous, scaling papules and plaques, sometimes involving hyperpigmentation or follicular eruption. [38, 39] Adnexal involvement often leads to anhidrosis and alopecia. [38-40] Palmoplantar involvement is also common, and can differentiate this from folliculotropic MF. [38, 40] These lesions often progress slowly and may co-exist with classic MF lesions elsewhere. [38]	A dense infiltrate of atypical, neoplastic lymphocytes within eccrine glands and ducts, eccrine hyperplasia with varying degrees of syringosquamous metaplasia (squamous transformation of the glandular epithelium). [38, 40]
Poikilodermatous mycosis fungoides	Atrophic plaques, alternating hyperpigmentation and hypopigmentation, and telangiectasia, often over large areas the breast and buttock region. [38, 39]	Epidermal atrophy with flattening of the dermal-epidermal junction, vacuolar degeneration/ alteration of the basal layer, and a lichenoid epidermotropic infiltrate of atypical lymphocytes. [38, 39]
Bullous mycosis fungoides	Flaccid or tense bullous vesicular lesions, usually affecting large areas of the trunk and limbs. [38] The bullae may be present on normal or erythematous skin or within typical plaques and tumours of MF.[39] They often co-exist with classic MF. [38]	Intraepidermal or subepidermal blisters with features of classic MF (typical lymphocytes, epidermotropism, and Pautrier microabscesses).[38] Negative results on direct and indirect immunofluorescence distinguishes this from autoimmune blistering diseases. [38]
Other extremely rare subtypes include: Hyperpigmented or Hypopigmented Poikilodermatous Ichthyosiform (spinulosic) Verrucous Acanthosis nigricans-like Palmoplantar Interstitial Angiocentric-angiodistructive Papuloerythroderma (Ofuji's) Perioral dermatitis-like Papular Purpuric Pustular Anetodermic 'Invisible'		

Table 2
Some of the most common differential diagnoses for mycosis fungoides.

Eczematous

Differential diagnosis	Diagnostic clues
Atopic eczema	Atopic eczema often affects flexural surfaces and follows a relapsing-remitting course, yet clinically, atopic eczema and MF are challenging to differentiate. Sometimes, neither the clinical history, first biopsy specimen nor T-cell gene rearrangement study can differentiate MF from atopic dermatitis. Therefore, regular follow up and repeated biopsies from various sites may be required.[41] Although clonality may be present in both, MF is often consistently monoclonal, and atopic eczema is typically polyclonal. [29] Dermoscopy shows dotted vessels distributed randomly or in clusters, with dilated capillaries in elongated dermal papillae, yellow scales and serocrusts.[42, 43] Histologically, eczematous lesions show mild epidermal hyperplasia, spongiosis and perivascular lymphocytic infiltrate.[42]
Allergic contact eczema	Allergic contact eczema is usually confined to the site of exposure to an allergen. Patch testing is often positive. Polyclonality is often observed, and histology and dermoscopy are similar to atopic dermatitis. [29, 42, 43]
Seborrhoeic eczema	Seborrhoeic eczema is commonly distributed in scalp, nasolabial folds, and eyebrows. It often rapidly resolves with antifungal and/or topical corticosteroid therapy. Dermoscopy often reveals patchy areas of dotted vessels, and fine yellow scales, other vascular patterns may be present (especially if the scalp is affected).[42] Histology often shows superficial perivascular infiltrate of lymphocytes, acanthosis, focal spongiosis, and focal parakeratosis.[44]

Scaling

Differential diagnosis	Diagnostic clues
Psoriasis	Psoriasis commonly has a symmetrical distribution on extensor surfaces, alongside scalp/ nail involvement. Additionally scale removal may lead pinpoint bleeding spots (Auspitz sign).[42] Dermoscopy often reveals uniformly distributed dotted vessels with diffuse white scales. [42, 43] Histologically, psoriasis presents with dilated capillaries in regularly elongated dermal papillae and parakeratosis. [42]
Tinea corporis	Tinea corporis presents as annular lesions with central clearing and active scaly edges. The diagnosis is confirmed through potassium hydroxide microscopy of skin scrapings, which reveals long, branching hyaline and septate hyphae. [45] It is also rapidly responsive to antifungals. [45]
Pityriasis rosea	Pityriasis Rosea typically presents with a 'herald patch'; a 2-5cm oval salmon pink patch with a collarette of scale on the trunk or proximal limbs. This is followed by a secondary

	eruption of smaller oval patches and plaques 1-2 weeks later. It is self-limiting and resolves within 6-8 weeks. Both the Herald patch and secondary lesions show peripheral whitish scaling on dermoscopy (Collarette sign), as well as patchy dotted vessels. Yellow/orange structureless areas may also be visible. [42, 43]

Erythematous

Differential diagnosis	Diagnostic clues
Sézary syndrome	Sézary syndrome presents with the triad of erythroderma (often with severe pruritis), generalised lymphadenopathy and the presence of malignant T-cell clones (Sézary cells) in the skin, lymph nodes and peripheral blood.[23]
Drug reaction	Some drug eruptions mimic mycosis fungoides closely in clinical and pathological appearance, for example including CD30 positivity. These may be termed drug-associated pseudolymphoma.[46] Resolution with withdrawal of the suspected causative agent may be the only distinguishing feature.[46] Drug reactions most commonly present acutely, with a diffuse erythematous maculopapular rash, but can have varying appearances.[47] It usually resolves after the offending drug is identified and stopped. Patients may also have a fever and eosinophilia.
Subacute cutaneous lupus	Subacute cutaneous lupus may present with photosensitive, annular lesions with central clearing, in sun-exposed areas.[42] As it is autoimmune, antibody testing (ANA, Anti-Ro and Anti-La) is often positive. Dermoscopy often reveals diffuse or peripheral white scales, and at least 2 types of vessels (dotted, linear-irregular, linear and branching vessels) over a pink/red base.[42]

Alopecia

Differential diagnosis	Diagnostic clues
Alopecia areata	Alopecia areata presents with acute onset, well demarcated areas of non-scarring hair loss. Dermoscopy may show yellow dots (keratin and sebum in follicular openings), black dots (broken hairs at scalp level) and typical exclamation mark hairs (tapered proximally, wider distally). Biopsy is essential in atypical/ refectory alopecia areata as it may often mimic folliculotropic MF. [48] Histopathology may show a 'bee-swarm pattern' of dense lymphocytic infiltrate around anagen hair follicles, and a decrease in the ratio of anagen to telogen follicles. [49]

Table 3

ISCL-EORTC revision of the TNM staging system for mycosis fungoides. [30]

Skin

Stage	Features
T1	Limited patches, papules and/or plaques covering <10% body surface area
T1a	Only patches
T1b	Patches and/or Plaques
T2	Patches, papules and/or plaques covering >10% body surface area
T3	One or more tumours (>1cm in diameter)
T4	Erythroderma (>80% body surface area)

Node

Stage	Features
N0	No clinically abnormal peripheral lymph nodes
N1	Clinically abnormal peripheral lymph nodes – firm, irregular, clustered or >1.5cm in diameter Histopathology Dutch grade 1 or National Cancer Institute (NCI) Lymph Node (LN) stage 0-2
N1a	Clone negative
N1b	Clone positive
N2	Clinically abnormal peripheral lymph nodes Histopathology Dutch grade 2 or NCI LN stage 3
N2a	Clone negative
N2b	Clone positive
N3	Clinically abnormal peripheral lymph nodes Histopathology Dutch grade 3-4 or NCI LN stage 4 Clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes, without histological confirmation

Visceral

Stage	Features
M0	No visceral organ involvement
M1	Visceral involvement with pathology confirmation

Blood

Stage	Features
B0	No significant blood involvement <5% of peripheral blood lymphocytes are atypical (Sezary) cells
B0a	Clone negative
B0b	Clone positive
B1	Low blood tumour burden >5% of peripheral blood lymphocytes are atypical (Sezary) cells but not meeting B2 criteria
B1a	Clone negative
B1b	Clone positive
B2	High blood tumour burden >1000/µL and clone positive

Table 4

Description of the three stages of MF, alongside the corresponding histopathological findings.

Stage	Description	Histopathology
Patch stage	Presents with poorly demarcated erythematous patches with an overlying fine scale/ atrophic skin. It can span from a few years to several decades, and is typically asymptomatic.[26] On dermoscopy, spermatozoan vascular structures are highly specific for patch stage, classic MF, alongside fine linear vessels and white scale.[50]	Epidermotropic infiltrate of small to medium-sized, haloed lymphocytes with hyperchromatic nuclei with irregular contours, lining up especially along the basal layers of the epidermis – as seen in figure 9 Collections of at least 4 lymphocytes around a Langerhans cell in the epidermis are known as a Pautrier (micro)abscess, and represent the T cells that have been mutated.[51] Often not conclusive due to overlap with other, more common, benign dermatoses.
Plaque stage	As MF becomes more infiltrative, it presents with a well circumscribed, annular or arciform plaque. Most are pruritic at this stage. Plaques can be red, violaceous or brown, and can become quite large with areas of central regression.[31]	As for patch stage but more extensive proliferation of atypical small and medium sized T-cells usually CD4+ [51, 52]
Tumour Stage	Tumours can develop from both the pre-existing plaques or even unaffected skin.[26]	The T cells are within the deeper layers of skin and subcutaneous tissue forming a mass lesion with or without epidermotropism. [51, 52]

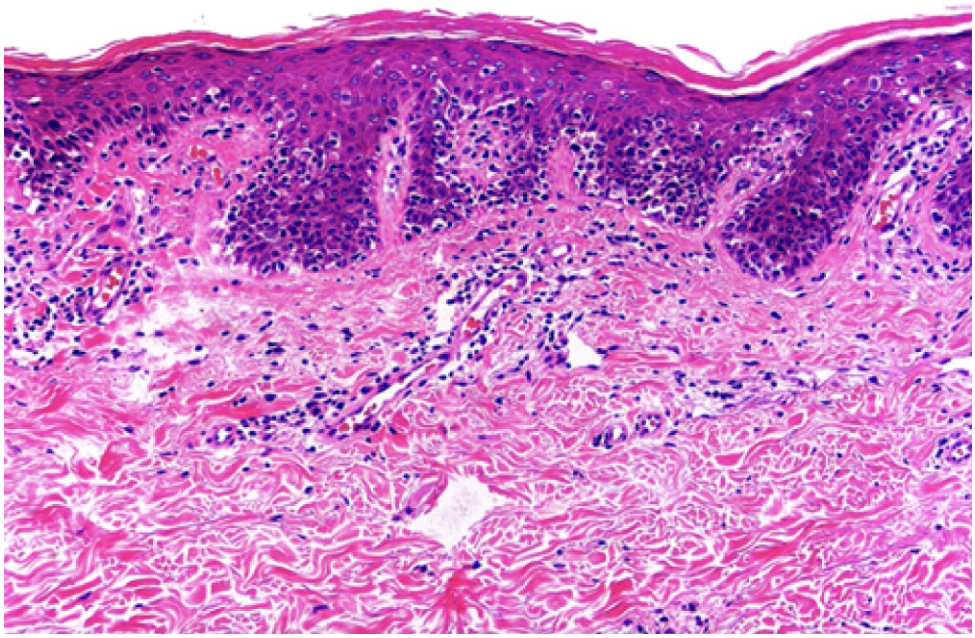

Figure 9
Haematoxylin and Eosin histology (x50) of patch or plaque stage mycosis fungoides.

This shows epidermotropism of lymphocytes in the absence of an inflammatory dermatosis

Table 5

Summary of the available skin directed therapy (SDT), including the highest level of evidence to support its use, the stage of MF in which it is recommended, reported side effects and current approval status.

Treatment	Highest level of evidence[6]	Stage used[6]	Side effects	Approval -Food and Drug Administration (FDA) -European Medical Agency (EMA)	Note:
Very potent topical corticosteroids	3	IA-IB	Reversible depression of serum cortisol, Minor skin irritation [53] Skin atrophy, stretch marks, easy bruising, localised skin acne, fungal infections[54]	*	Responses are rarely complete or durable[6]
Topical chlormethine (nitrogen mustard) 0.02% ointment	1+	IA-IIA	Irritant contact dermatitis [22] Erythema, pruritus, and blistering due to skin toxicity[32]	FDA,[55]and EMA approved [32]	Skin toxicity can be managed by taking breaks between treatment cycles. [56]
Topical Bexarotene gel	2+	IA-IB	Irritant contact dermatitis, erythema, sweating [22]	FDA approved[6, 32]	Not available in the UK/ Europe
Narrow-band UVB phototherapy	2-	IA-IB	Burning and blistering of the skin, chronic photodamage[6]	*	
Psoralen and ultraviolet A phototherapy (PUVA)	2+	IA-IB	UV induced erythema, Photo-toxic reactions[32] Chronic photodamage, Secondary skin cancers[6, 57]	*	Lifetime exposure should be limited to 1200 J cm^2 and/or 250 sessions [6] Patients with thicker plaques, FMF or darker skin may benefit more from PUVA[57]

*Not currently approved, but commonly used

Table 6

Summary of the available systemic therapies, including the highest level of evidence to support its use, the stage of MF in which it is recommended, reported side effects and current approval status.

Treatment	Highest level of evidence[6]	Stage used[6]	Side effects	FDA/MHRA approved	Note:
Interferon-alpha (IFN-alpha) and Pegylated IFN-alpha	2-	IA-IVB	Neutropenia, Fatigue, Anaemia, Flu-like symptoms, Hepatotoxicity, Elevated transaminases [32]	*	Licenced in the European Union. Response rates are higher in early stage MF with higher doses of interferon-alpha.
Rexinoids - Bexarotene	2+	IA-IVB	Dose dependent hypothyroidism, Hypertriglyceridemia, Hypercholesterolaemia, Neutropenia [32]	EMA, NICE and FDA approved[58]	
Antibody therapy - Alemtuzumab	2-	IIV-IVA	Infusion related reactions – fever, pruritus, headache and shortness of breath [59] CMV reactivation, bruising and bleeding, anaemia, diarrhoea [59]	Not yet approved	
Antibody therapy – Brentuximab vedotin	1+	IA-IVB	Fatigue, fever, diarrhoea and nausea[60] Anaemia, peripheral sensory neuropathy, nausea, diarrhoea, neutropenia[61]	FDA and EMA approved [61, 62]	Anti-CD30 monoclonal antibody attached to monomethyl auristatin E.
Antibody therapy – Mogamulizumab	2[32]	IIB+	Infusion related reactions – drug rash, diarrhoea and fatigue [32, 60] Upper respiratory infection[36]	FDA, NICE and EMA approved[36, 62]	

*Not currently approved, but commonly used

Table 7

The stage of MF and median survival in years.

Stage of MF	Median survival (years)[52]
IA	>33
IB/IIA	>11
Generalised erythroderma	4.5
Tumour stage	3
Extracutaneous disease	1.5