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Clinical staging and prognostic factors in folliculotropic mycosis fungoides

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FOLLICULOTROPIC MYCOSIS FUNGOIDES PRESENTING WITH A SOLITARY LESION: CLINICOPATHOLOGICAL FEATURES AND LONG-TERM FOLLOW-UP DATA IN A SERIES OF 9 CASES

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ABSTRACT

Background: Folliculotropic mycosis fungoides (FMF) is a distinct variant of mycosis fungoides, which in rare cases may present with a solitary lesion. Reported cases describe an excellent prognosis, but follow-up was generally short. Herein, clinicopathologic characteristics, long-term follow up data of 9 patients with solitary FMF are presented and differential diagnosis is discussed.

Methods: From a cohort of 203 patients with FMF, nine cases with solitary FMF were selected. Clinical data and histological sections obtained at diagnosis and during follow-up were reviewed.

Results: Skin lesions, in all patients located on the head, went into complete remission after treatment with radiotherapy (6 cases) or topical steroids (1 case) or regressed spontaneously (2 cases). After a median follow-up of 89 months (range 51-203 months), 5 patients were still in complete remission, 2 patients had developed multiple skin relapses, while 2 patients had progressed to extracutaneous and fatal disease. Histologically, all patients showed marked folliculotropism, associated with syringotropism (4 cases) and/or follicular mucinosis (5 cases). Large cell transformation was observed at first presentation (2 cases) and during follow-up (3 cases).

Conclusions: Long-term follow-up data indicate that patients with solitary FMF do not always have an indolent clinical course and therefore require long-term follow-up.

INTRODUCTION

Folliculotropic mycosis fungoides (FMF) is a rare but distinct variant of mycosis fungoides (MF), histologically characterized by the presence of folliculotropic infiltrates, often with sparing of the epidermis, and clinically by the preferential involvement of the head and neck region.[1] Clinical manifestations include the presence of (grouped) follicular papules, plaques and tumors, and in some patients acneiform or keratosis pilaris-like skin lesions.[2-4] Infiltrated plaques or tumors in the eyebrow region are a highly characteristic feature and often skin lesions are associated with alopecia. Very uncommonly FMF may present with a solitary skin lesion, with only 28 cases documented in literature to date.[5-14] There is however no consensus about the definition of this condition. In most reports, solitary or unilesional FMF is defined by a solitary skin lesion with histopathological features of FMF.[6-10,12,14] However, in other studies unilesional FMF is defined by skin lesions in a single skin area covering <5% of body surface, which may contain multiple papules or nodules.[5,11,13] Patients with a solitary skin lesion (19 of 28 cases) presented most frequently with an (infiltrated) plaque or tumor (14 of 19 cases)[6-10,13,14], which were primarily localized in the head- and neck area (17of 19 cases). In contrast, patients with multiple papules within a small single skin area presented mainly with lesions on the limbs and trunk (7 of 9 cases) and only two cases with facial or scalp involvement.[11,13] Irrespective of the clinical presentation, initial treatment consisted most frequently of local radiotherapy[5,6,8-11,13,] but also excision[7,10,11,13], psoralen with ultraviolet A therapy with or without retinoids[10,11], topical steroids[8] and in one case even multiagent chemotherapy was used[7] , resulting in complete remissions in most cases. Most reports emphasize the favorable course of patients with solitary or unilesional FMF. Disease progression was reported in only three cases, including two patients showing progression from either a patch or a plaque to tumor stage disease preceding treatment with local radiotherapy[9] , and one patient presenting with a solitary papule in the right eyebrow, who developed relapsing and progressive plaque-like lesions histologically showing large cell transformation.[7] Dissemination to extracutaneous sites or lymphoma-related deaths have not been reported thus far. However, in most reports duration of follow-up was relatively short.

Herein, we present another nine patients with solitary FMF. In contrast to previous studies, more than half of our patients showed large cell transformation, either at

presentation or during follow-up, and two of nine patients developed extracutaneous and ultimately fatal disease. Differentiation between FMF and other types of cutaneous T-cell lymphoma may be challenging, in particular in patients presenting with a solitary tumor. The aim of our report is to describe the clinicopathologic features and differential diagnosis of FMF patients presenting with a solitary skin lesion, and to emphasize the necessity of long-term follow-up.

PATIENTS AND METHODS

From a prospective study cohort of 203 patients with FMF that were included in the Dutch Cutaneous Lymphoma Registry between 1985 and 2014, nine cases (4%) that had presented with a solitary skin lesion were selected for this study. Clinical and follow-up data were retrieved from the Dutch Cutaneous Lymphoma Registry and from medical records. The study was performed in accordance with the Declaration of Helsinki and the Dutch Code for Proper Secondary Use of Human Tissue, approved by the ethics committee of the Leiden University Medical Center. In all cases the diagnosis of FMF met the criteria of the WHO-EORTC classification and was confirmed by an expert panel of dermatologists and pathologists of the Dutch Cutaneous Lymphoma Group.[1] One of these patients (Table 1; case 3) has been reported previously, at that time still designated as alopecia mucinosa, despite the presence of highly atypical peri- and intrafollicular infiltrates.[15] Histologic sections from the initial biopsy and in total 19 biopsies obtained from four patients during follow-up were reviewed. The following histological criteria were examined: localization and cellular composition of the malignant infiltrate, presence of large cell transformation defined by the presence of more than 25% or large clusters of blast cells, extent of folliculotropism (+ minimal, ++ pronounced, +++ follicular destruction), syringotropism (- absent, + present) and epidermotropism (- absent, + present), the presence of follicular mucinosis (- absent, ± focal, +pronounced). Immunohistochemical sections, routinely stained for CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD68, Ki-67 and cytotoxic proteins (TIA-1, granzyme B) were reviewed to determine the phenotype of the neoplastic cells and the presence of marker loss by these cells.

RESULTS

Clinical findings

The clinical characteristics of the nine patients are presented in **Table 1**. All nine patients (8 males, 1 female) had presented with a solitary skin lesion, localized in the head- and neck area. Median age at diagnosis was 57 years (range 19-68 years) and median time to diagnosis was 3 months (range 1-24 months). Two patients had presented with a typical eyebrow patch or plaque with associated alopecia. The other patients presented with an indurated plaque or tumorous lesion. Pruritus was reported in only one patient. Treatment with local radiotherapy (6 cases) or topical steroids (1 case) resulted in complete remission in all of them. The other two patients did not receive active treatment, because of complete spontaneous resolution of their skin lesion after biopsy (cases no. 5 and 8). Five of nine patients did not develop other skin lesions during a median follow-up of 59 months (range, 51-191 months). Two patients (cases 7 and 8) developed only multiple solitary skin relapses at distant sites, which were all successfully treated with low-dose radiotherapy (2 x 4 Gy), excision or topical steroids. The two remaining patients developed progressive skin lesions, five and 78 months after diagnosis, and ultimately developed extracutaneous disease with involvement of lymph nodes, bone marrow and visceral organs (see Table 1). Multiagent chemotherapy was unsuccessful and both patients died of their disease, 89 and 203 months after diagnosis, respectively. After a median follow-up of 89 months (range 51-203 months), six patients were alive without evidence of disease, one patient was alive with relapsing skin disease and two patients had died of lymphoma.

Histological findings

Histological characteristics of the initial diagnostic skin biopsies and a selection of follow-up biopsies are presented in **Table 2**. Initial biopsies of four cases (nos. 1-4) typically showed perifollicular to diffuse infiltrates with pronounced infiltration of the follicular epithelium by small to medium-sized pleomorphic T-cells with cerebriform nuclei and associated follicular mucinosis (**Figures 1A-F**). The other five cases (nos. 5-9) showed diffuse folliculotropic infiltrates and focal follicular mucinosis in one of them.

Table 1 – Clinical characteristics of nine patients with unilesional folliculotropic mycosis fungoides

Case no.	Sex/Age (years)	Clinical presentation	Initial treatment	Result	Course	Relapse (months)	Treatments relapse (result)	Status last follow-up (months)
1	M/25	Patch left eyebrow with alopecia	RT	CR	SCR	-	-	Ao, 55
2	M/19	Plaque left eyebrow with alopecia	Topical steroids	CR	SCR	-	-	Ao, 59
3	M/33	Plaque above left eyebrow	RT	CR	PD	plaque right eyebrow (78) fol-lowed by progres-sive skin lesions on face and trunk systemic disease (nodal and bone marrow) (178)	IL steroids, PUVA, topical nitrogen mustard, TSEBI, local RT (PD) Systemic chemo-therapy (PD)	D+, 203
4	F/59	Infiltrated plaque right forehead	RT	CR	SCR	-	-	Ao, 191
5	M/59	Firm papule chin	Spontaneous remission	CR	SCR	-	-	Ao, 51
6	M/50	Tumor scalp with alopecia	RT	CR	SCR	-	-	Ao, 65
7	M/61	Tumor glabella	RT	CR	RD	papule left eyebrow (39) papule left eyebrow (49)	Excision (CR) Topical steroids (CR)	Ao, 109
8	M/68	Tumor upper lip	Spontaneous remission	CR	RD	tumor glabella (29) follicle-based patches shoulder and leg (85) plaque lower lip(122) plaque on nose (134)	Low-dose RT (CR) Topical steroids (CR) Low-dose RT (CR) Low-dose RT (CR)	A+, 134
9	M/57	Tumor on tip of the nose	RT	CR	PD	plaque left side nose (5) followed by progressive skin lesions on face and trunk systemic disease (lung, nodal, CNS) (80)	PUVA+ interferon alpha, Low-dose RT (PD) Systemic chemotherapy (PD)	D+, 89

M: male, F: female, CR: complete remission, SCR: sustained complete remission, RD: relapsing disease (same stage), PD: progressive disease (to stage IV), D+: death of lymphoma, Ao: Alive without evidence of disease, A+: alive with disease; RT: radiotherapy, IL : intralesional CNS: central nervous system, TSEBI: total skin electron beam irradiation.

Table 2 - Histological characteristics of nine patients with solitary folliculotropic mycosis fungoides

No.	Clinical presentation (years after diagnosis)	Localisation of infiltrate	FT	ST	ET	Follicular mucinosis	Predominant morphology tumor cells	Immuno-phenotype	Blast cells (%)	LCT
1	Patch left eyebrow	Periadnexal	++	-	-	+	Small pleomorphic cells	CD4+	-	-
2	Flat plaque left eyebrow	Periadnexal	++	-	-	+	Small pleomorphic cells	CD4+	+	-
3	Plaque above left eyebrow	Periadnexal to diffuse	++	-	-	+	Small/medium-sized pleomorphic cells	CD4+	+	-
3FU	Plaque nose (14 yrs)	Diffuse	++	-	-	+	Small to large pleomorphic cells and (partially) CD30+ blast cells	CD4-	++	-
3FU	Plaque nose (16 yrs)	Diffuse	++	+	-	+	Small to large pleomorphic cells and (partially) CD30+ blast cells	CD4-	+++	+
4	Infiltrated plaque right forehead	Periadnexal to diffuse	++	-	-	+	Small/medium-sized pleomorphic and scattered CD30+ blast cells	CD4+	++	-
5	Papule chin	Diffuse	++	+	-	-	Small/medium-sized pleomorphic cells	CD4+	-	-
6	Tumor scalp	Diffuse	+++	+	-	-	Small/medium-sized pleomorphic cells and CD30+ blast cells	CD4+	+++	+
7	Tumor glabella	Diffuse	++	+	-	-	Small/medium-sized pleomorphic and scattered CD30+ blast cells	CD4+	+	-
7FU	Papule left eyebrow (4 yrs)	Periadnexal	++	-	-	-	Medium-sized pleomorphic and clusters of CD30+ blast cells	CD4+	++	+
8	Tumor upper lip	Diffuse	++	-	-	±	Small/medium-sized pleomorphic	CD4+	-	-
8FU	Tumor glabella (2 yrs)	Diffuse	++	-	-	-	Small/medium-sized pleomorphic and CD30+ blast cells	CD4+	+++	+
9	Tumor nose	Diffuse	+++	+	+	-	Small to large pleomorphic and CD30- blast cells	CD4-CD8-	+++	+
9FU	Tumors back and wrist (5 yrs)	Periadnexal	++	+	-	-	Small/medium-sized pleomorphic cells and scattered CD30- blast cells	CD4-CD8-	+	-

No.: number; FU: follow up biopsy; FT: folliculotropism + minimal, ++ pronounced, +++ follicular destruction; ST: syringotropism - absent, + present ; ET: epidermotropism - absent, + present, Follicular mucinosis: - absent, ± focal, + pronounced, Blast cells: - <5% + 5-10% ++ 11-25% +++ >25% LCT: large cell transformation

Infiltration of the eccrine sweat glands (syringotropism) was observed in four cases and pronounced epidermotropism with formation of Pautrier's microabscesses in one case (Table 2). The perifollicular infiltrates consisted of small to medium-sized pleomorphic T-cells and blast cells, admixed with histiocytes, small lymphocytes, eosinophils, which were abundant in four cases (nos. 2, 3, 5 and 8) and plasma cells. In three cases (nos. 4, 6 and 7) large clusters of small B-cells were observed. The proportion of blast cells varied between less than 5% to at most 15% in seven cases. Two cases met the criteria of large cell transformation with percentages of blast cells exceeding 25% (no. 9) or even 50% (no. 6). Apart from case 9, blast cells were predominantly CD30-positive. In one case (no.6) more than 80% of the neoplastic T-cells expressed CD30, more than half of them large blast cells. Because of the marked folliculotropism and syringotropism, nicely visualized by additional staining with a monoclonal antibody against keratin, as well as the presence of many small to medium-sized pleomorphic T-cells with cerebriform nuclei, both in the follicular epithelium and in the perifollicular infiltrates, the diagnosis transformed FMF rather than primary cutaneous anaplastic large cell lymphoma (C-ALCL) was preferred (**Figures 2A-E**). In another case (case 9), because of the density of the dermal infiltrates, mainly consisting of small to medium-sized pleomorphic T-cells with cerebriform nuclei, epithelial structures could hardly be recognized, and differentiation between FMF and a diagnosis of peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) was challenging. Also in this case a diagnosis of FMF was preferred because of the typical morphology of the neoplastic cells (cerebriform nuclei) and the presence of marked folliculotropism and syringotropism. Follow-up biopsies in this patient showed perifollicular infiltrates with pronounced follicular infiltration by small to medium-sized pleomorphic T-cells consistent with a diagnosis of FMF. In three cases (nos. 3, 7 and 8) skin lesions obtained during follow-up showed a marked increase in the number of blast cells (either CD30-positive or CD30-negative) compared to the initial biopsies and met the criteria of large cell transformation (see Table 2). Immunohistochemical examination demonstrated a CD3+CD4+CD8- phenotype with variable loss of pan-T-cell antigens in eight of nine cases. One case (no. 9) showed a CD3+CD4-CD8- phenotype, both in the initial and follow-up biopsies. An aberrant phenotype was also found in the two cases in which the skin lesions showed complete spontaneous resolution after biopsy. In case 5 the neoplastic CD4+ T-cells showed complete loss of CD7 and expressed cytotoxic proteins (TIA-1 and granzyme B), while case 8 showed (partial) loss of CD2 and CD5.

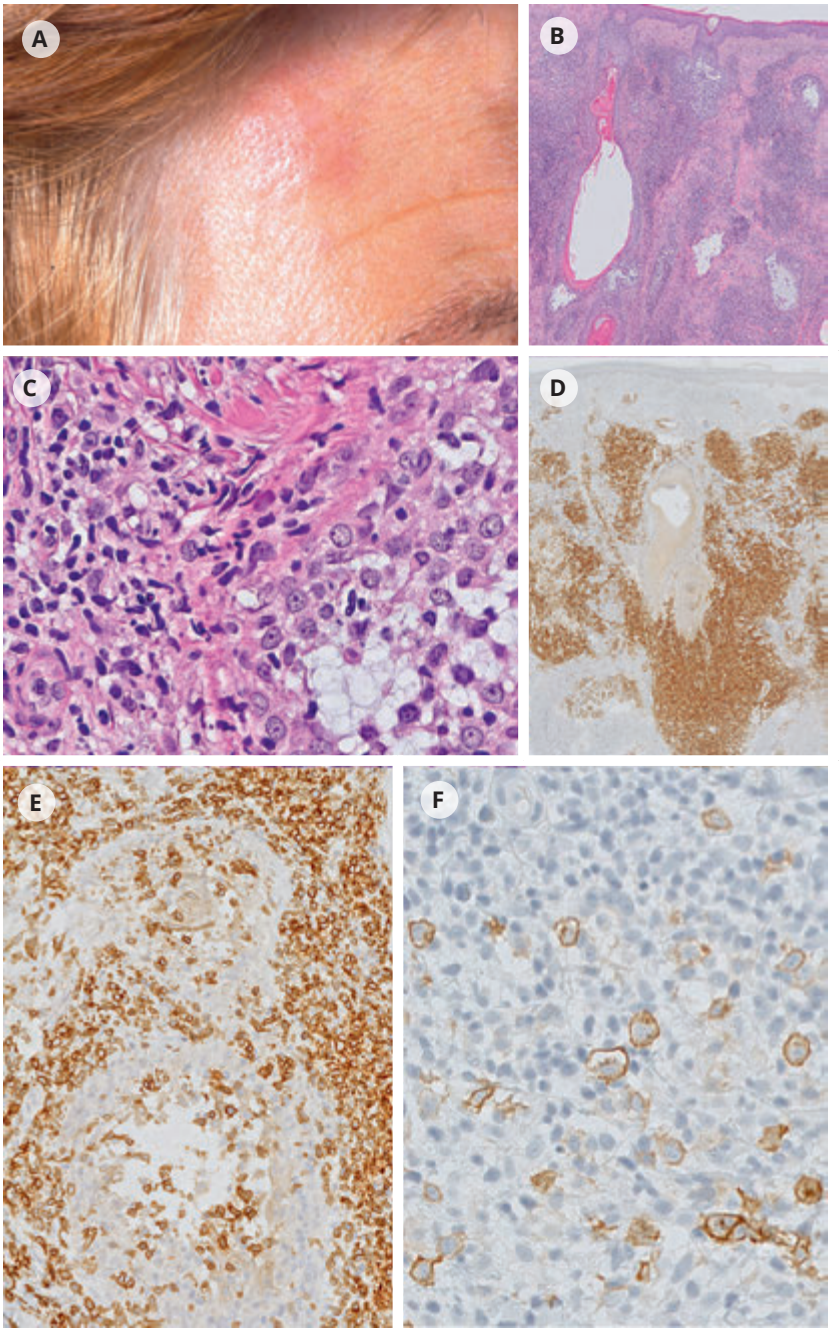

Figure 1. Case 4: Erythematous infiltrated plaque on the right forehead (A). Histology shows periadnexal to diffuse infiltrates with sparing of the epidermis and follicular mucinosis (B) and infiltration of the follicular epithelium by hyperchromatic small pleomorphic lymphocytes (C) that stained positive for CD3 (D and E). Perifollicular infiltrates show scattered CD30 positive blast cells (F).

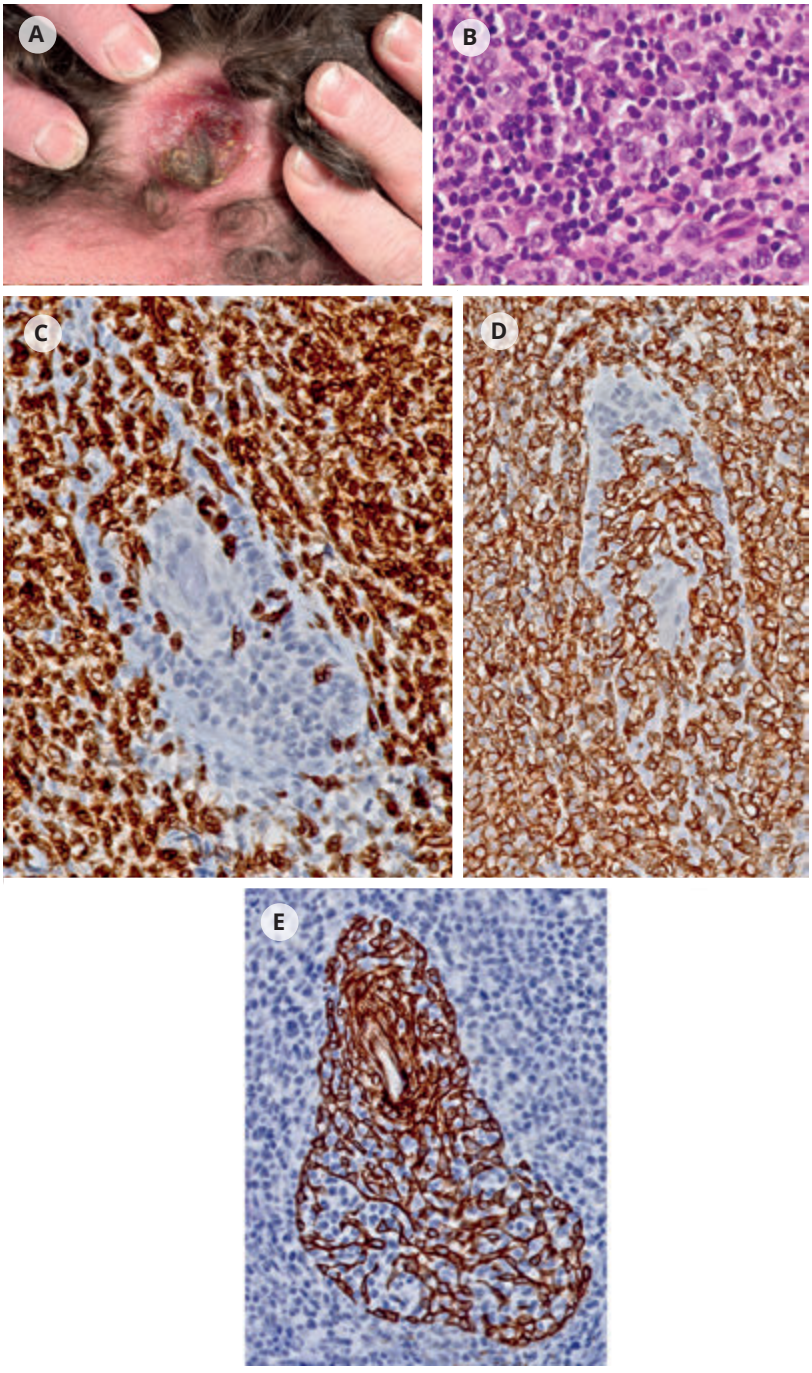

Figure 2. Case 6: Crusted tumor in the neck within an area of alopecia (A). Dermal infiltrate shows a mixture of small/medium-sized pleomorphic cells and blast cells (B). Folliculotropic infiltrates show a positive staining for CD3 (C) and CD30 (D). Folliculotropism is nicely visualized by a keratin staining (E).

DISCUSSION

The present study describes the clinicopathologic features and long-term follow-up data of nine patients with FMF presenting with a solitary skin lesion. This study included only patients presenting with one solitary lesion, who had been followed for a median of 89 months (range 4-17 years). All patients had presented with a skin lesion in the head- and neck area and achieved complete remission after initial treatment, which included local radiotherapy in six of nine cases. Interestingly, in two patients the skin lesions showed complete spontaneous resolution after biopsy (**Figures 3A-D**). Five cases achieved a long-lasting remission for several years after initial treatment. However, in contrast to previous studies, two of nine patients developed systemic disease and died of systemic lymphoma, 7.5 and 17 years after diagnosis. In addition, large cell transformation, either at presentation (case 6 and 9) or during follow-up (cases 3, 7 and 8) was observed in five of nine cases. These observations demonstrate that not all patients presenting with solitary FMF run an uneventful clinical course and indicate that long-term follow-up is warranted. Histologically, the diagnosis of solitary FMF was rather straightforward in seven of nine patients. Clinically, these patients presented with a solitary patch, plaque or tumor in the head- and neck area with the characteristic histological features of FMF, including perifollicular to diffuse folliculotropic (and syringotropic) infiltrates, that mainly consisted of atypical CD3+, CD4+, CD8- small to medium-sized cerebriform lymphocytes , variable numbers of mostly CD30+ blast cells and associated follicular mucinosis (4 of 7 cases). Since cases of advanced FMF often contain variable numbers of CD30+ blast cells, differentiation between FMF and C-ALCL may sometimes be difficult, in particular in FMF patients presenting with a solitary lesion and/or cases with a diffuse proliferation of CD30+ blast cells, as observed in case 6 of the present series. In this patient the diagnosis transformed FMF was based on the presence of marked folliculotropism and syringotropism as well as the presence of many small to medium-sized pleomorphic T-cells with cerebriform nuclei, both in the follicular epithelium and in between the blast cells in the perifollicular infiltrates.[16] The combination of folliculotropism and syringotropism has been described in previous reports on FMF, and is also referred to as adnexotropic MF.[17,18] In cases with diffuse dermal infiltrates with partial or even complete destruction of the epithelial structures differentiation between FMF and other types of CTCL may be extremely difficult or even impossible. In our previous study on 203 patients with FMF [19] a few patients with a diffuse proliferation of CD30+ blast cells and no discernible epithelial structures had initially been misclassified as C-ALCL.

The correct diagnosis could only be made after development of new skin lesions with the characteristic clinicopathologic features of FMF. In such cases staining with monoclonal antibodies against keratin may be useful to visualize infiltration of residual hair follicles and sweat glands by neoplastic T-cells and facilitate a definite diagnosis of FMF. In patients presenting with a solitary lesion histologically showing an atypical T-cell infiltrate, which disappears spontaneously after biopsy, as observed in two of our patients (cases 5 and 8), a diagnosis of cutaneous T-cell pseudolymphoma should be considered. However, in both cases the presence of a diffuse infiltrate of small to medium-sized pleomorphic T-cells, prominent folliculotropism and an aberrant CD4+ T-cell phenotype supported a diagnosis of FMF and argued against a diagnosis of T-cell pseudolymphoma.

In conclusion, the long-term follow-up data of our patients presenting with solitary FMF indicate that these patients do not always have an indolent clinical course, but may develop progressive cutaneous and extracutaneous disease, and therefore require long-term follow-up.

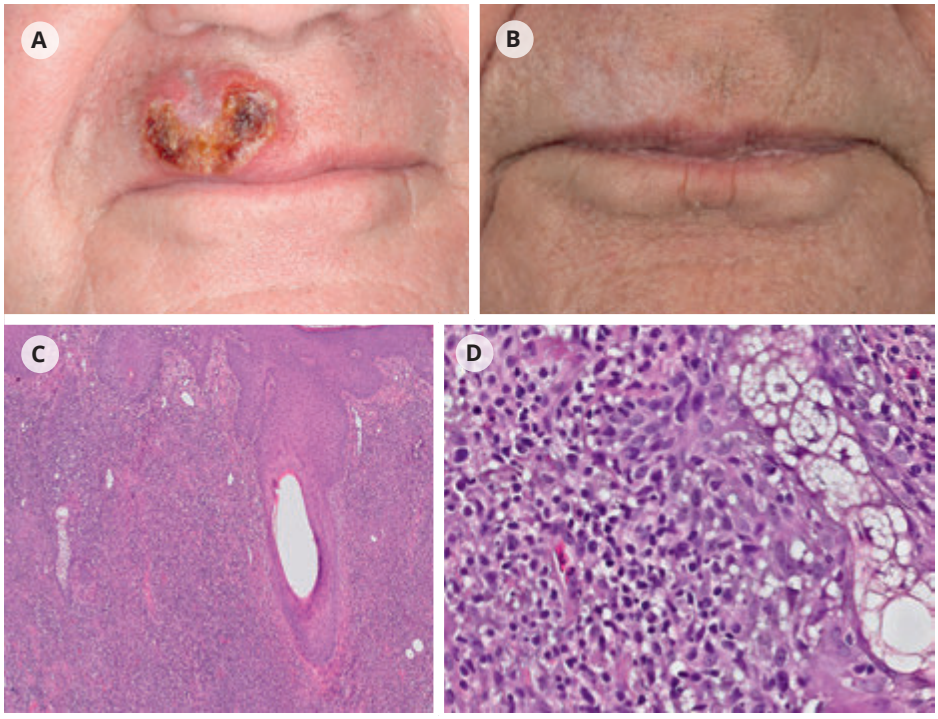

Figure 3. Case 8: Crusted tumor on the upper lip (A) that resolved spontaneously after skin biopsy (B). Histology shows a diffuse dermal infiltrate (C) mainly composed of small/medium sized pleomorphic cells with marked folliculotropism (D).

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