

Syringotropic Mycosis Fungoides: A Rare Form of Cutaneous T-cell Lymphoma Enabling a Histopathologic “Sigh of Relief.”

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Abstract: Syringotropic mycosis fungoides (STMF) is a very rare variant of cutaneous T-cell lymphoma. It follows a much milder disease course than its clinically indistinguishable adnexal counterpart, folliculotropic mycosis fungoides (FMF). We report a case of a 36-year-old man who presented with erythematous, studded papules and plaques on the left upper extremity and right anterior thigh diagnosed as mycosis fungoides (MF) Stage 1A on initial superficial shave biopsy. Lesions recurred after initial improvement with narrow-band ultraviolet light therapy demonstrating a concentration of abnormal lymphocytes around eccrine sweat glands on repeat biopsy consistent with STMF. Although the deeper, periadnexal infiltrate found in both STMF and FMF confers increased resistance to skin-directed therapies effective in classic MF, these entities diverge with respect to their clinical behavior. Syringotropism is a marker for increased disease-specific survival, whereas even FMF carries a prognosis worse than conventional MF. Increased awareness among the dermatopathology community of the histopathologic distinction between STMF and FMF is essential to guide treatment type, duration, and intensity in adnexal disease.

Key Words: syringotropic mycosis fungoides, cutaneous lymphoma, CTCL

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INTRODUCTION

Mycosis fungoides (MF) is an indolent or slowly progressive form of cutaneous T-cell lymphoma that affects 0.001%–0.003% of the US population with an estimated 1260 cases newly diagnosed each year (incidence 3.6 per one million people).^{1,2} Syringotropic MF (STMF) is a rare form of MF, first identified by Sarkany in 1969.^{3,4,7–19} It is characterized histopathologically by hyperplastic eccrine glands and ducts surrounded and permeated by a dense infiltrate of atypical lymphocytes in the deep dermis.⁴ Although the clinical presentation of STMF is similar to folliculotropic MF (FMF), STMF is much less aggressive.⁵ In the largest case series of STMF published to date, de Masson et al found 5-year

disease-specific survival approached 100% for STMF (n = 19) versus 74% individuals with FMF (n = 54).⁶

The clinical significance of lymphocytic syringotropism in STMF remains obscured in part because of its designation as a subtype of FMF under the World Health Organization's (WHO) European Organization for Research and Treatment of Cancer (EORTC) classification of cutaneous lymphomas.⁷ This is despite over a decade's worth of observations that began with Burg and Shmockel's 1992 proposal that STMF was a unique form of cutaneous T-cell lymphoma.⁸ Moreover, although the clinicopathologic importance of differentiating STMF from FMF is well established in the clinical dermatologic literature, it is notably missing from the dermatopathology literature.⁹

CASE

A 36-year-old man presented with history of bilateral proximal upper extremity faint, xerotic, ill-defined thin plaques with studded papules. He denied experiencing any recent night sweats, fevers, chills, change in appetite, or fatigue. No lymphadenopathy or temporal wasting was present on examination. He was otherwise healthy with medical history significant for seizure disorder well controlled on levetiracetam and a remote episode of gastrointestinal hemorrhage of unknown origin.

Initial superficial shave biopsy revealed atypical epidermotropic lymphocytes and Pautrier microabscesses consistent with a diagnosis of MF, stage 1A. No adnexal involvement was appreciated then. Twice weekly narrow-band UVB light (NB-UVB) therapy was initiated with moderate improvement at 12-week follow-up. Treatment was tapered to once weekly with return of bumpy lesions at 3 months follow-up. Decision was made to rebiopsy the left arm lesion to rule out the possibility of folliculotropic MF via punch method. Biopsy demonstrated a brisk syringotropic atypical lymphocytic infiltrate surrounding eccrine ducts and glands (Fig. 1). No significant epidermotropism or folliculotropism was identified. Immunoperoxidase studies revealed that the epitheliotropic lymphocytes were predominantly CD2, CD3, CD4, CD5 T cells, with loss of CD7 expression, and negative for CD20 (Fig. 2). The CD4:CD8 ratio was elevated to approximately 4:1. PCR analysis of TCR-beta demonstrated a clonal rearrangement (MOL1-16-050081; NeoGenomics, Aliso Viejo, CA). The microscopic appearance, immunophenotype, and molecular data were thus consistent with STMF.

Screening laboratory tests were negative for signs of systemic disease, liver or renal impairment, marrow suppression, or thyroid dysfunction. Given that STMF does not respond well to topical therapies, low dose bexarotene was initiated and titrated to 150 mg daily, which he tolerated without adverse effect. Skin examination 3 months postbiopsy, revealed persistent upper arm plaques with studded papules. NB-UVB therapy

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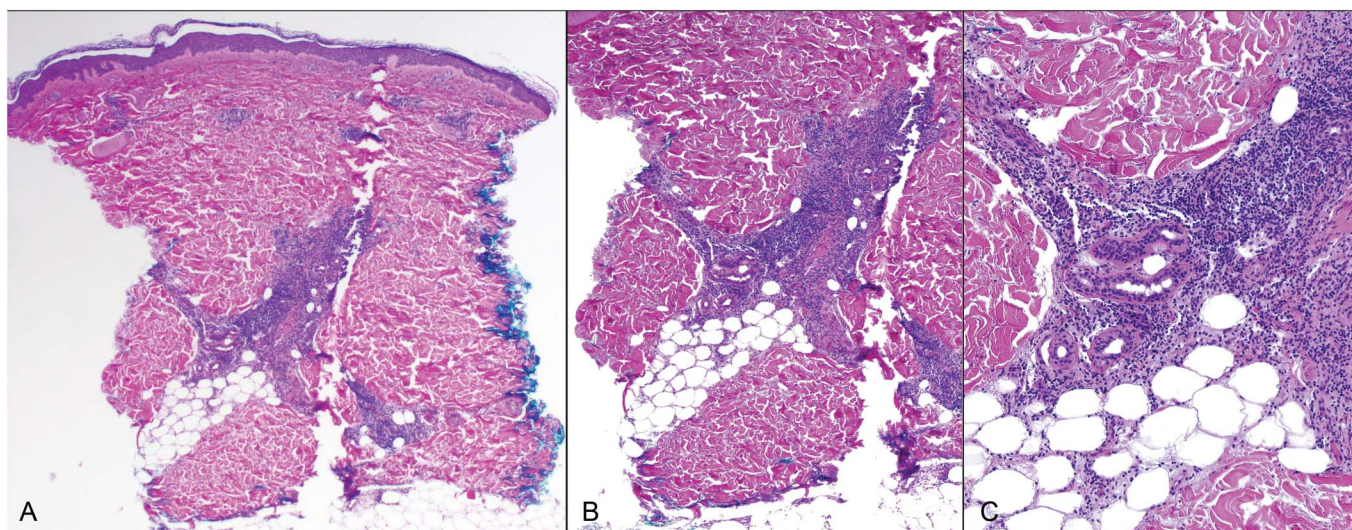


FIGURE 1. Syringotropic and focally epidermotropic atypical lymphocytic infiltrate with hyperchromatic nuclei, occasional irregular nuclear contours, and minimal amount of eosinophilic cytoplasm, surround and infiltrate eccrine ducts and glands. A, $\times 20$. B, $\times 40$. C, $\times 100$.

was restarted and his bexarotene dose was increased to 225 mg, resulting in almost complete clearance of his plaque.

DISCUSSION

In 1969, Sarkany first reported an erythematous, alopecic, anhidrotic lesion on the chest of a 54-year-old Lithuanian laborer histopathologically significant for a heavy dermal infiltrate concentrated around eccrine glands now known as STMF.³ It is an exceptionally rare form of MF. Including cases previously termed syringolymphoid hyperplasia, only 51 cases have been published in the intervening 48 years since its description. Rongioletti and Smoller found syringotropism to be even less common than folliculotropism on review of 104 biopsies from patients with indisputable patch/plaque stage MF.¹⁰

Clinically, STMF is indistinguishable from its aggressive adnexal counterpart, FMF. It presents as solitary or multiple erythematous infiltrated papules, plaques, or nodules frequently displaying distinct studded comedo-like nodules. In contrast, the anatomic distribution of lesions in STMF differs from that of classic MF, demonstrating a predisposition toward the extremities and palms/soles.⁶ Men are affected twice as often as women with the youngest case reported a 19-year-old in China¹¹ and the oldest an 86-year-old in France (mean age 55).⁶

Overlying alopecia is so common in STMF that it was historically termed “syringolymphoid hyperplasia with alopecia (SHLA),” with alopecia in 70% of the 14 cases reported by Pileri et al¹² Although SHLA and STMF were initially considered separate entities, the histopathologic discovery that the perieccrine infiltrate of SHLA was in fact comprised atypical monoclonal CD4⁺ T cells resulted in its reclassification as early manifestation of STMF.⁴ The clinically noticeable impact on hair growth in STMF reflects the 75% incidence of concomitant follicular involvement

observed over all literature-reported cases. Importantly, the clinical behavior of STMF with follicular epithelium involvement is significantly more benign than that of FMF,⁶ suggesting that despite similar early clinical presentations and frequent histopathologic overlaps, STMF and FMF are molecularly distinct diseases. Phenotypic analyses lend support to this hypothesis. This point is further discussed below. In addition to alopecia, hypohidrosis is also frequently encountered in association with STMF.^{13–15} Ulceration is not commonly associated with MF but has been documented in few cases of STMF.^{6,14,16,17}

Histopathologic characteristics of STMF include atypical lymphocytes surrounding eccrine coils, varying degrees of syringometaplasia, and conventional features of MF including epidermotropic atypical lymphocytes.¹² Far from a standard feature, of all cases of syringotropic MF published thus far, epidermotropism is present only 30% of the time. It should be noted that while focal adnexotropism is frequently seen in MF, hyperplasia of eccrine glands is not.¹⁰ However, even in STMF as the present case highlights, syringotropic atypical lymphocytes do not always induce syringoid hyperplasia.¹⁸ The phenotypic identity of the malignant cells was confirmed in this and other cases of STMF as T-lymphocytes via immunohistochemical profile (CD2⁺, CD3⁺, and CD4⁺). Monoclonal TCR gene rearrangements are found on molecular analysis of STMF in most cases.^{6,12}

The depth of the focus of malignant cells in the dermis of STMF renders skin-directed therapies, such as NB-UVB, used in classic epidermotropic MF less effective. Local radiotherapy,¹⁹ systemic alitretinoin,⁶ combination vorinostat and retinoids,¹⁵ VELP (vincristine sulfate, etoposide, L-asparaginase, and prednisone acetate) chemotherapy,¹¹ and psoralen and UVA⁶ have all been used to successfully treat STMF. Resistance to skin-directed therapies mirrors FMF which, in the rare instance it responds to treatment, requires systemic

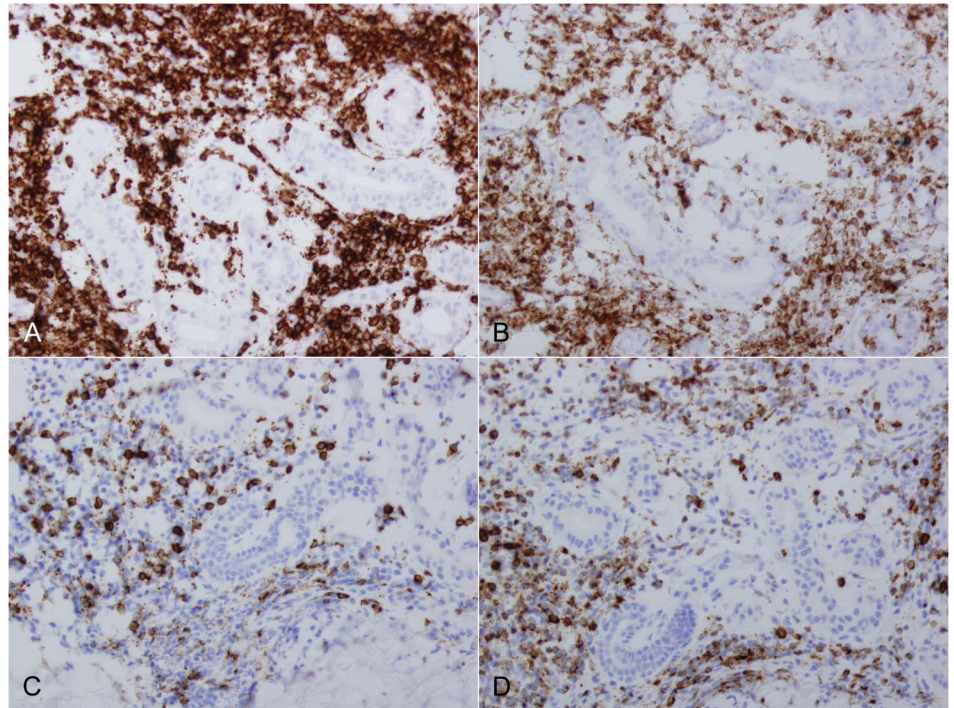


FIGURE 2. Perieccrine lymphocytes stained for (A) CD3, (B) CD4, (C) CD8, and (D) CD7.

agents.²⁰ However, even stubborn STMF lesions do not incur disease-specific mortality⁶ compared with the FMF, which even when treated aggressively has an 18% and 59% mortality rate at 10 and 15 years, respectively.¹⁹

All variants of MF involve atypical T-lymphocytes, however, the precise nature of the relationship between “classic” (ie, epidermotropic), syringotropic, and folliculotropic forms of MF remains to be determined. Observed differences in response to treatment, progression, and disease survival suggest classic MF, STMF, and FMF represent distinct entities with unique trajectories as opposed to points along a linear spectrum. One illustration of this is that early stage FMF carries a much worse outcome than that of even late-stage classic MF or STMF, even when there is clinical and histopathologic overlap between these adnexal variants.^{3,6} Molecular studies demonstrate a high concentration of CD1a cells localized to the infundibulum and isthmus exceeding a 10:1 ratio in 70% of lesional hair follicles of FMF analyzed,¹⁹ whereas this is not so for STMF even in instances of brisk follicular involvement indicating an intrinsic difference between the 2 entities.⁴ This variation in T-cell subtypes may account for the significant divergence clinical behavior. In addition, there have been no cases of transformation from one form of MF to another.

In conclusion, given that syringotropic and folliculotropic MF are virtually indistinguishable on clinical examination, obtaining a skin biopsy for histopathologic differentiation is invaluable to the provision of an accurate prognosis. Dermatopathologists should be cognizant of the fact that folliculotropism is not unusual in STMF. Because STMF with follicular involvement carries a better prognosis than FMF, the presence of atypical folliculotropic lymphocytes should prompt a search for syringotropic involvement.

Alerting the clinician of STMF can also aid in the determination of skin-direct versus systemic treatment.

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