Folliculotropic mycosis fungoides

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Abstract

Folliculotropic mycosis fungoides (FMF) is a variant of mycosis fungoides (MF) noted in the World Health Organization – European Organization of Research and Treatment of Cancer (WHO/EORTC) update of 2018. FMF is characterized as a subtype with a worse prognosis than classic MF.

The situation changed recently when authorities proposed dividing FMF into two prognostically different subtypes: indolent and aggressive. Indolent FMF allows 92% of patients to survive five years, and 72% 10 years. But only 55% and 28% of patients with aggressive FMF can survive respectively five and 10 years. FMF with internal organ involvement on the day of diagnosis shortens lives drastically (23% survive five years, only 2% survive 10 years).

There are many clinical subtypes (with plaques with follicular accentuation, alopecia, comedones, erythematous follicular papules, acneiform lesions mimicking rosacea, milia, ‘spikes’, and facial involvement known as leonine face), as well as histopathological variants (with pattern with intact hair follicles, folliculotropism with or without mucinosis, basaloid folliculolymphoid hyperplasia with folliculotropism, granulomatous dermatitis associated with folliculotropism, eosinophilic folliculitis, follicular cysts with folliculotropism) of FMF. This all makes diagnosis even more difficult. Combined topical and systemic treatment can be useful, with topical corticosteroids, phototherapy, radiotherapy, bexarotene, interferon, as well as with methotrexate and brentuximab vedotin. If the disease does not respond to these therapies, allogeneic hematopoietic stem cell transplantation (allo-HSCT) should be considered. Chemotherapy (gemcitabine, liposomal doxorubicin, polychemotherapy) is often associated with a merely temporary response, and that is why it should be employed only in non-responsive cases and/or as a bridge to allo-HSCT.

Key words: folliculotropic mycosis fungoides, variants, differential diagnosis, treatment

Introduction

Folliculotropic or pilotropic mycosis fungoides (FMF), a variant of MF, is characterized by a broad spectrum of clinical symptoms and histological pictures. It was previously believed that FMF is associated with an unfavorable prognosis [1, 2]. However, data from Hodak et al. [3] and van Santen et al. [4] has revealed that FMF can be divided into two prognostically different subtypes [3, 4]. Giovannini [5], and Mitteldorf et al. [6] described alopecia in a 13-year-old girl patient with MF. This was suggested later as the first case of FMF. Pinkus described deposits of mucin in hair follicles as alopecia mucinosa in 1957 [7]. Jabłońska named that condition follicular mucinosis in 1959 [8]. Follicular mucinosis was divided into two entities: one without symptoms and without association with lymphoma was named idiopathic follicular mucinosis (iFM); the second associated with cutaneous T-cell lymphoma as MF, lymphomatoid papulosis (LyP), Sézary syndrome (SS) or adult T-cell leukemia/lymphoma (ATLL). Willemze et al. [1] established FMF as a distinct variant of MF in 2005 in the WHO/EORTC classification. Male predominance is observed in FMF...
(M:F ratio 2–5:1) with mean age at onset 46–59 years [4, 9–13], although it can occur in childhood [14, 15].

**Clinical symptoms**

The head and neck are commonly involved in FMF, but more than 70% of patients display lesions on the trunk and extremities. Unilesional FMF is rare, and most patients present multiple lesions. Patches, plaques and tumors typical for classic MF are commonly associated with FMF, but follicular accentuation is observed (Figure 1). These plaques are frequently associated with alopecia (Figure 2) typical for 81% of patients, comedones (Figure 3), and erythematous follicular papules which can cause difficulties in differentiation from follicular lymphomatoid papulosis (Figure 4). Acneiform lesions mimicking rosacea can...
be a symptom of FMF in one in three patients (Figure 5), as well as milia on the face or trunk [4]. The eyebrows are involved very often in the early stages of the disease. Follicular hyperkeratosis can appear, known as ‘spikes’. Severe face involvement can lead to a leonine face. Less than 10% of patients present erythroderma. Pruritus is common, and severe in adults, but mild in children [4, 9, 16]. Yildizhan et al. [17] found a correlation between the presence of pruritus and disease progression in contrast to van Santen, who reported no effect of pruritus on survival or disease progression. Keratosis pilaris-like lesions are met quite often in children (although MF and FMF are extremely rare in children), mostly with a mild course of the disease [14]. It is worth mentioning that MF and FMF can appear as posttransplant lymphoproliferative disorder, with skin symptoms mostly on the trunk and a favorable prognosis [18].

Differential diagnosis

Depending on type of skin lesion, MF must be differentiated from many dermatoses [6]:

I. Patches and plaques:
   a) with classic MF, in which we do not observe follicular accentuation; histopathological characteristics reveal in MF epidermotropic infiltrate of atypical T-lymphocytes with Pautrier’s microabscesses:
       • it is important to take skin biopsy from area with hair follicles if possible so as to not misdiag-
         nose FMF;
   b) psoriasis — scaling is typical; localization: extensor of arms, belly button, auditory canal, nail changes (pitting, oil drop, onycholyisis, leukonychia); joints can be involved; histopathologically: acanthosis, hypergranulosis, parakeratosis, neutrophilic abscesses;
   c) lichen planopilaris — Wickham striae visible on polygonal papules; histopathologically — lichenoid inter-
      face dermatitis, wedge-shaped hypergranulosis, follicular involvement possible.

II. Nodules and tumors:
   a) classic MF — clinicopathological correlation necessary;
   b) other lymphomas — clinicopathological correlation e.g. anaplastic large cell lymphoma (ALCL) — no patches and plaques typical for MF; cohesive clusters of anaplastic CD30+ lymphocytes (CD30+ on 75% of neoplastic lymphocytes);
   c) other neoplastic tumors (e.g. Merkel cell carcinoma, basal cell carcinoma) — mostly on sun-exposed areas, no follicular accentuation, pathologist resolves problem.

III. Comedones, acneiform lesions, cysts:
   a) acne — typically on face and trunk, comedones, pustules, papules and cysts, biopsy unnecessary in most cases (if taken - mixed cellular infiltrate, no atypia of lymphocytes);
   b) nevus comedonicus — present since birth/before age of 12 months, circumscribed area with comedones; no inflammation around comedo-like dilatation of follicular infundibula in histopathological examination;
   c) lupus comedonicus — mostly on face — circumscribed lesion; comedo-like dilatation of follicular infundibula with lichenoid interface dermatitis, sometimes interstitial mucin deposits.

IV. ‘Spikes’:
   a) lichen spinulosus — follicular papules with spiny hyperkeratosis, histopathologically — without inflam-
      matory infiltrate;
   b) lichen planopilaris — as above, mucin deposits possible in histopathological examination, V-shaped fibrosis;
   c) pityriasis rubra pilaris — red-orange follicular papules initially, extensive erythema with islands of sparing skin, palmar and plantar hyperkeratosis; erythroderma is possible; histopathologically — uniform epidermal acanthosis, chessboard-like alter-
      nation between ortho- and hyperkeratosis;
   d) atopic dermatitis — history, other atopic disorders (asthma, conjunctivitis, hay fever) but clinicopath-
      ologic correlation necessary in some cases: broad-
      based acanthosis, spongiosis, focal parakeratosis,
superficial lymphohistiocytic infiltrate with eosinophils;

e) drug eruption — history; relation to drug use, neutrophils and eosinophils often found in histopathology.

V. Leonine face:

a) actinic reticuloid — with chronic eczematous skin lesions, particularly on face and neck (sun-exposed area), leonine face in severe cases is possible; histopathologically: exematous lesions, sometimes mimicking lymphoma — difficult to distinguish [clinical-copathological correlation — exacerbation after sun exposure, T-cell receptor (TCR) rearrangement molecular tests reveals polyclonality];

b) SS — hematological diagnostic criteria plus clinical findings (erythroderma and lymphadenopathy); skin histopathological examination rarely diagnostic (T-lymphocytic infiltrate in upper dermis with moderate atypia, mild pleomorphism), lymph node excisional biopsy necessary;

c) leukemia — hematologic diagnostic criteria.

VI. Alopecia

a) Lichen planopilaris — scaly perifollicular collar; histopathological examination as above;

b) chronic discoid lupus — cicatrical alopecia sometimes with scaling and obliteration of follicular ostia; histopathologically: epidermal atrophy with vacuolar interface dermatitis, apoptotic keratinocytes, involvement of follicular structures, interstitial mucin deposits.

Mitteldorf et al. [6] proposed five histomorphological patterns of FMF (modified after Gerami and Guitart) [19]:

- pattern with intact hair follicles, folliculotropism with or without mucinosis;
- basaloid folliculolymphoid hyperplasia with folliculotropism;
- granulomatous dermatitis associated with folliculotropism;
- eosinophilic folliculitis;
- follicular cysts with folliculotropism.

Histopathological examinations with correlation to clinical symptoms is necessary also in differentiating FMF from pseudolymphomatous folliculitis (S-100 positive and CD1a-positive cells as well as B cells are admixed in folliculotropically T-cells infiltrate) and follicular lymphomatoid papulosis (papules are waning and waxing spontaneously, but FMF and LyP can overlap with identical TCR rearrangement pattern) [6]. There is also discussion concerning the distinctiveness of iFM from FMF with mucinosis, because monoclonal rearrangement can be found in more than 50% of cases of iFM (compared to FMF-associated mucinosis) [20, 21].

The multitude of dermatoses from which to differentiate FMF, as well as several histopathological patterns, illustrate why the diagnosis is often made late: both the dermatologist and the pathologist can encounter difficulties. The diagnosis of FMF is established usually 18–48 months after the onset of skin symptoms [10, 12]. Immunohistochemistry can be helpful, but not in all cases thanks to antigen loss of CD2, CD3, CD4 and CD4:CD8 ratio shift mostly 6–10:1.

But we must underscore that CD4:CD8 shift is related not only to T cell but also Langerhans cells in some cases. CD30 can be expressed, and this is sometimes related to large cell transformation [6]. Mucin deposits can be found in 75% of skin biopsies in FMF [4, 11, 12]. Pericrinc infiltrates are observed (this is called syringotropism) in 4–33% of cases [22].

Prognosis

Not all patients with FMF have as unfavorable a prognosis as was thought 20 years ago (5-year survival rate has been established as 66–80%) [1]. Hodak et al. [3], and van Santen et al. [4] have revealed that FMF can be divided into indolent and aggressive variants. Indolent (early) FMF allows 92% of patients to survive five years, and 72% 10 years. But only 55% and 28% of patients with aggressive (advanced) FMF survive respectively five and 10 years. FMF with internal organ involvement on the day of diagnosis shortens lives drastically (23% survive five years, only 2% 10 years). Skin symptoms distribution is different: 100% of indolent FMF affects the trunk and extremities, only 37% the head, as opposed to the aggressive variant, where the head is affected in 100%, but the trunk only in 20%, of cases. Pruritus is more often met in the aggressive variant (80% vs. 47% indolent). Syringotropism is more often met in the aggressive variant, as well as higher density of infiltrate, deeper infiltrate, higher eosinophilia and the discovery of more plasma cells in skin biopsy, which make a diagnosis even more difficult in the context of inflammatory dermatoses mimicking FMF [3, 4].

It is important to note that all patients with infiltrated plaques in the study by Hodak et al. were upstaged and considered to have tumor-stage disease [3]. Van Santen evaluated 40 FMF patients with plaques, dividing them into early-plaque and advanced-plaque, and reported disease progression in 50% over a median follow-up of 80 months [4]. Similar observations by Kalay et al. suggest that the increased density and depth of perifollicular infiltrates in advanced plaque FMF lesions is a marker for progression [17].

Both studies also suggested factors that might impact disease progression and death in FMF: clinical stage, large cell transformation (LCT), increased LDH level (in Kalay et al. [17]), age over 60 years, and the presence of extensive secondary bacterial infections at the time of first presentation (in Van Santen et al. [4]). Wieser et al. reported age over 65, leucocytosis and advanced stages to be associated with an increased risk of death in FMF [23].
Treatment

Combination therapy of topical and systemic treatment is useful. Topical corticosteroid, bexarotene gel (no refund in Poland), mechloretamine (no refund in Poland), imiquimod (not registered for cutaneous T-cell lymphoma (CTCL), no refund in Poland), and resiquimod (in clinical trials) are among the topical methods of treatment. Radiation therapy can be useful locally in unilesional FMF, and total skin electron beam therapy (TSEB) can be considered in widespread patches and plaques. Phototherapy alone can be inadequate, and especially UVB311 is not recommended. PUVA therapy can be ordered in monotherapy or combined with systemic treatment (bexarotene, IFN alpha). Bexarotene and IFN alpha can be ordered as single treatments, as well as methotrexate (MTX).

If the disease does not respond to those therapies, extracorporeal photopheresis (ECP) should be considered, as well as allo-hematopoietic stem cell transplantation (allo-HSCT). But no studies have shown that ECP is effective in FMF. Yildizhan et al. concluded that ECP is not an effective option in FMF [17]. Allo-HSCT is suggested to be performed before LCT, but in advanced stages there must be awareness that almost 50% of transplanted patients relapse within the first 12 months after transplantation. A lower risk of relapse is observed in patients with a lower tumor burden, so the question is to when to transplant, due to the risk of allo-HSCT, remains open [17–24]. Therapy with brentuximab vedotin in CD30+ MF is approved and is now refunded in Poland (program B.66) [6, 23–27]. Chemotherapy (gemcitabine, liposomal doxorubicin, polychemotherapy) is often associated with only a temporary response, which is why it should be employed only in non-responsive cases and/or as a bridge to allo-HSCT. Pralatrexate and alemtuzumab are not available in Poland for MF/FMF patients [6, 23–27].

To avoid chemotherapy, a combination of different methods should be considered. Del Guzzo et al. proposed a therapeutic regimen combining IFN gamma, isotretinoin in a low dose (available but not registered for CTCL and not refunded in Poland) and/or topical carmustine (not available, and not refunded in Poland) for refractory advanced stage FMF [28].

Of six patients with FMF at stage IB-IIB without blood involvement and one patient in stage IIIB for whom prior therapies had failed (topical steroids, nitrogen mustard as single treatment, UVB311, PUVA, IFN alpha, bexarotene, TSEB, romidepsin (not available in Poland), acitretin, and local radiotherapy), four experienced a complete response (CR) and two a nearly CR. Local electron beam radiation was added in three cases, imiquimod in three cases (and in one case both methods were applied, and that patient was treated also with tretinoin); one patient was additionally treated with imiquimod and with PUVA. Time to response was 2–23 months with different terms of CR. Treatment was stopped not at any particular time but because of arthralgia on IFN gamma in one case and prohibitive costs of IFN gamma in a second case. The authors mentioned that IFN gamma can be more effective than IFN alpha in FMF. Higher efficacy is suggested for 0.04% carmustine ointment than topical nitrogen mustard ointment. With regards to conventional concentrations of both compounds currently in use in the USA in CTCL (nitrogen mustard is registered in Europe, but not refunded in Poland), measurable metabolites of carmustine can be found in the blood and urine of CTCL patients compared to metabolites of nitrogen mustard ointment (no metabolites can be found), which suggests deeper penetration to follicles by carmustine ointment. An isotretinoin mechanism of action in FMF is only suspected: probably the possibility of induction of apoptosis of sebaceous gland within the follicular unit can lead to atrophy of the sebaceous gland, which can affect the chemotheraxix and recruitment of malignant T-cells into the follicle in FMF. Isotretinoin may synergize with Th1 cytokines to enhance CD8+ T-cells [28, 29].

Because we now understand the existence of indolent FMF, it is important to not overtreat those patients with aggressive methods of treatment: topical treatment and phototherapy can be a good therapeutic approach [6, 23–27].

Conclusions

FMF has many clinical and histopathological faces, which makes diagnosis difficult and delayed. But knowledge concerning the possible indolent course of some patients with FMF is useful in treatment decisions. All therapies recommended in classical MF find their place in FMF treatment, but not all of them seem good therapeutic options (e.g. ECP). Allo-HSCT seems to be an option in FMF; not for indolent FMF, but for aggressive FMF with a low tumor burden. New multimodality therapies could be useful in advanced FMF, provided there is awareness of off-label use, the agreement of ethics committees, and close cooperation between dermatologists, oncologists and hematologists.

Author’s contributions
MS-W: 100% from concept to realization.

Conflict of interest
None.

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Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.
References


