

## Challenging case of folliculotropic mycosis fungoides in 11 years old girl with erythema cheek plaque: A case report

Caso desafiador de micose fungoide foliculotrópica em menina de 11 anos com placa eritematosa nas bochechas: Um relato de caso

Caso desafiante de micosis fungoides foliculotrópica en niña de 11 años con placa eritematosa en mejilla: Un informe de caso

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### Abstract

**Introduction:** Folliculotropic Mycosis Fungoides (FMF) is the most common case among all variants of Mycosis Fungoides besides Classic Mycosis Fungoides with a worse prognosis than other variants. An understanding of the clinical features and histopathological features of Mycosis Fungoides and its variants is greatly needed in establishing a diagnosis, especially in perspective of Pathology. **Methodology:** This descriptive study of the case report type and the data obtained from the patient's medical report. **Case Description:** A 11 years old girl came with a rash on her right cheek since 3 weeks ago and is increasing in size. On physical examination, there was an erythematous plaque on the right cheek about 2 cm from the nasolabial fold. Microscopic examination showed scattered and infiltrative atypical lymphocyte cells, infiltrative among follicles. The hair follicles showed a degenerated epithelial and cystically dilated epithelium containing follicular mucinosis. Immunohistochemistry shows positive CD3, CD4, CD5, and 10% of Ki67. **Conclusion:** Although it occurs in 50% of lymphoma cases, cases of Mycosis Fungoides are generally rare. The Folliculotropic Mycosis Fungoides variant is the most common among all the Mycosis Fungoides variants besides Classic Mycosis Fungoides with a worse prognosis than the other variants. It is important to carry out a biopsy examination to assess whether there is an MF lesion, especially Folliculotropic MF in the specimen being examined, moreover if the clinical manifestations in this case vary greatly depending on the stage of the lesion.

**Keywords:** Follicular mycosis fungoides; Plaque Lesion.

### Resumo

**Introdução:** A Micose Fungóide Foliculotrópica (FMF) é o caso mais comum entre todas as variantes de Micose Fungóide além da Micose Fungóide Clássica com pior prognóstico que outras variantes. A compreensão das características clínicas e histopatológicas da Micose Fungóide e suas variantes é muito necessária para o estabelecimento de um diagnóstico, especialmente na perspectiva da Patologia. **Metodologia:** Trata-se de estudo descritivo do tipo relato de caso e dos dados obtidos no prontuário médico do paciente. **Descrição do caso:** Uma menina de 11 anos apresentou erupção na bochecha direita há 3 semanas e está aumentando de tamanho. Ao exame físico, apresentava placa eritematosa na bochecha direita, a cerca de 2 cm do sulco nasolabial. O exame microscópico mostrou células linfocitárias atípicas dispersas e infiltrativas, infiltrativas entre os folículos. Os folículos capilares apresentavam epitélio epitelial degenerado e epitélio cisticamente dilatado contendo mucinose folicular. A imunohistoquímica mostra CD3, CD4, CD5 positivos e 10% de Ki67. **Conclusão:** Embora ocorra em 50% dos casos de linfoma, os casos de Micose

Fungoide são geralmente raros. A variante da Micose Fungóide Folliculotrópica é a mais comum entre todas as variantes da Micose Fungóide, além da Micose Fungóide Clássica, com pior prognóstico que as demais variantes. É importante a realização de exame de biópsia para avaliar se há lesão de MF, principalmente MF folliculotrópica na peça examinada, além de se as manifestações clínicas neste caso variam muito dependendo do estágio da lesão.

**Palavras-chave:** Micose fungóide folicular; Lesão em placa.

### Resumen

**Introducción:** La Micosis Fungoide Folliculotrópica (FMF) es el caso más común entre todas las variantes de Micosis Fungoide además de la Micosis Fungoide Clásica con peor pronóstico que otras variantes. Es muy necesario comprender las características clínicas e histopatológicas de la micosis fungoide y sus variantes para establecer un diagnóstico, especialmente en la perspectiva de la patología. **Metodología:** Se trata de un estudio descriptivo del tipo reporte de caso y de los datos obtenidos del informe médico del paciente. **Descripción del Caso:** Una niña de 11 años acudió con un sarpullido en la mejilla derecha desde hace 3 semanas y está aumentando de tamaño. Al examen físico se apreciaba una placa eritematosa en mejilla derecha a unos 2 cm del pliegue nasolabial. El examen microscópico mostró células linfocitarias atípicas dispersas e infiltrativas, infiltrativas entre los folículos. Los folículos pilosos mostraron un epitelio degenerado y un epitelio dilatado quísticamente que contenía mucinosis folicular. La inmunohistoquímica muestra CD3, CD4, CD5 positivos y 10% de Ki67. **Conclusión:** Aunque ocurre en el 50% de los casos de linfoma, los casos de Micosis Fungoide son generalmente raros. La variante de Micosis fungoide folliculotrópica es la más común entre todas las variantes de Micosis fungoide además de la Micosis fungoide clásica con peor pronóstico que las otras variantes. Es importante realizar un examen de biopsia para evaluar si existe una lesión de MF, especialmente MF folliculotrópica en la muestra que se examina, además si las manifestaciones clínicas en este caso varían mucho según el estadio de la lesión.

**Palabras clave:** Micosis fungoide folicular; Lesión en placa.

## 1. Introduction

According to the latest GLOBOCAN data, an estimated 509,600 new cases of NHL were diagnosed globally in 2018, comprising 2.8% of worldwide cancer diagnoses. The global age standardized risk of NHL was 6.7 among men and 4.7 among women, translating to a 0.72% and 0.35% cumulative lifetime risk for men and women, respectively. The incidence in high and low/medium human development index nations, respectively, was 7.8/100,000 and 4.3/100,000 among men and 5.6/100,000 and 2.9/100,000 among women. (Globocan, 2020). Common T-cell lymphomas make up only 10–15% of NHL diagnoses (WHO Classification of Tumor, 2023).

Primary Cutaneous Lymphomas (PCL) are a group of Non-Hodgkin Lymphomas (NHL) which are characterized by monoclonal proliferation of malignant lymphocytes in the skin. Primary Cutaneous Lymphomas are classified into 2, namely Cutaneous T-Cell Lymphoma (CTCL) and Cutaneous B-Cell Lymphoma (CBCL). In a consensus in Lyon, France (September 2003) and Zurich, Switzerland (January 2004) by the World Health Organization (WHO) and the European Organization on Research and Treatment of Cancer (EORTC), it was determined that Mycosis Fungoides (MF) is a type Cutaneous T-Cell Lymphoma is the most common and accounts for 50% of all cases of Primary Cutaneous Lymphoma. The Folliculotropic Mycosis Fungoides (FMF) variant is the most frequent case among all Mycosis Fungoides variants other than Classic Mycosis Fungoides with a worse prognosis compared to other variants because of the deep localization of the neoplastic infiltrate causing inaccessible for skin-targeted therapies, and management of the condition remains challenging (Kempf W, et al., 2023).

Folliculotropic Mycosis Fungoides differs from Classic Mycosis Fungoides in both clinical and histopathological features. Therefore, the disease is described as a distinct entity according to the World Health Organization (WHO) and European Organization on Research and Treatment of Cancer (EORTC) classifications. An understanding of the clinical picture and good histopathology of cases of Mycosis Fungoides and its variants is very necessary in making a diagnosis, especially in the field of Anatomical Pathology. In this case report, the case of Folliculotropic Mycosis Fungoides is reviewed primarily from the pathological aspect which is correlated with clinical manifestations (Wieser, et al., 2017).

## 2. Methodology

This is a descriptive study of the case report type. In general, case study research is centered on a phenomenon, which is described in as much depth as possible (Yin, 2017; Pereira et al., 2018). Analysis of the medical record for description of the clinical case, being presented in chronological order, and literature review using scientific databases. Our research ethics committee did not conduct any ethical clearance for the case report due to its already discussed at the clinicopathological conference and approved by the clinician, patient, and pathologist. Following ethical principles, the patient consented to disseminating the data and displaying images of his case for academic purposes through the signing of a Free and Informed Consent Form.

## 3. Case Description

A 11 year old girl came with a rash on her right cheek since 3 weeks ago and is increasing in size. On physical examination, there was an erythematous plaque on the right cheek about 2 cm from the nasolabial fold.

The results of the blood laboratory examination showed unremarkable blood level results, except for an increase in eosinophil  $0.99 \times 10^3/\mu\text{L}$  ( $0.0\text{-}0.55 \times 10^3/\mu\text{L}$ ).

**Figure 1** – Erythematous Plaque Lesion on Right Cheek.

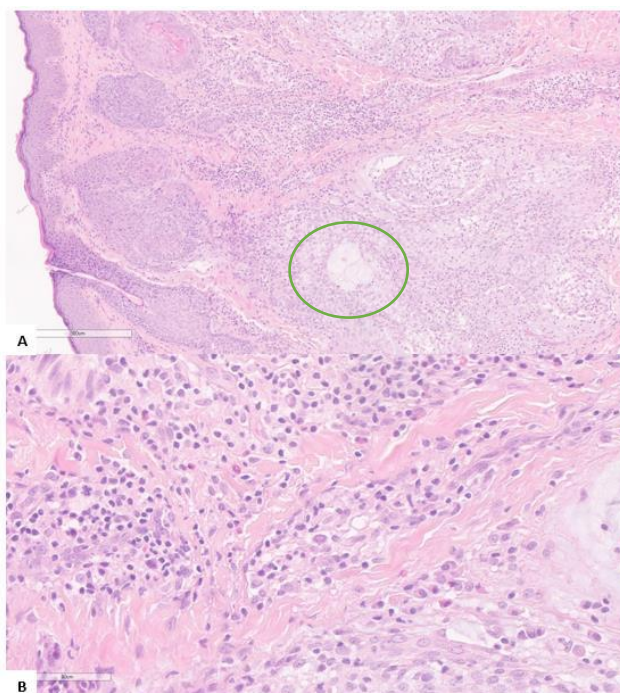


Source: Authors.

The patient underwent a punch biopsy on March 5<sup>th</sup> 2023 with biopsy tissue. Microscopic examination showed the distribution and aggregates of atypical lymphocyte cells that were scattered and infiltrative between the hair follicles. The hair follicles show degenerated and cystic dilated epithelium containing mucin material (follicular mucinosis).

The tissue was also subjected to immunohistochemical examination with positive CD3, positive CD4, positive CD5, negative CD7, and positive Ki67 results in 10% of tumor cells.

**Figure 2 – A.** The lesion shows the appearance of degenerated and cystic dilated follicles containing extensive mucinous material (follicular mucinosis) (H&E, 100x). **B.** A dense infiltrate of atypical lymphocyte cells can be seen, infiltrating to the interfollicular level. (H&E, 400x).



Source: Authors.

#### 4. Discussion

Mycosis fungoides (MF) is a clinically and pathologically distinct form of cutaneous lymphoma characterized by epidermotropic infiltration of small to medium-sized T lymphocytes. In the WHO/EORTC classification, this term is intended for cases that have classic characteristics where there is progression from spots, to plaques, then to tumors (Alibert-Bazin type) or variants that have a similar disease course (Patterson, et al., 2021).

Data show that transient antibiotic treatment is associated with decreased neoplastic T cell fraction, cell proliferation, and STAT3 signaling, suggesting that the microbiome may be involved in the evolution of malignant clones. Early MF is thought to be mediated by contact with immature antigen-presenting cells leading to constitutive TCR activation, which together with defects in the apoptotic pathway may lead to early clonal expansion of T cells, contributing to disease evolution (Krejsgaard T., et al., 2017).

Based on next generation sequencing data, genetic aberrations in signaling pathways and epigenetic processes have recently been identified that may contribute to the pathogenesis of MF, namely in the context of chronic antigenic stimulation of skin-dwelling T lymphocytes, and/or constitutive T cell activation, chromatin modification, cell cycle regulation, and altered NF- $\kappa$ B signaling downstream to the TCR may be involved in the regulation of T cell survival and proliferation. (Chang L.W., et al., 2018). Alteration of the JAK3/STAT3 signal transduction pathway and MAPK may contribute to the survival and proliferation of malignant T cells in MF. Marked hypo-methylation and hyper-methylation have been observed in MF cases; for example, DNMT3A, a gene encoding a methyltransferase, is frequently mutated or deleted in MF cases, indicating that genetic aberrations may underlie epigenetic dysregulation. To date, no specific chromosomal translocations have been identified in MF (Phyo, 2020).

Although this disease represents nearly 50% of all primary cutaneous lymphomas and 60% of all cutaneous T-cell lymphomas, it is still rare. The true incidence rate of MF is difficult to collect because the clinical subtypes of CTCL are not

clearly differentiated. MF can appear at any age with a peak incidence in the late fifties, with a greater prevalence in men (M : F = 2 : 1 ). However, MF can also appear in children and adolescents (4-11%) (Patterson, et al., 2021).

Lesions tend to appear on the lower body and thighs. Lesions can also appear on the breasts in women. In advanced stages, lesions may appear all over the body, including the face and scalp. The palms and soles of the feet also appear in some cases. MF usually has a slow progression over years or decades. In a study of the progression of MF from the patch stage to death from systemic spread, the overall mean disease duration was 12.4 years (Kamarashev, et al., 2007).

Classical MF is traditionally divided into patch stage, plaque stage, and tumor stage. However, this classification can change because all stages can appear simultaneously in one individual while other patients never progress beyond the patch stage. In addition, the patch stage lesion clearly merges with the plaque (Calonje, et al., 2020).

The patch stage consists of ill-defined patches of varying color, often with fine scales. They are irregular in size and shape and scattered randomly, usually on the body. This stage may persist for years before regression occurs (Patterson, et al., 2021).

**Figure 3** - Mycosis Fungoides (Patch Stage). The lesions appear irregular, erythema and scaling on the buttocks area.



Sources: *Mckee's Pathology of the Skin : With Clinical Correlations*. Fifth ed. (2020).

The plaque stage is characterized by well-demarcated lesions that are often annular or arciform in arrangement. They are red to violaceous in appearance and occasionally scaly. The plaques may develop de novo or from patches. In the early stages, lesions are often limited to less than 10% of the skin surface, but they may be more widespread, particularly in the late plaque stage (Patterson J.W., et al., 2021).

**Figure 4** - Mycosis Fungoides (Plaque Stage). The lesion appears as an erythematous plaque with scaling.



Sources: *Mckee's Pathology of the Skin : With Clinical Correlations*. Fifth ed. (2020).

Tumors usually develop in preexisting lesions. The tumors are violaceous to deep red in color, with a tense shiny surface. Ulceration may occur. The lesions usually measure 1 cm in diameter or more. In one series that examined the progression of the disease through various stages, the average duration of the patch stage was 7.2 years, the plaque stage 2.3 years, and the tumor stage 1.8 years (Patterson J.W., et al., 2021).

**Figure 5** - Mycosis Fungoides (Tumor Stage). There are multiple tumor nodules in a background of patches and plaques.



Sources: *Mckee's Pathology of the Skin : With Clinical Correlations*. Fifth ed. (2020).

The term d'emblee form, which was previously used to refer to cases with tumor symptoms that were not preceded by a patch or plaque, is no longer used because it has largely come to represent other T and B cell lymphomas that appear concurrently with the tumor (Patterson, et al., 2021).

There are many descriptions of nonclassical MF, although not the typical Alibert – Bazin type, which has properties similar to classical MF. These include hypopigmented, hyperpigmented, leukodermic, bullous, dyshidrotic, perioral dermatitis-like lesions, palmar-plantar lesions, papules, pustules, acneiform, hyperkeratotic, verrucous, poikilodermatous, anetodermic, erythema annula, granuloma annulare-like, pyoderma gangrenosum-like, and plaques resembling acanthosis nigricans, or keratosis lichenoid chronica (Patterson, et al., 2021).

Histopathologically, the histological picture differs according to the stage of the disease. The early stage lesion (patch stage) is characterized by a fine epidermotropic infiltrate of small to medium sized halo lymphocytes with hyperconvoluted (cerebriform) hyperchromatic nuclei, lining up along the basal and lower-middle layers of the epidermis, often associated with small lymphocyte cells and a mixture of histiocytes light to dense reactive forming band-like. As the lesion transitions to the plaque stage, lymphocytes may colonize more prominently in both upper layers of the epidermis, in a pagetoid pattern, or form clusters or 'clusters' (Pautrier Microabscesses) closely associated with Langerhans cell aggregates. Granulomatous infiltrates may be present, and may even mask lymphoid infiltrates, delaying diagnosis and treatment. Tumor stages in MF often fail to show the typical characteristics of epidermotropism, but instead fill the dermis with atypical cells of small, medium, to large size forming diffuse sheets (Lazar, et al., 2023).

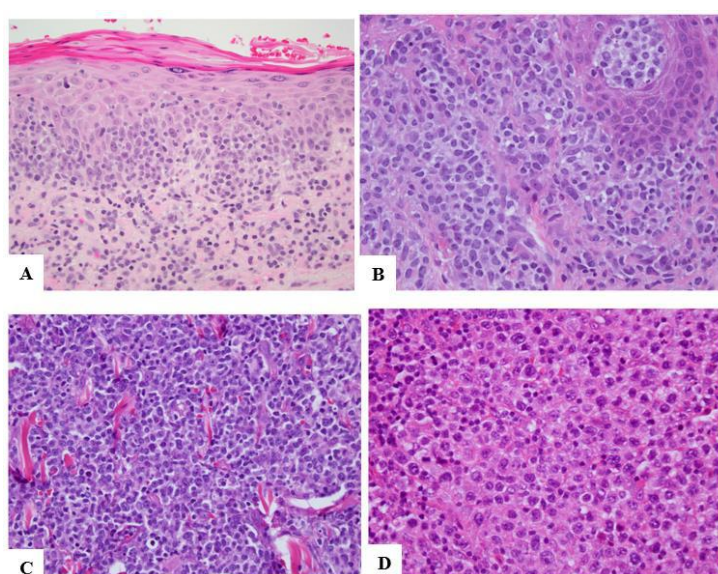
Large cell transformation, characterized by the presence of >25% large lymphoid cells, or clusters of large cells within the dermal infiltrate, may be a harbinger of or is commonly associated with disease progression. The designation of large cell transformation has poor reproducibility, possibly due to the dense tumor lesions, which occur most frequently (Gru, 2018).

Classic MF shows a CD2+, CD3+, TCR beta+, CD5+, CD4+, CD8 phenotype. CD7 is often absent or partially lost, especially in advanced disease. CD30 may be positive or negative, and like other T cell antigens, may show varying levels of expression on biopsies performed at that time. CD45 and CCR4, both associated with lymphocytes that migrate to the skin, were expressed in the majority of cases. Antigens indicative of immune exhaustion (PD1), also common in T follicular helper (TFH)

cells, are common in MF; however, other markers of the TFH phenotype are rare. Thymocyte selection-associated HMG (TOX) box protein may be an additional marker that differentiates early-stage MF. Advanced-stage MF may show multiple immunophenotypic abnormalities including loss of T cell antigens CD2 and CD5, reduced CD4, or loss of TCR $\beta$  expression, as well as partial expression of CD30. B cell aggregates can be identified in these tumor infiltrates and Ki-67 labels a greater percentage of neoplastic cells (Kempf., et al., 2023).

Clinically classic MF with a cytotoxic phenotype (CD8+ and/or TCR  $\gamma$ - $\delta$ ) is well known. Of note, pediatric CD8+ MF and CD8+ hypopigmented MF, common in black and Asian populations, may be associated with a more indolent disease course (Luo, et al., 2019). Nuclear expression of phosphorylated STAT3 can be found in most MF/Sezary syndromes regardless of JAK mutation.

**Figure 6 - Mycosis Fungoides A. Patch Stage B. Plaque Stage C. Tumor Stage D. Tumor Stage with Large Cell Transformation.**



Sources: WHO Classification of Tumors: Haematolymphoid Tumors 5<sup>th</sup> Edition.

Currently Folliculotropic Mycosis Fungoides (Folliculotropic MF) is considered a variant form of this disease, often called “Syringotropic MF”. The disease may present with punctate erythema.

**Figure 7 - Folliculotropic Mycosis Fungoides.** There are erythremic lesions with alopecia on the eyebrows, accompanied by erythema lesions around the hair follicles.

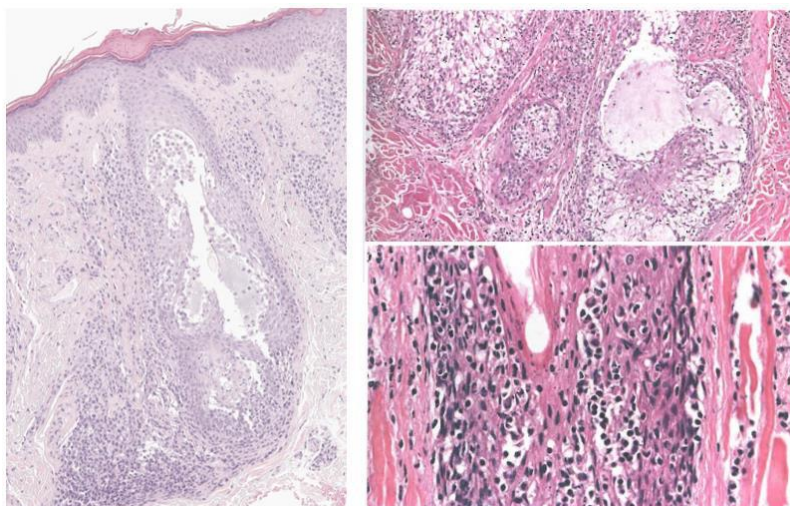


Sources: WHO Classification of Tumours: Skin Tumours, (4<sup>th</sup> edition).

Clinically, folliculotropic MF most commonly appears on the head and neck, upper extremities, and chest. Alopecia, pruritus, and palmar/plantar lesions are characteristic. Folliculotropic MF has a worse disease course than classic MF, unless the

pattern is at an early stage as opposed to more advanced tumor-like disease. Infiltrated plaques, acneiform lesions (comedo-like), and follicular-pillar keratosis-like lesions have been noted as prominent features of folliculotropic MF (Kempf, et al., 2023).

**Figure 8** - Folliculotropic Mycosis Fungoides. Hair follicle hyperplasia with large mucin deposits (follicular mucinosis) appears, accompanied by lymphocyte infiltrates.



Sources: WHO Classification of Tumors: Haematolymphoid Tumors (5<sup>th</sup> Edition).

In folliculotropic MF, atypical lymphocytes infiltrate the follicular epithelium, usually with little interfollicular epidermis. As identified on clinical examination, cystic dilatation or cornification obstruction can be confirmed microscopically. Follicular mucinosis and hyperplastic eccrine structures occur frequently with mucinous degeneration of the follicular epithelium occurring in 60% of cases ranging from dilated intercellular spaces to extensive mucin pools. Staging of the infiltrate allows for faster and more targeted prognostic and therapeutic measures. In particular, folliculotropic MF must be differentiated into mild (early stage) or exuberant (advanced stage). Advanced stage infiltrates consist of dense dermal interfollicular involvement. The intermediate stage Folliculotropic MF plaque group can be grouped into better or worse outcome groups based on large cell size, higher Ki67, inter-follicular epidermotropism, and absence of follicular mucinosis. Immunophenotypically, folliculotropic MF is CD4+ (Lazar, et al., 2023).

The most important differential diagnostic problem in MF is its distinction in early stages from benign, reactive inflammatory processes, particularly forms of spongiotic dermatitis, a prime example being allergic contact dermatitis. These inflammatory conditions can show rather dense dermal infiltrates and exocytosis of lymphocytes, including collections of cells within the epidermis that can mimic Pautrier microabscesses, although they are usually present within the context of spongiosis—a feature that is often (but not invariably) absent in MF. In addition, the Pautrier microabscess simulants in spongiotic dermatitis often assume a vase-like shape. Despite these problems, it is generally recognized that traditional light microscopic diagnosis is the gold standard for the early diagnosis of MF. Therefore, numerous studies have been undertaken to establish morphological criteria for diagnosis (Patterson, et al., 2021). Some few summaries of the most important differential diagnoses is provided in table below.



**Table 1** - Clinical differential diagnosis of folliculotropic mycosis fungoides.

Clinical manifestation of FMF in the foreground	Clinical differential diagnosis	Typical clinical findings	Histological characteristics
“Patches”/Plaques/Papels	Classic MF, Patches and Plaques	Patches and plaques, predominantly on the trunk; in particular, in the gluteal region; no follicular accentuation	Epidermotropic infiltrate of atypical T lymphocytes; lining-up phenomenon; Pautrier’s microabscesses
	Psoriasis	Erythematous plaques with scaling; affecting the extensor aspects of the arms, belly button, auditory canal, scalp; nail changes; joints may be affected	Psoriasiform acanthosis, hypergranulosis, parakeratosis, neutrophilic abscesses
	Lichen planopilaris	Polygonal papules, Wickham’s striae; difficult to distinguish in case of predominant follicular involvement	Lichenoid interface dermatitis, wedge-shaped hypergranulosis, follicular involvement
Nodules/Tumors	Classic MF, tumorous nodules	Definitive differentiation requires clinicopathologic correlation	Dermal infiltrates of atypical T lymphocytes; frequently only mild epidermotropism
	Other lymphomas associated with nodule/tumor formation, for example anaplastic large-cell lymphoma (ALCL)	For example ALCL: in some cases solitary/few nodules without other follicular skin lesions; definitive differentiation requires clinicopathologic correlation	Variable, depending on lymphoma type. ALCL: cohesive clusters of anaplastic CD30+ lymphocytes
	Other tumors (for example Merkel cell carcinoma, basal cell carcinoma, and others)	Frequently on sun-exposed skin, no follicular accentuation	Variable, depending on tumor type. Solid tumor cell aggregates. Caution: small-cell Merkel cell carcinoma: immunohistochemistry is useful
Cysts/comedones/ acneiform	Acne vulgaris, acne conglobate, and others.	Typically on the face, chest, and mid-back; comedones, papules, pustules, and cysts. Biopsy should be taken in case of atypical courses and recalcitrant disease	Frequently mixed cellular infiltrate; no atypia of lymphocytes; ruptured follicles, cyst formation. Differentiation may be difficult in some cases. Immunohistochemistry and molecular diagnostic tests may be useful
	Nevus comedonicus	Circumscribed area with comedones; present since birth	Comedo-like dilatation of follicular infundibula without significant inflammatory infiltrate
	Lupus comedonicus	Usually circumscribed lesion, especially on the face	Comedo-like dilatation of follicular infundibula; vacuolar, frequently lichenoid interface dermatitis; interstitial mucin deposits

Sources: Mitteldorf, et al., (2018).

Clinical stage, as assessed based on the TNMB classification, is a key prognostic factor for disease progression and survival, with tumor stage of the disease, as well as involvement of blood, lymph nodes, and visceral organs correlating with a poor prognosis. Patients with limited disease generally have an excellent prognosis, with survival similar to that of the general population. Imaging is usually not recommended in early stage MF. In advanced disease, CT scan or PET/CT scan with/without contrast media may be indicated at the time of disease progression, before starting chemotherapy and to evaluate response or visceral progression after full treatment. Ultrasound scans may be helpful in the interpretation of enlarged lymph nodes. The presence of circulating clones without phenotypic evidence of blood involvement, older age (>60) at diagnosis, elevated lactose dehydrogenase, and folliculotropism were correlated with poorer survival.

## 5. Conclusion

We reported a case of Folliculotropic Mycosis Fungoides. It can be concluded that the case reported in this case report is a unique case to report because although this case occurs in 50% of lymphoma cases, Mycosis Fungoides cases are generally

rare. The Folliculotropic Mycosis Fungoides variant is the most frequent case among all Mycosis Fungoides variants other than Classic Mycosis Fungoides with a worse prognosis compared to other variants.

It is important to carry out a biopsy examination to assess whether there are MF lesions, especially folliculotropic MF, in the specimen examined, especially if the clinical manifestations in this case vary greatly depending on the stage of the lesion. Special examinations such as immunophenotype and immunohistochemistry are also very influential in establishing the diagnosis of Folliculotropic MF and Classic MF. The earlier (early stage) the diagnosis can be made is very useful for improving the patient's prognostic factors. For this reason, it is very important to understand this case, both Folliculotropic MF and Classic MF, especially in Pathological aspects.

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