Unusual variants of mycosis fungoides

Pooja Virmani
Patricia L Myskowski
Melissa Pulitzer

Abstract

Conventional presentations of mycosis fungoides may be diagnostically challenging, particularly in light of the controversial boundaries defining the disease. Variant presentations of this cutaneous T-cell lymphoma add a further layer of complexity, requiring a sophisticated and informed perspective when evaluating lymphoid infiltrates in the skin. Herein we discuss well-defined (WHO-EORTC) variants pagetoid reticulosis, granulomatous slack skin and folliculotropic mycosis fungoides as well as less well-defined morphologic/architectural variants, and divergent immunohistochemical presentations of this typically indolent T-cell lymphoproliferative disease.

Keywords cutaneous T-cell lymphoma; granulomatous slack skin; lymphoproliferative disorders; mycosis fungoides; non-Hodgkin; pagetoid reticulosis; peripheral T-cell lymphoma

Introduction

Mycosis fungoides (MF), the most common primary cutaneous T-cell lymphoma (CTCL), is a clinicopathologically distinctive neoplasm of epitheliotropic skin resident effector memory T-cells.

MF mostly affects older people, and predominantly males. The disease course is protracted and indolent although marked by discomfort and disfigurement. Most patients present with early stage disease[1] that responds well to skin directed therapy with recurrences, but no impact on life expectancy compared to age, sex, and race matched controls. A quarter of patients progress to late stages, with significantly diminished overall survival (1.4–4.7 years).[2]

MF classically presents with the stepwise appearance of patches, plaques and tumours on non-sun exposed skin with or without eventual extracutaneous involvement.[1] Microscopically, epidermotropic infiltrates of medium-sized lymphocytes with hyperconvoluted cerebriform nuclei are found. These cells may increase in size, becoming less epitheliotropic with progression to tumour stage. The tumour cells in MF express a mature T-helper memory phenotype, CD3+/CD4+/CD8−/CD45RO+, with monoclonal T-cell receptor (TCR) gene rearrangements of the α/β heterodimer.

The International Society of Cutaneous Lymphoma consensus algorithm for the diagnosis of MF relies upon clinico-pathological correlation supported by immunophenotyping and molecular gene rearrangement studies.[3] The diagnosis becomes difficult in the absence of classic clinical or histopathologic features. Several clinical variants of MF have been described (Box 1) which may correspond to consistent pathological features. Similarly, pathologic/immunophenotypic variants of MF exist (Box 2), which may correspond to distinct clinical features. The 2005 WHO-EORTC classification recognizes three variants of MF including folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin.[1] In this review we discuss these and other unusual variants of MF highlighting their clinical and histopathologic/immunophenotypic features.

WHO/EORTC variants

Pagetoid reticulosis

Described by Woringer and Kolopp in 1939, it was later renamed pagetoid reticulosis (PR) because of similarity of the epidermotropic lymphocytes to intraepidermal adenocarcinomatous cells of Paget's disease (PD) of nipple.[4] PR presents as a single slow-growing hyperkeratotic patch or plaque on acral skin. The clinical differential diagnosis includes solitary plaque psoriasis, Bowen's disease, unilesional MF, and MF palmaris et plantaris. The typical indolent course does not distinguish PR from these entities, but the pathologic findings are pathognomonic, allowing appropriate treatment by localized irradiation and/or surgical excision, which result in good response although common local recurrence.

Select clinical variants of mycosis fungoides

- Pagetoid reticulosis
- Folliculotropic mycosis fungoides
  - Spiky mycosis fungoides
  - Follicular mucinosis
- Granulomatous slack skin
- Verrucous/hyperkeratotic mycosis fungoides
- Hypopigmented mycosis fungoides
- Hyperpigmented mycosis fungoides
- Poikilodermatous mycosis fungoides
- Erythodermic mycosis fungoides
- Bullous/vesicular mycosis fungoides
- Vegetating/papillomatous mycosis fungoides
- Icthyosiform mycosis fungoides
- Pigmented purpura-like mycosis fungoides
- Unilesional mycosis fungoides
- Palmoplantar/acral mycosis fungoides
- Pustular mycosis fungoides
- Mucosal mycosis fungoides
- Intertriginous mycosis fungoides

Box 1

Pooja Virmani *MBBS Department of Medicine/Dermatology Service, Memorial Sloan Kettering Cancer Center, New York, USA. Conflicts of interest: none declared.*

Patricia L Myskowski *MD Department of Medicine/Dermatology Service, Memorial Sloan Kettering Cancer Center, New York, USA. Conflicts of interest: none declared.*

Melissa Pulitzer *MD Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA. Conflicts of interest: none declared.*

Pathologic/immunophenotypic variants of mycosis fungoides

- Folliculotropic mycosis fungoides
  - Basaloid follicular hyperplasia
  - Cysts/comedones
  - Typical folliculotropic with or without mucinosis
  - Granulomatous folliculodestructive
  - Eosinophilic folliculitis-like
- Syringotropic mycosis fungoides
- Granulomatous mycosis fungoides
  - Interstitial mycosis fungoides
  - Granulomatous slack skin
- Spongiotic mycosis fungoides
- Mycosis fungoides with epidermal mucinosis
- Mycosis fungoides with pseudoepitheliomatous hyperplasia/ hyperkeratotic mycosis fungoides
- Pigmented purpuric dermatosis-like mycosis fungoides
- Transformed mycosis fungoides
- CD8+ mycosis fungoides
  - Pagetoid reticulosis pattern
  - Interface predominant pigment-altering variants (hypo/hyperpigmented, poikiloderma)
  - Granulomatous pattern
- CD4/CD8 double negative mycosis fungoides
- CD4/CD8 double positive mycosis fungoides
- CD20+ mycosis fungoides
- Gamma delta + mycosis fungoides
- T-follicular helper cell + mycosis fungoides
- CD30+ mycosis fungoides
- Cytotoxic marker (CD56 or TIA-1) + mycosis fungoides
- CD45+ mycosis fungoides

Box 2

Histopathologically, PR is an exuberantly epidermotropic small-to-medium sized atypical lymphoid infiltrate spanning an acanthotic and hyperkeratotic epidermis. Sponge-like disaggregation of the epidermis describes the buck-shot spread of pagetoid lymphocytes in these lesions. Lymphocytes exhibit abundant vacuolated cytoplasm and a haloed appearance. Eosinophils are characteristically absent which may distinguish PR from unilesional or other acral presentations of MF. Superficial spreading melanoma and PD can be excluded with attention to histology. Melanoma typically exhibits irregular nests with melanin pigment, while PD may form ducts, with the "eyeliner sign" of a compressed basal layer below aggregates of Paget's cells. Occasionally, immunohistochemistry including melanocytic differentiation markers for melanoma or cytokeratin 7 for PD is needed.

Immunophenotypically, PR expresses T-helper cell markers CD3 and CD4 and is negative for CD8. However, CD3+/CD4−/CD8+ and CD3+/CD4−/CD8− cases are well-described. Prognosis does not differ for these cases. CD30 may be positive and the Ki-67 proliferation index is high. The neoplastic T-cells of PR are derived from TCR alpha/beta positive T-cells with rare reported TCR-gamma positive cases. Rare co-expression of TCR α/β and TCR γ in PR is consistent with the suggested origin from TCR gamma/delta positive T-cells.[5]

Folliculotropic mycosis fungoides

Patients with folliculotropic MF (FMF) present with follicular papules, comedones, acneiform lesions, cysts or indurated plaques and tumours. The lesions are often associated with patches of alopecia (hair or eyebrows) (Figure 1a) and severe pruritus with occasional erythroderma. The disease characteristically involves the face, head and neck. Most cases occur in adults, with a male predominance. Occasional cases can be seen in young children and adolescents. Clinically, FMF should be differentiated from other disorders of the pilosebaceous unit including causes of alopecia which may co-exist with FMF.

A recently reported clinicopathologic finding, "spiky MF", is an early presentation of FMF presenting as localized or disseminated variably hyperkeratotic follicular papules (Figure 1b, d) in the absence of typical lesions of FMF. Unlike FMF, a head and neck distribution and severe pruritus are not characteristic. Patients may progress to classic FMF. The clinical course is mostly indolent which may be attributed to the relatively superficially located infiltrate.

Histopathologically, FMF is a folliculocentric atypical lymphocytic infiltrate with sparing of the interfollicular epidermis (Figure 1c). Mixed inflammatory cells including plasma cells and eosinophils are prominent in perivascular and periadnexal spaces. There may be syringotropism with infiltration of eccrine glands and ducts. Approximately half of FMF show mucinous degeneration of hair follicles, ranging from intercellular spaces expanded by mucinous deposits to mucin lakes compressing epithelium with follicular rupture. Cystic dilation of hair follicles with follicular plugging may be seen. Guitart et al. noted five patterns of FMF including basaloid folliculolymphoid hyperplasia, granulomatous dermatitis with destruction of the follicular unit, eosinophilic folliculitis-like FMF, dilated follicular cysts or comedones, and prototypical folliculotropism in intact follicles with or without follicular mucinosis. Suppurative folliculitis has also been described. Different patterns may occur synchronously in patients, and within single biopsy samples. In one series of 38 cases, the most common folliculotropic pattern was observed in 97% of patients, with follicular mucinosis in 87%. Cystic and granulomatous patterns were seen in 37% and 26% patients respectively, while eosinophilic folliculitis-like and basaloid folliculolymphoid hyperplasia—associated MF were observed in only a few cases.[6]

Follicular epithelium must be present within the biopsy sample in order to diagnose FMF. A common error is failure to perform adequate deeper level sectioning in biopsies intended for evaluation for FMF, resulting in false negative diagnoses. Tiers of parakeratosis, intracorneal neutrophils and arrector pili muscle serve as clues that deeper sections will show evaluable hair follicles.

FMF may be microscopically difficult to distinguish from tumour lesions of classic mycosis fungoides involving hair-bearing skin, granulomatous mycosis fungoides with follicular involvement, folliculocentric lymphomatoid papulosis (LyP), adult T-cell leukemia/lymphoma (ATLL) with a prominently folliculocentric distribution, and T-follicle helper lymphomas which commonly present in hair-bearing skin. FMF often