

A Rare Case of Unilesional Follicular and Syringotropic Mycosis Fungoides: A Case Report and Review of the Literature

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Abstract

Mycosis fungoides (MF) is the most common cutaneous lymphoma. It has three newly classified variations, one of which is follicular mycosis fungoides. Follicular mycosis fungoides (FMF) can further be divided into the rare variants unilesional follicular mycosis fungoides and syringotropic mycosis fungoides. We present a case with overlapping unilesional follicular mycosis fungoides and syringotropic mycosis fungoides. These rare variants can often appear clinically as benign inflammatory skin conditions and are frequently misdiagnosed for years. Close follow-up with repeated biopsies can lead to a diagnosis as the disease progresses. The disease has a poor prognosis compared to similar-staged diseases of classic mycosis fungoides. This is attributed to the location of the pathology, deep in the dermis and subcutaneous tissue, which requires more aggressive treatments to reach the depth of the disease.

Introduction

Mycosis fungoides (MF) is the most common cutaneous lymphoma, estimated to occur in approximately 0.55 per 100,000 person-years.¹ This cutaneous T-cell lymphoma (CTCL) is characterized by a T-cell lymphocytic infiltrate in the papillary dermis, the presence of atypical lymphocytes with cerebriform nuclei, and evidence of epidermotropism.² MF has multiple variants presenting with different clinical and vastly different histologic presentations. The etiology of MF is unclear, with infectious, occupational, and genetic mutations presenting possible causes.^{1,3} It has been noted to be a challenging diagnosis histologically, as there can be significant overlap between MF and benign inflammatory conditions.^{1,4} Many of the clinical and histopathological features of MF can be absent in early disease, often causing a delay of diagnosis and treatment.¹ While many clinical and histological variants have been described over the years, MF has recently been divided into three variants. The World Health Organization and World Health Organization for Research and Treatment of Cancer held consensus meetings in 2003 and 2004 to align the classifications of cutaneous lymphomas by resolving controversy over definitions and terminology between the two organizations.⁵

MF variants reclassified during the meeting include the most common Aliber-Bazin type and three variants including folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin.⁵ Folliculotropic mycosis fungoides (FMF) is characterized by the presence of medium to large, hyperchromatic T-cell infiltrates within the follicular epidermis known as folliculotropism. The disease most often spares the epidermis of the surrounding skin. While classic MF is often reported with follicular manifestations representing follicular mucinosis, FMF reveals involvement of the hair follicles and eccrine glands by lymphoma cells.⁵⁻⁷ Clinically, the lymphoma is most commonly found on the head and neck.¹ Patients often present with acneiform lesions, indurated plaques, or follicular-centered papules, with occasional tumors. Most often, patients

Table 1. Comparison of overall 5-year and 10-year survival rates^{1,2,4,18}

Classification	Overall survival rates (%)	
	5 year	10 year
Mycosis fungoides (MF)*		97-98
Folliculotropic mycosis fungoides (FMF)	62-68	26
Syringotropic mycosis fungoides (SMF)	100	83-97

*Limited patch/plaque stage

can be found with multiple plaques throughout the body. There have been few published cases of FMF to date.⁸ Infiltrated plaques of the eyebrows with alopecia are common and highly characteristic findings with severe pruritus.^{1,4} In multiple cases, infiltration of the eccrine sweat glands is also present.¹

Further classifications exist within each variant, including rare forms of unilesional FMF and syringotropic MF.^{8,9} Unilesional FMF is characterized by a single area of involvement of less than 5% body surface area. Syringotropic MF is characterized by prominent involvement of the eccrine glands with syringolymphoid hyperplasia.⁹ There is significant overlap between folliculotropic and syringotropic MF, causing difficulty for clinicians as the two have shown variations in prognosis (Table 1).^{8,10} We report a complicated case of unilesional follicular and syringotropic MF.



Figure 1. Right supraorbital plaque with alopecia, two months after onset.

Case Report

A 45-year-old Caucasian male presented to our office for a second opinion of a localized, indurated plaque over the right eyebrow with alopecia (Figure 1). The patient had no significant past medical or family history. The lesion started four months prior as a pimple with symptoms of itching and burning. The lesion progressed over the next two months into a firm plaque with alopecia. No lymphadenopathy or further plaques were noted on physical exam.

The lesion was biopsied prior to presenting at our office and read as follicular mucinosis. Prominent adnexal involvement within the follicular epithelium was noted. Superficial and deep perivascular infiltrates were also present. Follicular mucin was noted within the follicular epithelium, as well as prominent eosinophils. No significant lymphoid atypia was noted at that time. The patient was informed that the T-cell dyscrasia had the potential to be attributed to benign as well as malignant causes.

The patient presented to our office, and two further biopsies were performed. The patient's lab work showed a mild leukocytosis with all other labs within normal limits. The patient was started on clobetasol 0.05% cream twice a day after the initial visit. The slides (Figures 2, 3, 4) were reviewed by multiple dermatopathologists as well as a dermatopathologist specializing in cutaneous lymphomas. A marked atypical, cerebriform, lymphocytic infiltrate was noted surrounding as well as permeating the hair follicles. Eccrine ducts and glands were also affected, with sparing

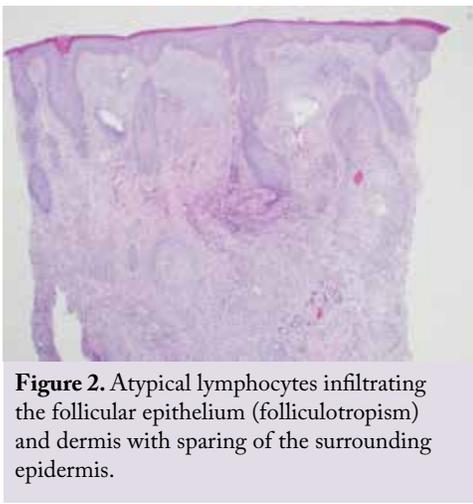


Figure 2. Atypical lymphocytes infiltrating the follicular epithelium (folliculotropism) and dermis with sparing of the surrounding epidermis.

of the surrounding epidermis. Close examination of the infiltrate demonstrated marked nuclear irregularity with hyperchromasia. An admixture of histiocytes and eosinophils were present. The lymphocytic infiltrate was also present in the intrafollicular dermis and subcutaneous fat. An Alcian blue stain confirmed the presence of mucin within the hair follicles. The findings were suspicious for incipient tumor-stage development.

Phenotypic studies were performed, demonstrating a T-cell infiltrate represented by an almost exclusive CD4⁺, CD8⁻, CD7⁻ phenotype. This pattern is characteristic of FMF as well as MF.⁹ Other positive T-cell markers included CD3 and CD5. A CD68⁺ marker representing macrophages was also present. PD-1 was negative and most often found in small/medium-sized (pleomorphic) T-cell lymphomas. Contradictory data on PD-1⁺ T-cells in FMF have been reported, with anywhere from 9% to 80% of cases harboring positive T-cells.^{9,13} The proliferative index was found to be low at 15% to 20%. The CD 4/8 ratio was noted to have an absence of CD8 within the hair follicles and eccrine glands. However, an admixture of CD8 lymphocytes was noted within the intrafollicular dermis, adnexal dermis, and subcutaneous fat. Gene rearrangement studies were negative for both the biopsy specimen and peripheral blood.

Considering the extent of lymphoid atypia, degree of lymphocytic infiltration of the dermis and subcutaneous tissue, and the abnormal phenotypic profile, the patient was diagnosed with unilesional follicular and syringotropic mycosis fungoides. He was referred to a tertiary clinic that specializes in cutaneous lymphomas for treatment. The lesion had slightly decreased with topical clobetasol 0.05% cream. The patient was continued on clobetasol twice daily on Tuesday, Thursday, Saturday and Sunday. He was also instructed to apply bexarotene 1% gel, a synthetic retinoid that binds to the RXR ligand, on Monday, Wednesday, and Friday mornings. This was paired with clobetasol in the evenings. After six weeks, the lesion had decreased in vertical growth. The patient was instructed to replace the clobetasol with triamcinolone 0.1% for six weeks, and then hydrocortisone 2.5% for an additional six weeks. After 18 weeks of

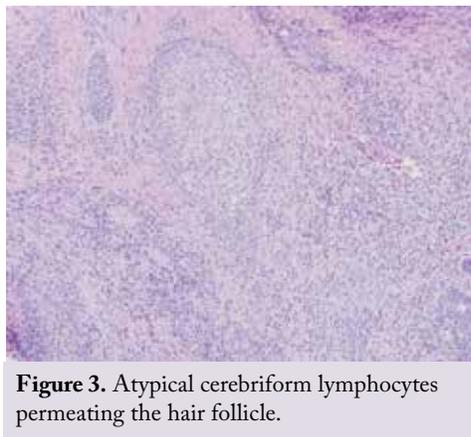


Figure 3. Atypical cerebriform lymphocytes permeating the hair follicle.

treatment, the lesion had no further progression, but the plaque persisted. The site was again biopsied, demonstrating persistence of the follicular and eccrine involvement. The patient was then referred for radiotherapy with follow-up pending.

Discussion

Our patient presents a rare case of unilesional follicular and syringotropic mycosis fungoides. The diagnosis of FMF or SMF can be very difficult, often requiring multiple biopsies over time. The clinical and histopathological presentation is often mistaken for follicular mucinosis (FM).^{4,7,11} Some debate exists on whether FM represents a precursor to FMF or a benign variant of MF with a non-aggressive clinical course.^{4,11,12} It should be noted that follicular mucinosis in younger patients most often is characterized by spontaneous regression after two months to two years, without any further progression to MF.¹¹ Cerroni attempted to review the clinical and histopathologic differences between FM and malignant FMF. He noted that despite looking at the age of the patient, location of lesions, number of lesions, amount of mucin deposited within the follicles, as well as gene rearrangement studies, significant overlap exists between the two disease states.¹¹ This leads most often to delays in diagnosis averaging two to five years.¹⁴ Early diagnosis is important considering the poor five-year overall survival rate of 62%.⁴ The overlap between FM and FMF shows the importance of close follow-up and the need for multiple biopsies for persistent and changing lesions not responding to conventional treatments.¹³

The histology of our patient's lesion also demonstrated prominent involvement of the eccrine-duct epithelium, known as syringotropic mycosis fungoides (SMF). SMF is described as atypical lymphocytes surrounding the eccrine ducts and glands and infiltrating the eccrine epithelium, with associated syringolymphoid hyperplasia.⁹ Some authors consider SMF and FMF to be closely related, but with separate disease processes.⁶ Other authors believe it to be a variation or progression of the same disease process.^{4,14} The current WHO-EORTC guidelines place SMF and FMF in the same group as a single variant of MF.⁵ Many articles describe FMF also affecting the eccrine ducts

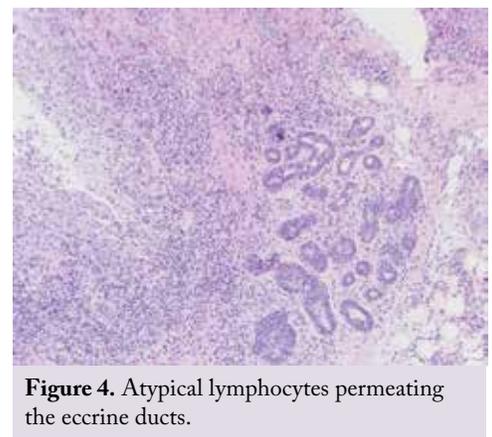


Figure 4. Atypical lymphocytes permeating the eccrine ducts.

and cases of SMF demonstrating follicular involvement.⁹ Our case demonstrates an overlap of FMF with SMF.

FMF has multiple differences from MF, including head and neck involvement, which is typically spared in MF and often SMF.⁴ The pathogenesis and cause of accumulating lymphocytes within and around the follicular epithelium and eccrine glands, and sparing of the surrounding epidermis, is poorly understood. However, multiple studies have noted an increased expression of ICAM-1 within follicular keratinocytes, which is thought to be induced by neoplastic T lymphocytes. This is hypothesized to lead to the obstruction of follicular orifices by neoplastic T-cells.¹⁵⁻¹⁷ Pereyo explains the relationship of FMF to MF as one similar to that of lichen planopilaris to lichen planus.¹⁴ The immunohistochemical analysis of FMF and MF are similar, most commonly demonstrating a CD4⁺ T-cell dyscrasia with a common loss of CD7 and often clonal T-cell gene rearrangements.¹ However, T-cell gene rearrangements can be conflicting, as they can be negative in many malignant cases and positive in benign conditions such as spongiotic dermatitis, further confusing the diagnosis.^{1,4,14} A few studies have required positive monoclonal gene rearrangements to make the diagnosis of FMF. Cerroni demonstrated that monoclonal gene rearrangements were noted in six out of 11 cases of idiopathic FM and only nine out of 19 cases of lymphoma-associated FM.^{7,10} This shows that gene rearrangements, although helpful if found, cannot be heavily relied upon to make the diagnosis.

FMF was reclassified as a separate entity from MF due to its distinctive clinical and histological features, as well as its worse prognosis and resistance to standard treatments.⁵ Fewer than 10% of patients with classic MF will progress to more advanced stages, and less than one third of those patients will develop extracutaneous disease with disease-related death in the first 10 years after diagnosis.¹⁵ Most FMF patients are clinically classified as stage IA or IB; however, they demonstrate worse five- and 10-year survival rates, more similar to survival rates of patients with tumor-stage MF. Multiple studies have noted disease-specific survival rates at five years and 10 years averaging 68% and 26%, respectively (Table 1).¹⁸ Many studies stress the importance

of treating all FMF patients as tumor-stage regardless of the clinical appearance.¹⁸ This demonstrates the need for early diagnosis with more aggressive treatments.¹⁷

Effective treatment options for FMF vary compared to classic MF, which often responds to photochemotherapy (PUVA) and topical creams including mechlorethamine, nitrogen mustard, retinoids and steroids.^{5,18} Although no standard treatment exists, many case reports have demonstrated the ineffectiveness of these more superficial treatments.^{14,17} It is thought that deep follicular involvement allows the disease to persist beyond their reach. Common, more aggressive treatments with beneficial results include radiotherapy for localized lesions and total-skin electron-beam therapy (TSEBT) for diffuse lesions, leading many to claim them as the treatment of choice.^{10,17,19}

Conclusion

Our case demonstrates a rare presentation of MF with unilesional follicular and syringotropic mycosis fungoides. Debate continues regarding whether FMF and SMF are distinct entities or variations of the same disease process. Our patient had prominent, marked follicular involvement as well as eccrine-duct involvement with syringohyperplasia. As noted, FMF has a worse prognosis compared to classic MF. This is in contrast to SMF, which has a prognosis similar to early-stage classic MF.¹⁰ Both FMF and SMF have higher fail and recurrence rates with topical and superficial treatments, as was noted in this case. The case demonstrates the importance of follow-up in patients presenting with plaques or rashes consistent with benign inflammatory conditions that fail to respond to conventional treatments. Oftentimes, these processes can represent early stages of MF, requiring repeated biopsies with further cytological and serum testing in order to make the diagnosis. Most cases with unilesional plaques are associated with an indolent course; however, our case demonstrates that rarely they can be due to more aggressive forms such as FMF, requiring aggressive treatments. Further studies and case reports are required to better classify the differences and similarities between FMF and SMF.

References

1. Ahn C, ALSayyah A, Sanguenza O. Mycosis Fungoides: an Updated Review of Clinicopathologic Variants. *Am J Dermatopathol.* 2014;36(12):933-948.
2. De Masson A, Battistella M, Vignon-Pennamen MD, et al. Syringotropic Mycosis Fungoides: Clinical and histologic features, response to treatment, and outcome in 19 patients. *J Am Acad Dermatol.* 2014;71(5):926-934.
3. Carrington P. Follicular mycosis fungoides. *J Am Acad Dermatol.* 1998;38(3):502-503.
4. Lehman J, Cook-Norris R, Weed B, et al. Folliculotropic Mycosis Fungoides: Single-Center Study and Systematic Review. *Arch Dermatol.* 2010;146(6):607-613.
5. Willemze R, Jaffe E, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood.* 2005;105(10):3768-3785.
6. Lacour JP, Castanet J, Perrin C, et al. Follicular Mycosis Fungoides. *J Am Acad Dermatol.* 1993;29(2):330-334.
7. Rongioletti F, Reboro A. Cutaneous mucinosis: microscopic criteria for diagnosis. *Am J Dermatopathol.* 2001;23(3):257-267.
8. Kempf W, Kazakov D, Schermesser M, et al. Unilesional follicular mycosis fungoides: report of two cases with progression to tumor stage and review of the literature. *J Cutan Pathol.* 2012;39(9):853-860.
9. Pileri A, Facchetti F, Rutten A, et al. Syringotropic mycosis fungoides: a rare variant of the disease with peculiar clinicopathologic features. *Am J Surg Pathol.* 2011;35(1):100-109.
10. Yost J, Thy T, Kovalszki K, et al. Two cases of syringotropic cutaneous T-cell lymphoma and review of the literature. *J Am Acad Dermatol.* 2009;61(1):133-138.
11. Cerroni L, Fink-Puches R, Bäck B, et al. Follicular Mucinosis: A Critical Reappraisal of Clinicopathologic Features and Association With Mycosis Fungoides and Sézary Syndrome. *Arch Dermatol.* 2002;138(2):182-189.
12. Bonta M, Tannous Z, Demierre MF. Rapidly progressing mycosis fungoides presenting as follicular mucinosis. *J Am Acad Dermatol.* 2000;43(4):635-640.
13. Iorizzo M, El Shabrawi Caelen L, Vincenzi C, et al. Mycosis fungoides masquerading as alopecia areata. *J Am Acad Dermatol.* 2010;63(2):50-52.
14. DeBloom J, Severson J, Gaspari A, et al. Follicular mycosis fungoides: a case report and review of the literature. *J Cutan Pathol.* 2001;28(6):318-324.
15. Pereyo N, Requena L, Galloway J, Sanguenza O. Follicular mycosis fungoides: A clinicohistopathologic study. *J Am Acad Dermatol.* 1997;36(4):563-568.
16. Grau F, Point V, Matarredona J, et al. Follicular mycosis fungoides: presentation of a case and review of the literature. *J Eur Acad Dermatol Venereol.* 1999;13(2):131-136.
17. Monopoli A, Annessi G, Lombardo G, et al. Purely follicular mycosis fungoides without mucinosis: Report of two cases with review of the literature. *J Am Acad Dermatol.* 2003;48(3):448-452.
18. Van Doorn R, Scheffer E, Willemze R. Follicular Mycosis Fungoides, a Distinct Disease Entity With or Without Associated Follicular Mucinosis: A Clinicopathologic and Follow-up Study of 51 Patients. *Arch Dermatol.* 2002;138(2):191-198.
19. Thein M, Ravat F, Orchard G, et al. Syringotropic cutaneous T-cell lymphoma: an immunophenotypic and genotypic study of five cases. *Br J Dermatol.* 2004;151(1):216-226.

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