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REVIEW

Folliculotropic Mycosis Fungoides: Current Guidance and Experience from Clinical Practice

Gabriele Roccuzzo*, Luca Mastorino*, Giuseppe Gallo, Paolo Fava, Simone Ribero, Pietro Quaglino

Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, Italy

*These authors contributed equally to this work

Correspondence: Giuseppe Gallo, Department of Medical Sciences, Section of Dermatology, University of Turin, Via Cherasco 23, Torino, Turin, 10126, Italy, Tel +39 0116335843; +39 0116335034, Email giuseppegallomd@gmail.com

Introduction: Folliculotropic mycosis fungoides (FMF) is the most frequent variant of mycosis fungoides (MF), with clinical features which differ from the classic form. As for therapeutic options, the latest guidelines on MF agree on a stage-driven strategy, in consideration of clinical presentation, symptom burden and patient's comorbidities.

Materials and Methods: A search on MEDLINE, PubMed, Scopus and Cochrane Library was conducted to gather the latest evidence on FMF clinical management. Manuscripts published in the last five years (January 2017–April 2022) were included. Our single-center experience was also described.

Results: A total of 15 articles were analyzed, with a total of 432 patients (disease stage from IA to IVA2). The most widely-used treatment was psoralen ultra-violet A (PUVA) in monotherapy or in association with other drugs. Oral retinoid-based therapy was also described as a therapeutic option alone or in combination. Other therapy reported were based on Brentuximab Vedotin, Mogamulizumab, Carmustine, topical steroids, tazarotene and excimer laser, interferon, nitrogen mustard, imiquimod, systemic chemotherapy, extracorporeal photopheresis and stem cell transplantation.

Discussion: FMF is characterized by specific clinical-pathologic features. Advanced forms assume characteristics more similar to classic MF (infiltrated plaques and nodules), whilst early stages can present in a wide range of clinical forms (acneiform lesions, follicular-like keratoses, erythematous patches). As for therapeutic options, in absence of specific guidelines, a high number of treatments are described in clinical practice, with variable results. Phototherapy in all its forms, especially as PUVA, appears to have the greatest initial therapeutic success. Retinoids, although widely used, appear to be poorly effective in monotherapy, particularly acitretin. Combination treatment with phototherapy seems to be advisable. Ionizing treatments, such as radiotherapy and TSEBT, appear effective, at least in the short term. Overall, an integrated approach is mandatory for the inconstant course of the disease and its multidisciplinary nature.

Keywords: mycosis fungoides, folliculotropic mycosis fungoides, cutaneous lymphoma, primary cutaneous T-cell lymphoma, therapy

Introduction

Primary cutaneous lymphomas (PCL) are a group of non-Hodgkin's lymphomas (NHL) characterized by monoclonal proliferation of malignant lymphocytes in the skin.[1] Among them, around three-fourths are represented by cutaneous T-cell lymphoma (CTCL), with mycosis fungoides (MF) as the most common form. According to the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms,[2] folliculotropic MF (FMF) is the most frequent variant of MF and is characterized by invasion of hair follicles by atypical T-cells, with clinical features which differ from classic MF[3] (Figure 1). Recently, two distinct histopathologic patterns, referred to as early FMF (patch/thin plaque type) and advanced FMF (thick plaque/tumor type), have been described.[4,5] The former is characterized by follicle-based patch/flat plaques, keratosis pilaris-like lesions, acneiform lesions and has good prognosis, like early-stage classic MF; the latter is distinguished by follicle-based infiltrated/thick plaques and/or tumors with worse prognosis. As for special populations, the FMF subtype has been recently found to be over-represented in solid organ transplant

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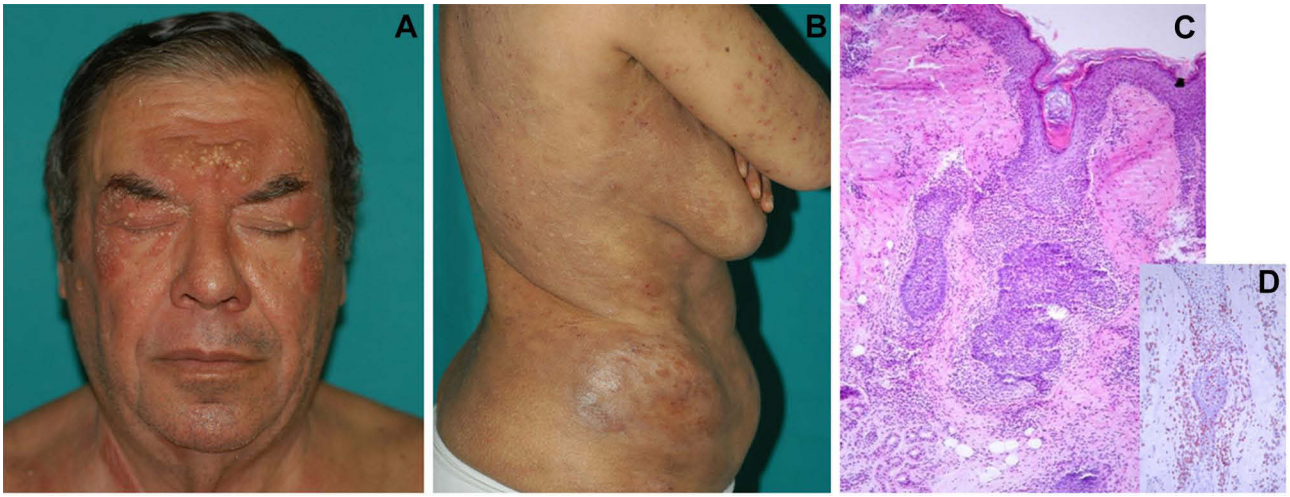

Figure 1 Clinical manifestations of folliculotropic mycosis fungoides with erythematous patches and plaques involving the head/neck area (**A**) and trunk area (**B**); histopathology perivascular and perifollicular infiltrate of lymphocyte with invasion of hair follicles by atypical T-cells [haematoxylin-eosin 20x] (**C**); immunohistochemistry: CD3-positive T lymphocytes (**D**).

recipients and in paediatric patients, compared with other CTCL variants.[6,7] Recent studies reported 10-year survival rates of 72% in skin-limited early stages, 28% in skin-limited advanced stages, and 2% in FMF with extracutaneous localizations at first presentation.[5] As for therapeutic options, the latest guidelines on MF agree on a stage-driven strategy, in consideration of clinical presentation, symptom burden and patient's comorbidities.[8,9] In early stages (ie, IA, IB, and IIA), skin-directed therapies (SDTs), such as topical corticosteroids, UVB, PUVA, localized radiation therapy and mechlorethamine, represent the first therapeutic option.[10,11] Those refractory to the first line may be considered for systemic therapies, such as retinoids, interferon alpha, total skin electron beam therapy (TSEB) or low-dose methotrexate, which conversely represent first-line treatments for stage IIB.[10,11] Stage III patients may benefit from extracorporeal phototherapy (ECP), alone or in combination with skin-directed and other systemic therapies, whilst refractory and stage IV patients have been traditionally treated with chemotherapy regimens (gemcitabine, pegylated liposomal doxorubicin, CHOP and CHOP-like polychemotherapy).[9,12] Lately, new monoclonal antibodies, such as anti-CD52 alemtuzumab, anti-CD30 brentuximab vedotin, anti-CCR4 mogamulizumab, and histone deacetylase inhibitors (though currently not approved in Europe), have represented promising options in the therapeutical armamentarium available to clinicians.[13–16] According to the multi-center prospective international study PROCLIPI, real-life treatment decisions in MF patients are often influenced by the presence of the folliculotropic variant, as early-stage FMF patients are more likely to receive systemic first-line therapies.[17] Moreover, recent findings have confirmed cutaneous stage to be the major predictive variable associated with disease-specific survival in FMF patients.[18] Since FMF has been found to have worse prognosis and to be less responsive to SDTs, compared with classic MF, optimal treatment still needs to be defined.[5] Herein we describe the experience of a tertiary referral center for CTCL and provide a synoptic overview of the articles concerning FMF treatment published in recent years.

Materials and Methods

A review of the literature was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search on MEDLINE, PubMed, Scopus and Cochrane Library was conducted using the combination of the following keywords and medical subject heading (MeSH) terms "folliculotropic mycosis fungoides", "therapy", "treatment", via the Boolean term "AND". Manuscripts published in the last five years, from January 2017 to April 2022, were included. Articles in a language other than English and/or not dealing with humans were excluded. No restriction related to article type was applied: case reports, letters to the editor, case series, and original articles were all included. Studies were selected if they provided information on therapy response in FMF. Two investigators extracted the data independently (GR, LM) and a third author (GG) was consulted in case of disagreements.

Articles were first screened by reading the title and the abstract. Articles considered relevant were then read in their totality and those meeting the inclusion and exclusion criteria were selected. For each study, the following details were considered: authors, nation, type of article, number of patients, staging of disease, therapy response as CR (complete response), PR (partial response), PD (progressive disease) and NR (non-response), if available. Two authors (GR, LM) independently assessed the risk of bias of each included study, in accordance with methods recommended by National Institutes of Health Quality Assessment Tool for Case Series Studies.[19] A third author (GG) was consulted in case of disagreements. Prisma flowchart is depicted in Figure 2.

Results

A total of 38 records was initially identified through a literature search, 19 of which were duplicates. After screening for eligibility and inclusion criteria, 15 articles were ultimately included[20–32] (Table 1). Most publications were case reports (n=7), followed by case series (n=4), original articles (n=3), and clinical image (n=1). All the studies included were rated as level 4 or 5 evidence for clinical research as detailed in the Oxford Centre for Evidence-Based Medicine 2011 guidelines.[33] A total of 432 patients with FMF were gathered. Treatment and type of response were evaluated within the limits of individual data exposure. Disease stages exhibited in the literature ranged from stage IA to IVA2; in 8 studies only earlier stages (maximum IIA) were evaluated, in 7 studies more advanced stages (from IIB) were also included. The most widely used treatment was Psoralen Ultra-Violet A (PUVA), reported in 8 studies, in 3 as monotherapy (1 case report with CR, 1 original article with CR 70% and PR 26%, 1 original article with ORR of 76%)[5,24,25] and in 5 studies in association with other drugs: in 2 case reports PUVA was combined with bexarotene, with CR in both cases and subsequent stem cell transplantation following progression in one of them,[27,28] whilst in another report it was associated with Interferon, with CR.[31] This treatment, among others, was mentioned in the Japanese case series by Kamijo et al, yet it was less commonly used compared to UVB therapy (ie, 10% vs 50% of the patients in the cohort).[29] In the Dutch experience, PUVA was administered as monotherapy to 31%, combined with retinoid or IFN-alpha to 9%, and with RT to 13% of the patients, respectively, with ORR of 76%.[5] In the American experience, both phototherapy (47 patients) and

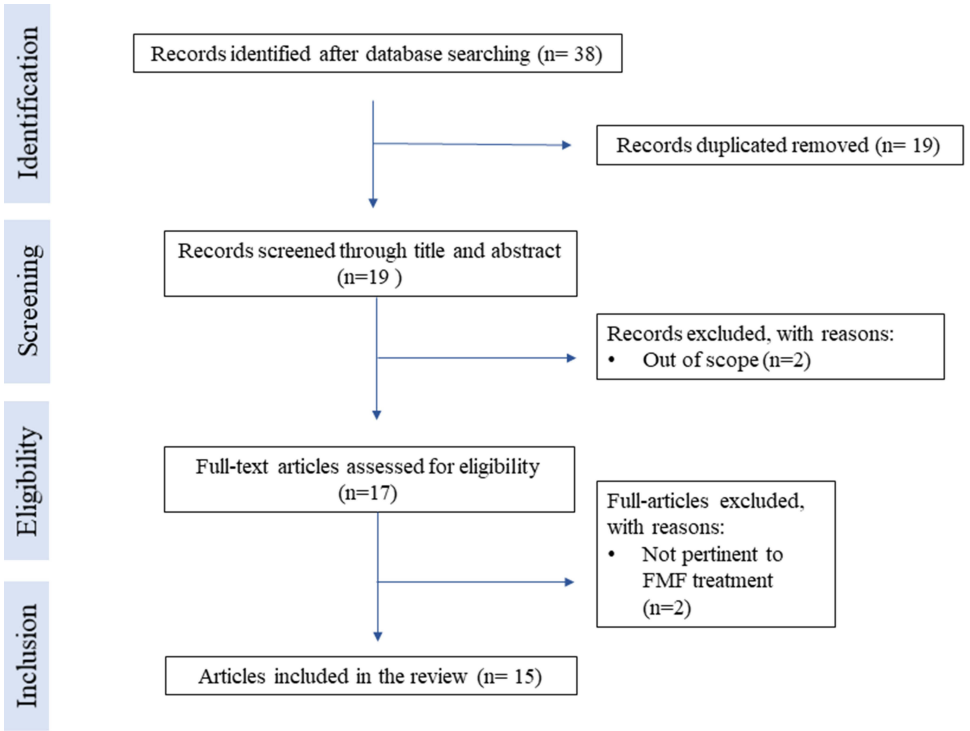

Figure 2 PRISMA flowchart.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.[43]

Table 1 Overview of Recently Published Articles on FMF Treatment

Authors	Year	Nation	N°	Article Type	Stage	Therapy						Response
Kinsella et al[20]	2017	UK	1	Case report	IVA2	Brentuximab vedotin						PR
Fujimura et al[21]	2017	Japan	1	Case report	IB	Mogamulizumab + RT						CR
Jiang et al[22]	2017	China	1	Case report	IIA	Methotrexate						PR
MacArthur et al[23]	2017	USA	13	Case series	IA-IIIB	Carmustine						CR 38% PR 62%
van Santen et al[5]	2017	Netherlands	203	Original article	84 early 102 advanced 17 extracutaneous		N 203	CR 25	PR 51	OR 76	SD 15	PD 8	SCR 12
						Topical steroids	22 (11%)	23	50	73	27	0	18
						UVB	11 (5%)	0	55	55	45	0	0
						PUVA	62 (31%)	23	53	76	18	6	13
						PUVA + retinoid or IFN-alpha	18 (9%)	0	65	65	24	12	0
						PUVA + local RT	27 (13%)	15	52	78	4	19	7
						Local RT	21 (10%)	62	38	100	0	0	29
						TSEB	20 (10%)	53	47	100	0	0	15
						Systemic CT	15 (7%)	13	33	47	20	27	7
						Miscellaneous	7 (3%)	29	43	71	14	14	14

Wieser et al[3]	2017	USA	114	Original article	IA (50) IB (23) IIA (7) IIB (23) IVA (8) IVB (3)	Topical corticosteroids (97) Oral Bexarotene (53) Topical Bexarotene (33) Nitrogen mustard (51) Phototherapy (47) Total skin electron beam radiation (31) Local radiation (27) Isotretinoin (32) Interferon (13) Methotrexate (15) Brentuximab vedotin (8) Imiquimod (7) Extracorporeal photopheresis (9) Stem cell transplantation (9)	Responses to RT	Local RT n (%)	TSEB n (%)	Both n (%)
							CR	10 (50)	8 (33.3)	3 (42.8)
							CR with relapse	3 (15)	2 (8.3)	0
							PR	5 (25)	5 (20.8)	0
							PD	1 (0.5)	3 (12.5)	3 (42.8)
							Palliative	0	2 (8.3)	0
							Palliative to prepare for stem cell transplant	1 (0.5)	4 (16.7)	1 (14.3)
							Total	20	24	7
Amitay-Laish et al[24]	2018	Israel	47	Original article	IA-IIA	PUVA	CR 70% PR 26%			
Boix-Vilanova et al[25]	2018	Spain	1	Case report	IA	PUVA	CR			
Wang et al[26]	2019	USA	1	Case report	IA	Clobetasol + Tezarotene + excimer laser (pediatric patient)	CR			
Caccavale et al[27]	2019	Italy	1	Case report	IA	Bexarotene + PUVA	CR			
Doerschner et al[28]	2019	Switzerland	1	Image	IIB>IVA	Bexarotene + PUVA > ASCT	Progression after CR. Followed by ASCT			
Kamijo et al[29]	2019	Japan	10	Case series	IA-IIB	nbUVB, oral retinoid, topical steroids, RT, Mogamulizumab, CHOP, Denileukin diftitox, uBMT, IFN gamma, PUVA	PR 60% PD 30%			
Kurihara et al[30]	2020	Japan	1	Case report	IA	Etoposide + prednisolone	CR			
Valencia Ocampo et al[31]	2020	Colombia	1	Case series	IA	PUVA+ IFN	CR			
Laggis et al[32]	2021	USA	36	Case series	IA-IIIB	Acitretine-based therapy (+/TSEBT, ± RT) (n=21)	CR 24% PR 48% NR 28%			

Abbreviations: PUVA, psoralen ultra-violet A; RT, radiation therapy; ASCT, autologous stem cell transplantation; IFN, interferon; nbUVB, narrow band ultra-violet B; CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; uBMT, unrelated bone marrow transplant; TSEB, total skin electron beam therapy; CT, chemotherapy; CR, complete response; PR, partial response; OR, overall response; SD, stable disease; PD, progressive disease; SCR, sustained complete remission.

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bexarotene (53 oral, 33 topical) represented a common line of therapy in the 114-patient presented cohort.[3] Oral retinoid-based therapy was also described as a therapeutic option in two other studies. Laggis et al reported, for acitretin in combination with RT or TSEB, response rates of 24% (CR), 48% (PR) and 28% (NR);[32] single-agent isotretinoin (32 patients) was a common therapy in Wieser et al's cohort,[3] though response rates were specifically described only for radiation therapy protocols (ie, CR rates of 50%, 33.3%, 42.8% for local RT, TSEB and both, respectively). Complete and partial response rates of 62% and 38% in the local RT group and 53% and 43% in the TSEB group, respectively, were reported in the Dutch experience.[5] Brentuximab vedotin was used in a case report with PR in an advanced stage IVA2 and in 8 patients in the American experience.[3,20] Mogamulizumab was used in stages ranging from IB to IIA and in one case combined with RT, obtaining a CR.[21,29] As for methotrexate, Jiang et al described one case with CR, while 18 patients received this treatment in the American cohort.[3,22] Carmustine was used in a case series of 13 patients with stage IA to IIIB with PR 62% and CR 38%.[23] Etoposide in combination with prednisone was described in a stage IA patient, with CR.[30] Clobetasol in combination with tezarotene and excimer laser was used in a stage IA pediatric patient, with CR.[26] Topical steroids were reported to be used in the American (97 patients), Dutch (22 patients) and Japanese cohorts.[3,5,29] In these three reports, other less commonly used reported therapies were UVB, Denileukin diftitox, interferon, nitrogen mustard, imiquimod, systemic chemotherapy, extracorporeal photopheresis and stem cell transplantation[3,5,29] (Figure 3).

A Single-Center Experience

In 2021, 22 patients with a biopsy-proven diagnosis of FMF, according to the international criteria, were visited at the dermatologic clinic of the University of Turin, Italy. The diagnosis had been made on average 9 years earlier (range 0–21). A male prevalence (63.6%) and a mean age of 69 (range 28–89) were recorded in our cohort. The most represented stage was IB with 14 patients (63.6%), followed by IIB with 4 patients, IA with 3 patients and IIA with 1 patient each. Ten patients (45%) presented with severe pruritus as most relevant symptom. Six stage progressions were documented in the available records (five patients from IA to IB and one patient from IIA to IIB). As for the most used therapies, 17 patients (77.3%) received topical steroids, 13 patients (59.1%) UVB phototherapy, and 9 patients (40.1%) systemic steroids. As for oral retinoids, bexarotene and acitretin were prescribed to 10 (45.5%) and 12 (54.5%) patients, respectively. As for radiation therapy, 7 patients (31.8%) received local radiotherapy and 3 received TSEB (13.6%). Other recorded treatments were PUVA (3 patients), interferon, brentuximab vedotin, mogamulizumab (2 patients each), and methotrexate (1 patient). At the time of data collection, patients had already received on average 3 different treatments (range 2–7), either topical or systemic. The most experienced

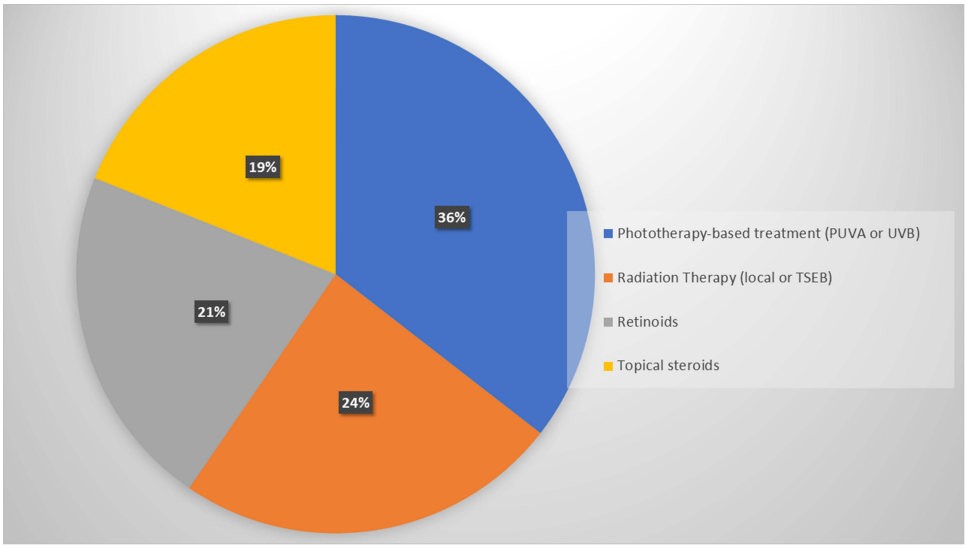

Figure 3 Most prescribed treatments in FMF patients according to our review.

side effects were blood lipid disorders and cutaneous reactions with oral retinoids (51% of the patients), transient radiation-induced dermatitis after RT (80% of the patients), one case of mogamulizumab-induced rash, and one case of psoriasis onset during brentuximab vedotin treatment.[34–37] Best overall response was assessed in conformity with standardized skin response definitions.[38] A total of 7 CRs, 8 PRs, 3 SDs and 4 PDs were observed at the time of analysis. As for the complete responses, they were all achieved in early-stage patients (ie, 5 stage IB, 1 stage IA, 1 stage IIA), whilst PRs were achieved in six stage 1B and two stage 2B patients, respectively. Stable disease responses were seen in two stage 2B patients and one stage 1A patient, while progression affected three stage 1B patients and one stage 1A patient.

Discussion

Folliculotropic mycosis fungoides (FMF) represents the most common subtype of MF and is characterized by specific clinical-pathologic features.[3,39,40] First, early and advanced stages differ in predilection of site, as the former more commonly affects the trunk and limbs, whilst the latter the head/neck region.[4] Moreover, advanced forms assume characteristics more similar to classic MF, such as infiltrated plaques and nodules, whilst early stages can present in a wide range of clinical forms, such as acneiform lesions, follicular-like keratoses, or erythematous patches.[4,5] As for histology, advanced forms seem to show more conspicuous cellular infiltrates (ie, eosinophils, plasma cells, lymphocytes with syringotropism), characterized by pronounced depth and density.[4] Hodak et al highlighted how FMF can be distinguished in two distinct forms, a low-stage indolent form and a high-stage aggressive form, addressing the lack of long-term follow-up and small sample studies as major limitations to thoroughly grasp the nature of FMF forms.[4]

Looking at the recent data reported in the literature, more than half of the analyzed papers did not include advanced disease stages (≥IIB), thus showing generally higher ORR rates for the therapies reported.[20–32] On the contrary, looking at those studies which included more advanced stages, such as the papers by van Santeen et al and Laggis et al, a significantly higher fluctuation of ORR could be observed (ie, PR and CR ranging from 25–24% to 48–51%, respectively).[5,32] Our case history shows quite similar responses, with CR achieved mainly in early stages. Moreover, despite being traditionally considered an aggressive variant of MF, metastatic cases of FMF described in the literature in the last 5 years are in line with our case series and generally represent a small percentage of the patients. Regarding the treatments used in FMF, in the absence of specific guidelines and clinical prospective studies, a high number of treatments are described in clinical practice, with variable results.[20–32] Phototherapy, retinoids (ie acitretin, bexarotene, isotretinoin) and topical steroids represent the most widely described non-ionizing therapies (Figure 3), with different results.[3,5,24–32] Phototherapy in all its forms, especially as PUVA, appears to have the greatest initial therapeutic success, although it is more commonly proposed in the early stages of the disease. Both in the literature and in our case history, the first line of treatment is topical steroid therapy, often already initiated by the patient before the actual diagnosis of FMF. Retinoids, although widely used, appear to be poorly effective in monotherapy, particularly acitretin. Combination treatment with phototherapy seems to be advisable.[27,28] Ionizing treatments such as radiotherapy and TSEBT, especially if combined with bexarotene, appear effective, at least in the short term, yet the need for coordination between different specialists and, in the case of TSEBT, between different centers can represent a limitation for their use in clinical practice[3,5,32,41](Figure 3). Moreover, a TSEBT-based therapeutical approach has proved to significantly improve emotional domains of quality of life in MF patients.[42] Overall, the large number of treatment options and high treatment resistance of FMF are reflected in the numerous therapeutic lines adopted in clinical practice. In contrast to classic MF, extra-corporeal photopheresis (ECP) does not seem to play a relevant part in the treatment of the folliculotropic variant, as it was adopted in only one study in our analysis.[3] While in the literature it is often difficult to identify the various therapies adopted, our case series shows that patients undergo numerous treatments ranging from 2 to 7 with an average of 3.8. Overall, the design and poor-quality evidence of retrospective single-center experiences do not allow for the defining of clear therapeutic directions of FMF. Given the peculiar nature of FMF, specific guidelines based on prospective clinical studies are desirable to ensure significant and clear evidence on the treatments to be preferred in this variant. The inconstant course of the disease and the multidisciplinary nature of the feasible treatments mandatorily

call for an integrated approach between the various specialists involved, such as dermatologists, oncologists, hematologists and radiotherapists.

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Disclosure

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