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Spiky follicular mycosis fungoides: a clinicopathologic study of eight cases.

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#### Abstract

**Background:** The early stages of follicular mycosis fungoides (FMF) have not been described previously in the literature.

**Objective:** Our goal was to better categorize the clinicopathologic features of early stages of FMF.

**Methods:** The clinical notes of patients with a diagnosis of FMF seen during the previous 5 years were reviewed to identify any cases that at presentation had only hyperkeratotic follicular lesions.

**Results:** Eight patients (five male, three female) with a mean age of 55.4 years were enrolled. Noteworthy, FMF was not a clinical consideration in any of these patients initially. Patients presented with disseminated, slightly erythematous, hyperkeratotic, spiky follicular papules which, histopathologically, showed hyperkeratotic columns protruding from follicular plugging in concert with selective infiltration of the infundibular epithelium by atypical, mostly CD4+, lymphocytes. T-cell clonality was demonstrated in four of eight cases. The mean duration of the lesions before diagnosis was 17.1 months. The course was indolent in most of the cases (median follow up: 18 months), whilst progression to overt FMF was noted in two patients.

**Limitations:** The number of cases is small and follow up relatively short.

**Conclusions:** Spiky FMF is a deceptive clinicopathologic presentation of FMF that has been poorly described and that can mimic numerous follicular disorders.

**Keywords:** Follicular mycosis fungoides, Hyperkeratotic spicules, Keratosis pilaris, Spiky

Mycosis fungoides (MF) is a low-grade cutaneous T-cell lymphoma characterized by epidermotropic T lymphocytes with clonal skin expansion that usually presents with scaling erythematous patches which, over time, may progress to plaques and tumors.<sup>1</sup> As there are numerous distinct variants of MF, diagnosis may be a challenge, especially in their early stage; as there is a low clinical suspicion for MF histopathologic findings may be subtle.<sup>2</sup> However, early recognition is important as some of these variants are associated with a more aggressive clinical course than the classic MF. In the new WHO-EORTC (World Health Organization-European Organization for Research and Treatment of Cancer) classification scheme, follicular MF (FMF) is recognized as a distinct entity where malignant T lymphocytes selectively surround and infiltrate hair follicles, whereas the epidermis is often spared or minimally involved.<sup>3</sup> Clinical manifestations preferentially involve the head and neck and often present with grouped follicular papules associated with alopecia, acneiform lesions, comedones, cysts and plaques.<sup>4–12</sup> The formation of different follicular lesions in FMF is likely a result of the extent and degree of infiltration, obstruction, or both, of the hair follicle by the neoplastic infiltrate. As the clinicopathologic findings of FMF differ greatly from those of classic MF, diagnosis is often delayed, with a likely adverse impact on prognosis.<sup>4</sup> To date, unlike classic MF,<sup>13</sup> the clinical, histopathologic, immunophenotypic and molecular-genetic parameters to determine early diagnosis of FMF have not yet been established. This report describes the clinical, histopathologic, immunohistochemical and genotypic features of eight FMF patients, who presented at onset with multiple, localized or disseminated, variably hyperkeratotic, spiky follicular papules. To the best of our knowledge, this peculiar clinical presentation of FMF has received little, if any, attention and may well represent an early manifestation of this MF variant. Therefore, the pitfalls involved in clinical and

histopathologic differential diagnosis are herein discussed.

### **Materials and methods**

The files of a total of 102 adult patients with a clinicopathologic diagnosis of FMF who attended the Departments of Dermatology of the University of Turin (Italy), Zurich (Switzerland) and Rome (Italy) in 2009–2013 were reviewed in an effort to identify any cases that had only hyperkeratotic spiky and/or cone-shaped follicular lesions at onset. FMF was defined by the presence of clinical lesions with a follicular base and folliculotropism as the dominant histopathologic findings.<sup>3–5</sup> Patients with associated patches or plaques typical of MF were excluded. The recorded clinical features were gender, age at symptom onset, anamnesis, drug treatment, physical examination, clinical course, interval between symptom onset and histopathologic diagnosis of FMF, type of therapy, response to therapy and outcome at last follow up. Photographic clinical documentation at FMF diagnosis was available for review in all cases. Other clinical characteristics were associated symptoms and the presence of haematological, oncological or other comorbidities as well as the results of the routine laboratory tests, which included a blood smear, complete blood cell count and biochemistry along with the peripheral blood flow, cytometric immunophenotype, chest X-ray and abdomen echotomography.

#### *Histopathologic, immunohistochemical and molecular evaluation*

From each patient 5mm punch biopsies from the follicular hyperkeratotic lesions were obtained. When available, previous lesion specimens, taken before the FMF diagnosis, were retrospectively reviewed. The skin specimens were fixed in 10% buffered formalin, embedded in paraffin and stained with haematoxylin–eosin. Immunophenotypic studies on frozen sections and/or paraffin-embedded sections were performed in all cases by immunohistochemical staining using the standard EnVision™ FLEX peroxidase detection system (Dako, Denmark), with monoclonal antibodies against the T-cell antigens CD2, CD3, CD4, CD5, CD7, CD8, CD25, CD26, CD30, CD45RA, CD45RO, CD56, CD103, granzyme B, TIA-1, Mib-1.

Molecular clonality testing was also carried out in all cases on the DNA extracted from paraffin-embedded tissue of each patient. The tests were performed by the heteroduplex method<sup>14</sup> for patients diagnosed before 2012 and by the BIOMED2 protocol<sup>15</sup> for patients diagnosed after that date. The phenotype of circulating lymphocytes was investigated by flow cytometry in 3 of 8 cases and no atypical cells were detected.

### **Results**

#### *Clinical findings*

Among a total of 102 adult patients with a clinicopathologic diagnosis of FMF, we identified eight patients (five male and three female; 7.8%) who presented with tiny, variably hyperkeratotic, spiky and/or cone-shaped follicular papules in the absence of typical lesions of FMF. The lesions were scattered on the trunk and/or limbs, whilst the head and neck were spared (Figs. 1–3) (Table 1).

In the remaining 94 cases, at the time of diagnosis of FMF, patients presented with a variable combination of follicular-based lesions (grouped follicular papules, alopecia, keratosis pilaris-like papules, comedones, cysts, nodules and plaques)

In the group of patients with hyperkeratotic spiky papules as the sole findings of the disease, the main symptoms at the onset were a sensation of rough skin and only mild, if any, pruritus. No cases had involvement of the palms or soles, nor was there any palpable lymphadenopathy, family history of similar lesions, malignancy, retinoid or other drug therapy, arsenic exposure, radiotherapy or immunosuppression. The mean interval between symptoms onset and diagnosis of FMF was 17.1 months (range: 2–60 months). On the basis of the literature data, the mean age at FMF diagnosis was below that of classic MF (55.4 vs. 59 years).<sup>16</sup>

The first clinical suspicions in our series included mainly keratosis pilaris, lichen spinulosus, lichen planopilaris, multiple minute digitate hyperkeratoses and hyperkeratotic spicules. In two patients (cases 1 and 8), hyperkeratosis was striking with the presence of innumerable, flesh-coloured or

slightly erythematous, keratotic spicules, mostly affecting the chest, abdomen and back (Fig 1A, 3D). This clinical scenario was less prominent in the remaining six cases. In all but one of these patients there were no other co-existing follicular lesions such as keratosis pilaris or lichen spinulosus.

#### Histopathologic, immunohistochemical and genotypic findings

The biopsy specimens obtained from the hyperkeratotic follicular skin lesions revealed histopathologic findings suggestive of early FMF in all cases. They showed a moderate to dense infiltrate of small to medium-sized lymphocytes both around and within a slightly dilated hair follicle infundibulum in the upper dermis (Figs. 1–3). A constant finding was an orthokeratotic or parakeratotic column protruding from the follicular plugging, which was more prominent in some cases (Figs. 1D and 3E).

Single small to medium-sized atypical lymphocytes, accompanied by minimal, if any, spongiosis were present within the basal layer and peppered the epithelium. There was no accompanying follicular mucinosis. There was a noticeable absence of other inflammatory cells, i.e. eosinophils and plasma cells. The interfollicular epidermis was minimally involved or completely spared in all patients.

Immunophenotypically, the classic T-helper phenotype CD3+CD4+, CD8– of folliculotropic lymphocytes was observed in seven of eight cases at immunohistochemistry, whilst one case was CD8+ (Fig. 3F); CD7 was lost in three of eight cases. Molecular analysis demonstrated the presence of a monoclonal population of T lymphocytes in four of eight cases, whilst in one case molecular technique provided an uncertain result (Table 1).

#### Further examination and course

Laboratory investigations, including full blood chemistry, chest X-ray and echotomography of the abdomen were within the normal limits in all cases. A diagnosis of FMF was established in all patients on the basis of histopathologic, immunohistochemical and/or genotypic molecular findings. Skin-targeted therapy (topical corticosteroids, PUVA, UVA alone or in association) was the first line therapy in all patients except in patient 2, where systemic treatment with bexarotene was administered first. The lesions almost completely regressed in one patient, whilst in seven patients they slightly improved, but did not regress. Interestingly, in two patients (cases 2 and 6) infiltrated papules, comedones and small cysts developed during follow up. All patients are alive and median follow up is 18months (range : 3–120 months) (Table 1).

### **Discussion**

Herein, we report a series of eight patients with an unusual presentation of FMF that is characterized by multiple, disseminated or localized, variably hyperkeratotic, dome-shaped and/or spiky follicular papules located on the trunk and/or extremities that should be included among the protean clinical manifestations of this disease. The prevalence of this presentation in our cohort of adult FMF appears to be low (7.8%), whilst the average age at diagnosis is younger than those with MF (55.4 vs. 59). Noteworthy is the fact that there was no clinical suspicion of FMF in any of these patients at presentation. The presence of hyperkeratotic follicular lesions has occasionally been observed during the course of FMF, but has usually been pooled with more typical lesions of the disease and there has been no detailed description of the histopathologic, immunophenotypical and/or molecular genotypic findings of these lesions.<sup>4,5,12,17,18</sup> Recently, Al-Niaimi et al.<sup>19</sup> have described two patients with Sezary syndrome who developed innumerable follicular hyperkeratotic spicules on the head and scalp. The histopathologic changes were suggestive of epidermotropic CTCL, even if there was no confirmation by immunohistochemistry and/or T-cell rearrangement analysis. The clinical and histopathologic differential diagnosis of FMF includes disorders presenting with hyperkeratotic, cone-shaped and/or spiky follicular lesions in a variety of follicular keratotic disorders of different etiopathogenesis, including keratosis pilaris, lichen spinulosus, multiple minute digitate hyperkeratosis, hyperkeratotic spicules and lichen planopilaris (Table 2). Keratosis pilaris is a keratinization disorder affecting the infundibulum of the hair follicle,

characterized by lesions that vary from subtle follicular excrescences to more prominent follicular spikes with mild, if any, surrounding erythema, more commonly found on the posterior aspect of the upper arms and the lateral aspect of the thighs and buttocks of children and young adults.<sup>20</sup> In lichen spinulosus, best considered as a variant of keratosis pilaris, the keratotic papules have a striking spiky appearance and a characteristic grouped arrangement.<sup>21</sup> Histopathologically, in keratosis pilaris and lichen spinulosus, a keratin plug fills the infundibulum and protrudes above the surface for a variable distance in concert with a superficial perifollicular mild lymphocytic infiltrate, without folliculotropism. Another matter of major concern in the differential diagnosis of our patients' eruptions was multiple minute disseminate hyperkeratosis (MMDH), a rare, familial or sporadic, chronic keratinization disorder of unknown aetiology, first described by Goldstein in 1967<sup>22</sup> and later reported under a variety of synonyms.<sup>23–27</sup> Characteristic clinical findings of MMDH are multiple, small, predominantly non-follicular keratotic spiky protuberances with a normal skin colour, predominantly involving the chest, shoulders, upper arms, thighs and popliteal fossae. Histopathologically, MMDH is characterized by compact columnar hyperkeratosis, of orthokeratotic or parakeratotic type, arising from a finely pointed epidermal elevation. Hyperkeratotic spicules are follicular digitate keratoses that most frequently involve the face (mainly the nose) and sometimes the scalp, trunk or limbs, often associated with paraproteinemia, multiple myeloma and cryoglobulinemia,<sup>28–30</sup> but may also be idiopathic.<sup>31</sup> Histopathology reveals columns of orthokeratotic or parakeratotic hyperkeratosis in monoclonal gammopathy associated cases, along with eosinophilic, PAS-positive material within the infundibular epithelium, which corresponds largely to the monoclonal protein of the underlying gammopathy. Lichen planopilaris is a clinically heterogeneous variant of lichen planus that typically affects middle-aged women and men, where keratotic, red-violaceous follicular papules are present, often in association with the classical manifestations of the dermatosis.<sup>32,33</sup> Histopathology shows a lichenoid reaction with vacuolar changes and apoptotic keratinocytes involving the basal layer of the follicular epithelium in concert with a dense perifollicular infiltrate of lymphocytes and perifollicular fibroplasia with mucin deposits. To a lesser extent, other dermatoses presenting with keratotic follicular plugs, such as phrynoderma, post-irradiation digitate keratoses, trichodysplasia spinulosa, follicular ichthyosis, pityriasis rubra pilaris, psoriasis and dermatomyositis, may be considered in the differential diagnosis as well. However, the different clinical settings and/or histopathologic features usually allow for a clear-cut differentiation.<sup>27</sup>

The diagnosis of early FMF in this study was based on clinical, pathologic, immunohistochemical and molecular criteria. The persistent and mildly pruritic character of the eruption and recurrence despite treatment, along with the tendency of the lesions to increase in size and number over time, were helpful clinical findings for the diagnosis of early FMF. This was particularly true where the hyperkeratotic follicular lesions preferentially involved skin sites typical of classic MF, such as the lower back and trunk. Furthermore, in two patients progression to overt FMF with development of infiltrated papules, cysts and comedones was observed. Histopathologically, selective tropism of the follicular epithelium by small- to medium-sized lymphoid cells with hyperchromatic and convoluted nucleus was a constant finding and the hallmark for diagnosis of early FMF.

The immunophenotype of folliculotropic lymphocytes was typically CD4+ in seven of eight cases, while a CD8-positive phenotype was observed in one case. T-cell receptor genes were clonally rearranged in four of eight cases, reinforcing the diagnosis of FMF. Noteworthy was the fact that, although none of these criteria is *per se* absolutely specific for MF,<sup>34–36</sup> their diagnostic value is preserved by their mutual interdependence, enabling a diagnosis of early FMF to be established.<sup>13</sup>

According to some recent clinical studies on large series of patients, FMF appears to have a worse prognosis than does classic MF, with a disease-specific 5-year survival of 62% and progressive disease in 35% of cases.<sup>4,5,12</sup> The more aggressive behavior of FMF is usually ascribed both to the extension of the neoplastic lymphocytes into the deep portion of the hair follicles that may limit the response to skin-directed therapy modalities and to the biologic profile of folliculotropic lymphocytes.<sup>4</sup> The data obtained in this study suggest that the course of patients presenting with spiky hyperkeratotic papules, in the absence of more typical lesions of the disease, is indolent and

similar to that of patch stage MF. One patient obtained almost complete remission after first line therapy at a 5 year follow up, five had stable disease, whilst two developed infiltrated papules, cysts and comedones typical of FMF. The discrepancy between the relatively favorable course of the disease in our patients and the more aggressive clinical behaviour of FMF patients reported in some large series-based studies is intriguing. One explanation could be the more indolent behaviour of this peculiar presentation of FMF, where the disease is confined to the upper part of the hair follicles, as opposed to the overt FMF, where there is extensive infiltration of the lower portion of the follicles by malignant lymphocytes. Alternatively, one might argue that a bias does exist in the recognition of early clinical FMF lesions, as findings can be subtle and/or misinterpreted as common follicular disorders. Indeed, patients with FMF at the time of diagnosis usually present a rather advanced clinical stage of the disease compared to those with classic MF. Although a characteristic stepwise progression from patches to plaques and tumors accompanied by distinctive histopathologic changes is well known in classic MF, this kind of lesion evolution has not yet been well established in FMF. If we were to use the clinical staging system recently proposed for MF by the International Society for Cutaneous Lymphomas (ISCL)-European Organization for Research and Treatment of Cancer (EORTC),<sup>37</sup> some FMF patients would most likely fit into stages IB or IIB. Thus, it is not surprising that the disease runs a more aggressive course in these more advanced stages. However, in some patients, FMF run a less aggressive and/or different course, challenging the concept of FMF as an entity in its own right with an intrinsically worse prognostic factor.<sup>38</sup> The diagnosis of early MF is one of the most debated issues in dermatopathology. The distinction and relationship between some persistent, often clonal and usually epitheliotropic T-cell infiltrates and cutaneous T-cell lymphoma have not been resolved.<sup>39,40</sup> The series of cases described herein share similarities with some cases of folliculotropic T-cell lymphocytosis,<sup>41,42</sup> a recently described unique form of T-cell lymphoproliferative disease with characteristic clinical manifestations and histopathologic features that differ from follicular mucinosis by virtue of the lack of intrafollicular mucin deposition. The clinical manifestations include non-infiltrative patches with variable follicular prominence, hypopigmentation, alopecia, infiltrative, erythematous, scaly plaques and/or papules, cysts and follicular keratotic plugs involving the head, neck and/or trunk. The morphologic, phenotypic and molecular hallmarks of this entity include a mildly atypical CD4+ (and frequently CD7-) T-cell folliculotropic infiltrate, typically of low density and confined mainly to the superficial isthmus and infundibulum and occasional T-cell receptor gamma gene rearrangement.<sup>41,42</sup> Interestingly, although the course was generally indolent, there was progression to overt FMF in a minority of cases,<sup>41-43</sup> which probably implies selection of autonomous T-cell clones with a more aggressive biologic profile. It is most likely that folliculotropic T-cell lymphocytosis indeed represents a manifestation of early FMF. Recently, Hodak et al.<sup>44</sup> provided new insights into the clinicopathologic features of early FMF. In their comprehensive analysis of 50 patients with juvenile MF, FMF had a relative high prevalence and resulted characterized by an indolent course and more superficial clinical and histopathologic features than adult FMF, possibly suggesting that pediatric FMF may be under-recognized by both dermatologists and pathologists. Interestingly, in some patients FMF lesions were exclusively manifested by grouped spiky hyperkeratotic follicular papules on an erythematous base located on the outer aspects of the extremities. In summary, herein we describe a series of patients who presented with an indolent disorder characterized by small, folliculocentric, spiky and/or cone-shaped hyperkeratotic papules which showed histopathologic, immunophenotypic and often molecular findings of FMF in the absence of more typical lesions of that disease. The persistent character along with the tendency to slow progression with development of more typical lesions of FMF in some of our patients support the view that the cases herein described may well represent an early FMF stage. An increased awareness of this deceptive presentation of FMF could be relevant, not only to allow for early diagnosis and therapy of this lymphoma, but also to better understand the clinicopathologic stages and progression involved.

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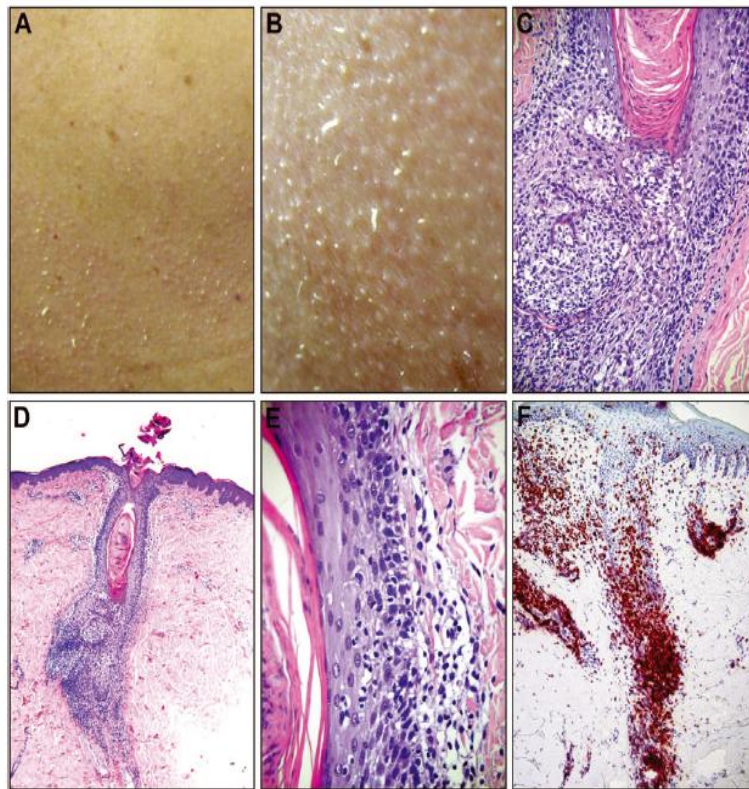
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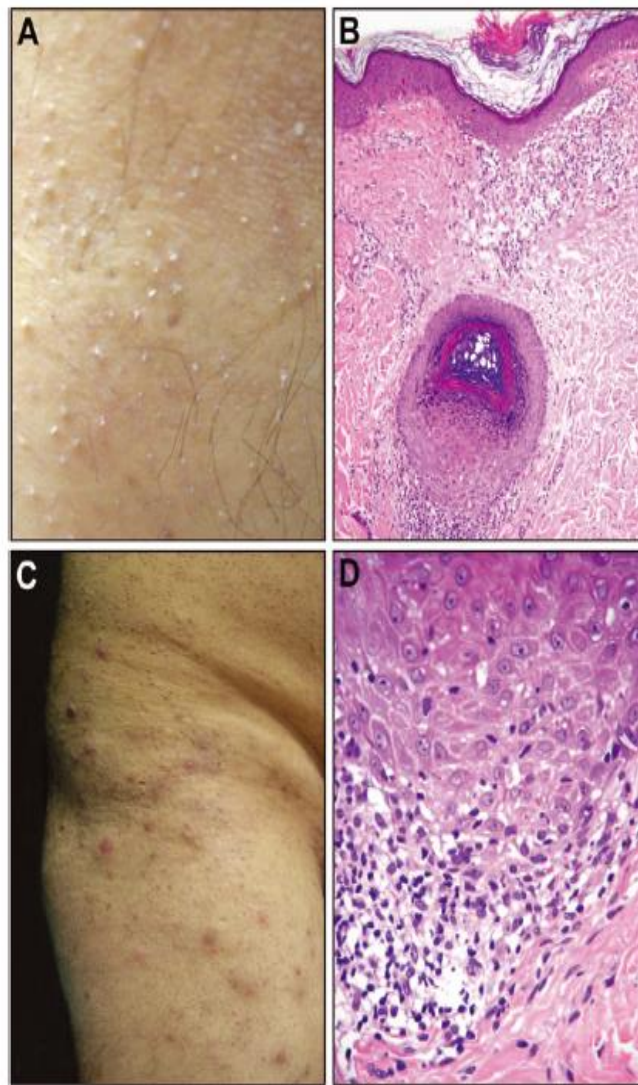
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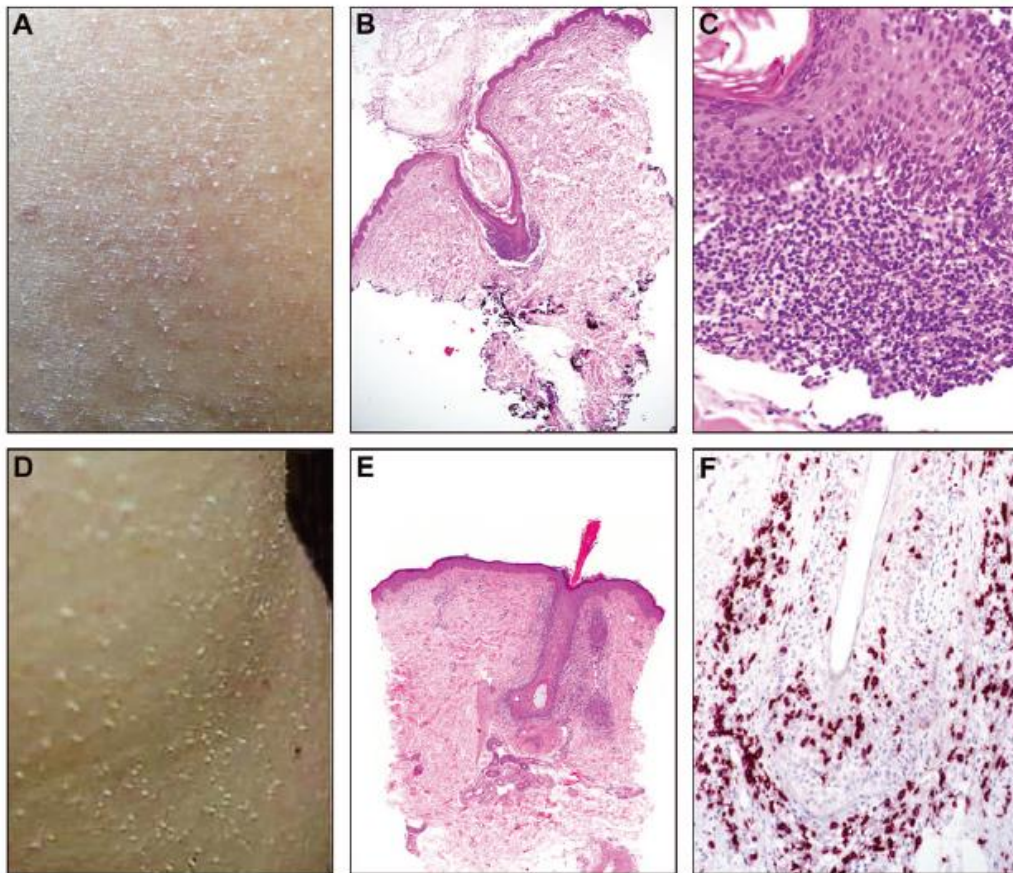
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*Fig. 1.* Patient 1: A) Innumerable whitish finger-like and spiky hyperkeratotic projections on the back resemble multiple minute digitate hyperkeratosis. B) Detail of the lesions. C) Characteristic histopathology shows a dilated follicle filled with keratin surrounded and permeated by a dense lymphocytic infiltrate. A parakeratotic column protruding from the follicular opening is seen. (D and E) Small to medium sized lymphocytes pepper the infundibular epithelium. F) Immunohistochemical labeling with CD4 shows striking infiltration of the follicular epithelium with lymphocytes.



*Fig. 2.* Patient 2: A) Spiky hyperkeratosis on the arm at presentation. (B and D) A folliculotropic lymphocytic infiltrate with slight invagination of the infundibular opening from which a parakeratotic column protrudes. C) Development of infiltrated papules, comedones, small cysts and folliculitis-like lesions intermingled with follicular hyperkeratosis on the abdomen and thigh at 1 year of follow up.



*Fig. 3.* A–C). Patient 7: A) Acuminate hyperkeratosis on the buttock. B) A dilated infundibulum with an orthokeratotic keratin plug protrudes above the skin surface. At the base of the infundibulum, a dense folliculotropic lymphocytic is seen. C) Peppering of infundibular epithelium by lymphocytes. (D–F) Patient 8: D) There are countless papules with minute spiky hyperkeratosis on the lower back. E) A band-like lymphocytic infiltrate is apparent along the upper portion the hair follicle. Note the exclamation mark appearance of the follicular hyperkeratosis. F) The CD8 stain highlights the extent of the perifollicular and folliculotropic lymphocytic infiltrate.

<b>Patient n, Age(y), sex</b>	<b>Duration before diagnosis (months)</b>	<b>Site of involvement</b>	<b>Clinical diagnosis</b>	<b>Follow-up (months)</b>
1 (71) M	6	Trunk	Follicular keratosis, Lichen planopilaris, multiple minute digitate hyperkeratosis	60 AWD
2 (48) M	6	Trunk, upper and lower extremities	Follicular keratosis	60 AD
3 (46) M	8	Trunk, upper and lower extremities	Follicular keratosis, follicular mucinosis	24 AWD
4 (47) M	9	Trunk, extremities	Follicular keratosis, lichen nitidus	8 AD
5 (61) F	36	Trunk, extremities	Follicular keratosis, lichen nitidus	8 AD
6 (47) F	36	Trunk	Lichen nitidus, lichen spinulosus	12AD
7 (74) F	10	Trunk	Follicular keratosis	120 AD
8 (49) M	2	Trunk, extremities	Pityriasis rubra pilaris, psoriasis, secondary syphilis	12 AD *