DOI: 10.1515/sjdv-2016-0019

Folliculotropic Mycosis Fungoides - A Case Report

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UDC 616.59-006.44-07/-08

Abstract

Mycosis fungoides (MF) belongs to a group of primary cutaneous T-cell lymphomas, with characteristic small- to medium-sized neoplastic T-lymphocytes with hyperchromatic and cerebriform nuclei. Folliculotropic mycosis fungoides (FMF) represents a variant of mycosis fungoides, which is histologically characterized by folliculotropic T-cell infiltrates, with or without mucinous degeneration of the hair follicles. Clinical features of FMF are characterized by appearance of grouped follicular papules, acneiform lesions, indurated plaques, sometimes tumors, which usually involve the head and neck region. The diagnosis is based on clinical presentation, histopathological and immunohistochemical (IHC) findings of skin biopsy specimens. The treatment of FMF, and generally MF, should be stage-adapted. Case report: We present a case of a 33-year-old male with an eight-month history of erythematous papules on his forehead accompanied by intense pruritus. Histopathological findings showed folliculotropic and perivascular lymphocytic infiltrates. An increased CD4/CD8 ratio of interfollicular lymphocytes with accumulation of Langerhans cell confirmed the diagnosis of FMF. Our patient was diagnosed with an early stage - IA, and P-UVA phototherapy was recommended due to ineffectiveness of prescribed topical corticosteroids that had short-term effects. Conclusion: Folliculotropic mycosis fungoides represents a diagnostic challenge due to the great diversity of clinical manifestations. We presented a rare case of folliculotropic mycosis fungoides in a young adult, who presented with erythematous papules, accompanied by intense pruritus on the forehead, which lasted for several months. Histopathological and IHC analysis confirmed the diagnosis of folliculotropic mycosis fungoides stage IA. Due to an inadequate response to a topical corticosteroid, P-UVA phototherapy was administered, as well as close follow-up, essential for timely treatment of this frequently therapy-resistant disease.

Key words

Mycosis Fungoides; Case Reports; Skin Neoplasms; Hair Follicle; Diagnosis; Signs and Symptoms; PUVA Therapy; Phototherapy

Mycosis fungoides (MF) belongs to a group of primary cutaneous T-cell lymphomas, with characteristic small- or medium-sized neoplastic T-lymphocytes with hyperchromic and cerebriform nuclei. This primary cutaneous lymphoma is one of the indolent types, and the disease progression may take years, even decades. The clinical course of MF goes through different stages: patch, plaque and tumor stage, erythroderma, lymph node involvement, and bone marrow and visceral organ involvement in most advanced stages. Also, a number of different clinical variants of MF have been described: bullous MF, palmoplantar, erythrodermic, folliculotropic, granulomatous, hyper- and hypo-pigmented, MF similar to ichthyosis, interstitial, invisible, purpura pigmentosa-like, pustular, syringotropic, solitary, verrucous (hypertrophic) and zosteriform MF (1 - 5), making it a "great imitator"(5).

Folliculotropic MF (FMF) represents a special variant of MF, which is histologically characterized by folliculotropic T-cell infiltrates, with or without mucinous degeneration of the hair follicles. It occurs mainly in adults, rarely in children and adolescents. Gender distribution shows male to female ratio of 3:1 (6).

Clinical features of FMF are characterized by grouped follicular papules, acneiform lesions, indurated plaques, sometimes tumors, which usually involve the head and neck region. It is often associated with hair loss within the lesions, intense pruritus, and secondary bacterial infections (7). FMF represents a very rare, sometimes aggressive variant of MF, accounting for <10% of cases of MF (8). The diagnosis is based on clinical presentation, histopathological and immunohistochemical (IHC) findings of skin biopsy specimens.

The treatment of FMF, and generally MF, should be stage-adapted, aiming to alleviate the symptoms. Thus, according to the European guidelines for the treatment of early stages of the disease, utilization of topical corticosteroids, phototherapy (P-UVA, Re-P-UVA), electron beam therapy, and topical mechlorethamine is recommended, while radiotherapy is the treatment of choice for tumors. In treatment resistant cases, as well as in advanced stages of the disease, systemic therapy is used, in particular interferon-alpha. In advanced cases, with involvement of bone marrow and visceral organs, chemotherapy or biological therapy may be appropriate (9).

Case report

A 33-year-old male presented with an eight-month history of erythematous papules on the forehead accompanied by intense pruritus. The patient was treated with topical corticosteroid therapy, but without favourable results. On admission, several small, discrete, pruritic erythematous papules, without scales, up to 2.5 mm in diameter, were seen over his forehead (Figure 1).

Figure 1.
Histopathological examination revealed superficial and deep perivascular lymphocytic infiltrates, with a heavy infiltration of hair follicles, without involvement of the intervening epidermis (Figure 2A). The alcian blue staining did not demonstrate an increase of mucus within the follicles, but colloidal iron staining showed some deposits of mucus in the dermis and only minimal deposits within the hair follicles, which clinically matched the so-called acneiform follicular mucinosis. IHC examination showed diffuse CD3 reaction, with predominance of CD4+ over rare CD8 positive cells, approaching 10:1 ratio (Figures 2B, C). The CD7 immunostaining was reduced (approximately 20% of cells), and there were numerous CD1a positive intra- and perifollicular Langerhans cells (Figure 2D). T-cell receptor-γ gene rearrangement analysis of skin biopsy specimens showed a monoclonal T-cell population. Histopathological, IHC and T-cell receptor-γ gene rearrangement analysis of skin biopsy specimens were consistent with the diagnosis of FMF.

Figure 2.
Complete blood count parameters, blood biochemistry, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, IgG, IgA, IgM, IgE were within normal ranges. The cytology of peripheral blood smears was within normal limits. T-cell receptor-γ gene rearrangement analysis of peripheral blood showed a polyclonal T-cell population. Patch testing with standard European battery, after 48 and 72 hours, revealed sensitivity to cobalt chloride and nickel sulphate. Ultrasonography of the neck, axilla and inguinal regions, showed no pathological findings. Staging of the disease revealed no significant lymphonodopathy, polyclonal population of T-lymphocytes was found in peripheral blood, and thus the patient was diagnosed with stage IA (tumor, node and metastasis (TNM) staging). Because of inadequate response to topical corticosteroid therapy, P-UVA phototherapy and regular follow-up were indicated.

Discussion

Mycosis fungoides is the most common primary cutaneous T-cell lymphoma and it accounts for 50% of all cases (10). FMF is very rare and often an aggressive clinical variant of MF which includes <10% of all cases of MF. The disease is more common in the adult population, with an average age of 60 years. In reviewing the literature, several case series were published and the largest included 203 patients (11), as well as 27 individual cases. It is extremely rare in children and adolescents. There are only few pediatric cases described so far. Also, a report of four Indian cases revealed a mean age of 17.5 years with less aggressive disease course and better treatment outcomes (12). Males are predominantly affected, as in our case, with male to female ratio of 3:1 (6).

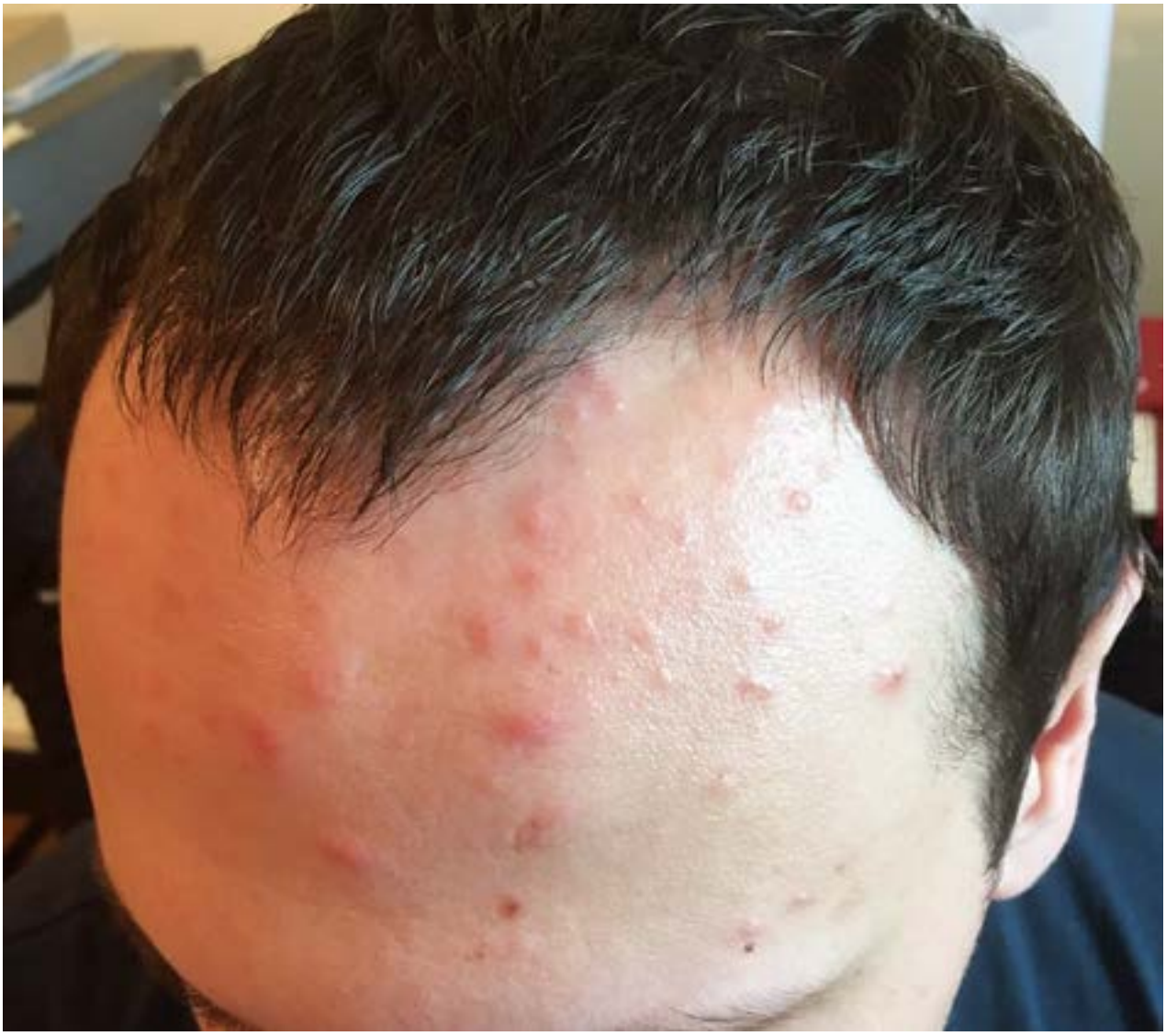

Figure 1. Small, discrete, erythematous papules, up to 2.5 mm without scales

FMF manifests with erythematous, grouped papules or indurated plaques, acneiform lesions, cysts, rarely tumors and patches of scarring alopecia. Lesions are commonly associated with severe pruritus (13, 7). Unlike the common clinical findings of MF, where patches and plaques affect the sun-protected skin, in FMF, papules and plaques occur preferentially on the head and neck region (1).

The differential diagnosis of FMF plaque lesions includes sarcoidosis, leishmaniasis, lymphomatoid contact dermatitis or deep fungal infection. For acneiform lesions, acne and milia are considered as differentials (14). Previously, this variant of MF was called follicular mucinosis or alopecia mucinosa. Early lesions of alopecia mucinosa show mucus deposits in the outer root sheath and replacement of the entire pilosebaceous unit by pools of mucus in advanced lesions. In our case, a colloidal iron staining showed some deposits of mucus in the dermis and only minimal deposits within the hair follicles, which clinically matched the so-called acneiform follicular mucinosis. The association of this form with classic mycosis fungoides is described, but rare and similar cases (if clear-cut signs of mycosis fungoides at other body sites are not present) are classified as "idiopathic" follicular mucinosis. According to Cerroni and van

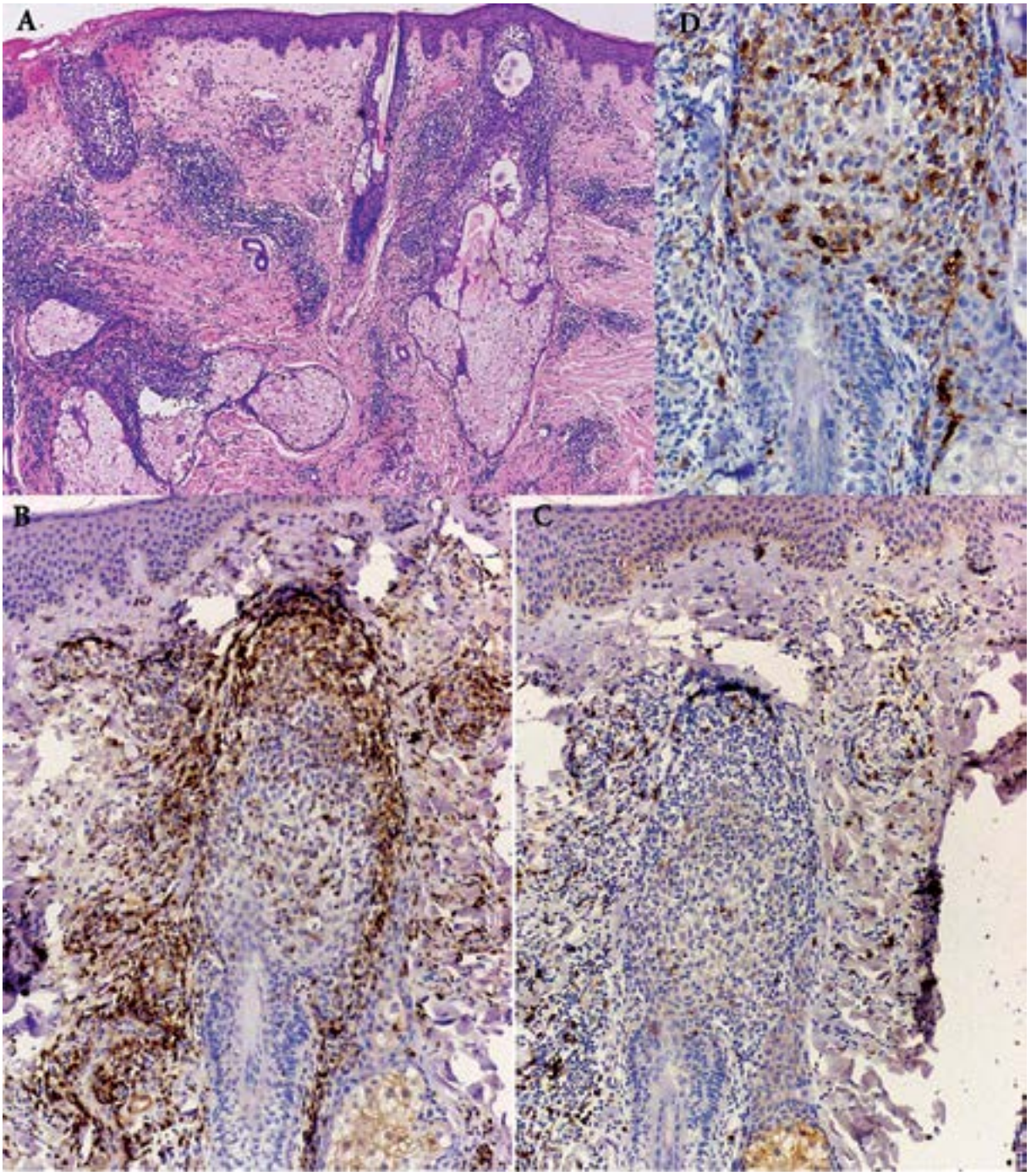

Figure 2. Microscopic features of folluculotropic mycosis fungoides with intra- and perifollicular lymphocytic infiltration that spares the epidermis (A); immunohistochemical stain showed CD4 positive cells (B) that highly outnumbered CD8 lymphocytes (C), and numerous CD1a positive Langerhans cell (D) (A - hematoxylin&eosin, magnification 40 x; B, C - CD4 and C immunostain, 100 x; D - CD1a immunostain, 200 x).

Doorn, idiopathic follicular mucinosis may represent a FMF with indolent course and excellent prognosis (15, 16). In this context, the skin should be checked for potential extrafacial lesions. In our case, the eight-month history of erythematous papules, accompanied by intense pruritus, localized only on the head and neck, supported the clinical findings of FMF. The diagnosis of FMF was confirmed with a correlation of clinical findings, histopathological, IHC and clonality analysis of the skin biopsy.

Histopathology and IHC findings are essential for diagnosis, but should be always correlated with clinical manifestations. Histopathology of FMF is characterized by atypical lymphocytic infiltration of hair follicles with or without follicular mucinosis and epidermotropism. Presence of eosinophils and granulomata may be seen, and necessitates exclusion of infectious etiology (12). IHC shows predominance of CD4 lymphocytes. Increased CD1a+ Langerhans cell density has also been reported (13). In our case, histopathological findings showed folliculotropic and perivascular infiltrates of lymphocytes. Increased CD4/CD8 ratio of interfollicular lymphocytes with accumulation of Langerhans cell is characteristic for folliculotropic variant of mycosis fungoides, and has been recently described as a frequent finding in folliculotropic MF (17, 18), but its diagnostic and prognostic importance has not been fully elucidated.

Lymphomatoid contact dermatitis may be included in the differential diagnosis of cutaneous T-cell lymphomas (19). The accurate diagnosis depends on consideration of the clinical history, histopathological, IHC and molecular findings (20). The distribution of lymphomatoid contact dermatitis on the pelvis, upper legs and buttocks is considered to be classic for the 'bathing trunk' distribution, most common in early mycosis fungoides, but in FMF papules and plaques occur preferentially on the head and neck region (1). Histopathological findings of T-cell lymphomatoid contact dermatitis resemble MF and show a superficial band-like T-cell infiltrate with epidermotropism (21), but epidermal spongiosis or spongiotic microvesiculation may be present, and this helps to differentiate it from MF (21, 22), where there may be spongiosis but not microvesiculation. IHC analysis of lymphomatoid contact dermatitis may show a predominance of CD4+ or CD8+ cells, but such findings alone are clearly not reliable (23, 24, 25). T-cell receptor-γ gene rearrangement analysis of skin biopsy specimens in lymphomatoid contact dermatitis show a polyclonal T-cell population, whereas lymphomas, as in our case, were mostly monoclonal (22). In our patient, patch testing with standard European battery, after 48 and 72 hours, revealed sensitivity to cobalt chloride and nickel sulphate. Due to the fact that these are the most common allergens in population, and not associated with clinical findings of typical distribution, nor with professional exposure to these allergens, we consider this finding as clinically irrelevant.

The treatment of FMF should be stage-adapted: based on the type and extent of skin lesions, lymph nodes and visceral organs involvement. The presence of malignant cells in the peripheral blood, is associated with the prevalence of skin lesions and lymph node involvement. Our patient was diagnosed with early stage IA, and P-UVA phototherapy was recommended, due to unavailability of topical bexarotene gel, and ineffectiveness of prescribed topical corticosteroids that had short-term effects. Regular follow-up was also advised.

There is no specific treatment for primary and idiopathic follicular mucinosis. A "wait and see" approach is usually recommended, and most cases resolve within 2 to 24 months. Current treatment options include: topical, intralesional and systemic corticosteroids, dapsone, antimalarials (hydroxychloroquine), isotretinoin, indomethacin, interferon, minocycline, and photodynamic therapy (26).

Treatment modalities for early FMF include topical corticosteroids, P-UVA phototherapy, electron beam therapy, topical mechloretamine and local radiotherapy for tumors. Treatment options for FMF include P-UVA therapy, bexarotene gel and radiotherapy (local or total skin electron beam), and these were the treatment of choice in the majority of published cases, in early stage of the disease (6, 11, 14, 27). Also, in individual cases, narrow band UVB (28), topical cytarabine combined with topical carmustine (29), monotherapy with topical imiquimod 5% cream (30), were also successfully employed. In case of treatment resistance, interpheron alpha (monotherapy, or combination with retinoids), P-UVA phototherapy in combination with retinoids or interpheron alpha,

bexaroten and low-dose methotrexate should be used. In advanced stages, chemotherapy (CHOP), biological therapy (denileukin diftitox, and alemtuzumab), irradiation, and allogeneic bone marrow transplant are used (9, 31, 32).

FMF is considered to have a worse prognosis and more aggressive disease course than conventional MF, but "idiopathic" follicular mucinosis in majority of patients may represent a FMF with indolent course, and excellent prognosis. Regardless of this, patients with so-called idiopathic FM should be carefully followed-up for a long time (15).

Due to its polymorphic clinical presentation, FMF is diagnosed with delay and at a later stage than classic MF. Early skin biopsy can be recommended in patients with therapy-resistant pruritic skin lesions. Early stage is associated with a 10-year survival of 82% of patients, and 15-year survival of 42%. Late stage has similar prognosis as classical MF (91% at both 5 and 10 years). Due to the paucity of FMF, these considerations are mainly based on case reports, and a few case series with limited follow-up periods (13).

Conclusion

Folliculotropic mycosis fungoides represents a diagnostic challenge, due to the great diversity of its clinical manifestations. We presented a rare case of folliculotropic mycosis fungoides variant in a young adult, in whom the erythematous papules, accompanied with intense pruritus on the skin of the forehead, lasted for several months. Histopathological and immunohistochemical analysis confirmed the diagnosis of folliculotropic mycosis fungoides, stage IA. Due to inadequate response to topical corticosteroids, P-UVA phototherapy, and close follow-up were employed, which is essential for timely treatment of this, frequently, treatment-resistant disease.

Abbreviations

MF - mycosis fungoides
FMF - folliculotropic mycosis fungoides
IHC - immunohistochemical
P-UVA - psoralen and ultraviolet light A
Re-P-UVA - retinoid, psoralen, and ultraviolet light A
UVB - ultraviolet light B

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Folikulotropni *mycosis fungoides* – prikaz slučaja

Sažetak

Mycosis fungoides (MF) pripada grupi primarnih kutanih T-ćelijskih limfoma malih ili srednjih neoplastičnih T-limfocita sa karakterističnim hiperhromnim, cerebriformnim nukleusima. Folikulotropni tip MF (FMF) predstavlja veoma retku, često agresivnu varijantu MF, koja se patohistološki odlikuje prisustvom folikulotropnog T-ćelijskog infiltrata, sa mucinoznom degeneracijom folikula dlake ili bez nje. Kliničkom slikom dominiraju grupisane folikularne papule, akneiformne lezije, indurirani plakovi, ponekad tumori, koji su uglavnom lokalizovani u predelu glave i vrata i često su praćeni intenzivnim pruritusom. Dijagnoza se postavlja na osnovu kliničke slike, patohistološkog i imunohistohemijskog nalaza uzorka izmenjene kože. Terapija FMF, kao i uopšteno MF, zavisi od stadijuma bolesti. Prikazujemo pacijenta starosti 33 godine sa osmomesečnom evolucijom promena u vidu eritematoznih papula na koži čela koje su bile praćene intenzivnim pruritusom. Histopatološki nalaz pokazao je folikulotropni i perivaskularni infiltrat limfocita, a imunohistohemijski povećan odnos CD4 : CD8 intrafolikularnih limfocita sa akumulacijom Langerhansovih ćelija potvrdio je dijagnozu folikulotropne varijante MF. S obzirom na to da kod pacijenta nisu uočeni morfološki izmenjeni limfni nodusi i da je u uzorku periferne krvi ispitivanjem rearanžmana gena za T-ćelijski receptor detektovano prisustvo poliklonske populacije T-limfocita, promene kod ovog pacijenta pripadaju stadijumu IA (TNM klasifikacija). Zbog neadekvatnog odgovora na kratkotrajnu topijsku terapiju kortikosteroidima i nedostupne lokalne terapije beksaroten gelom, predložena je P-UVA fototerapija.

Zaključak. Folikulotropni tip MF predstavlja dijagnostički izazov, zbog velike raznolikosti u svojim kliničkim manifestacijama. U radu je prikazan veoma redak slučaj FMF kod mlađe odrasle osobe, kod koje su eritematozne papule na koži čela, praćene intenzivnim pruritusom, trajale nekoliko meseci unazad. Histopatološka i imunohistohemijska analiza potvrdili su dijagnozu FMF u stadijumu IA. Zbog neadekvatnog odgovora

na topijsku kortikosteroidnu terapiju, indikovana je P-UVA fototerapija i redovno praćenje pacijenta, što je od ključnog značaja za blagovremeni tretman ove, često na terapiju rezistentne bolesti.

Ključne reči

Mycosis fungoides; Prikazi slučajeva; Kožne neoplazme; Folikula dlake; Dijagnoza; Znaci i simptomi; PUVA terapija; Fototerapija