

# Follicular Mucinosis

## *A Critical Reappraisal of Clinicopathologic Features and Association With Mycosis Fungoides and Sézary Syndrome*

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**Context:** Beginning in 1957, patients have been described with localized alopecia characterized histopathologically by mucin deposition within hair follicles (follicular mucinosis [FM]). At least 2 distinct diagnostic entities have been proposed: one occurring in children and young adults without association with other diseases ("idiopathic" FM), the other occurring in elderly patients and associated with mycosis fungoides or Sézary syndrome ("lymphoma-associated" FM).

**Objective:** To determine whether idiopathic and lymphoma-associated FM are distinct or related entities.

**Design:** Case series.

**Setting:** Department of Dermatology, University of Graz, Graz, Austria.

**Patients:** Forty-four patients with FM were divided into 2 groups. Group 1 comprised 16 patients (mean age, 37.5 years) with no associated mycosis fungoides or Sézary syndrome; group 2 was made up of the other 28 (mean age, 52.2 years), who had clinicopathologic evidence of cutaneous T-cell lymphoma.

**Results:** Mean age was lower in patients with idiopathic FM, but a considerable overlapping among the 2 groups was present. Location on the head and neck region was common in both groups, but most patients with lymphoma-associated FM had lesions also on other body sites. In fact, solitary lesions at presentation were common in patients with idiopathic FM (11 [68.8%] of 16 patients), but uncommon in those with lymphoma-associated FM (2 [7.1%] of 28 patients). Histopathologic findings did not allow clear-cut differentiation of the 2 groups. Finally, a monoclonal rearrangement of the T-cell receptor  $\gamma$  gene was demonstrated by polymerase chain reaction analysis in about 50% of tested cases from each group.

**Conclusions:** Criteria previously reported to differentiate idiopathic from lymphoma-associated FM proved ineffective. In analogy to localized pagetoid reticulosis (Woringer-Kolopp disease), small-plaque parapsoriasis, and so-called solitary mycosis fungoides, idiopathic FM may represent a form of localized cutaneous T-cell lymphoma.

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**I**N 1957, Hermann Pinkus<sup>1</sup> described a group of 6 patients with localized alopecia characterized histopathologically by mucin deposition within hair follicles. In the following years, the term *follicular mucinosis* (FM) proposed by Jablonska et al<sup>2</sup> in 1959 slowly replaced *alopecia mucinosa*, the designation originally coined by Pinkus himself. Subsequent reports suggested that at least 2 distinct entities were encompassed under this diagnosis: one occurring in children and young adults without association with other cutaneous or extracutaneous diseases ("idiopathic" FM), the other occurring in elderly patients and associated with mycosis fungoides or Sézary syndrome ("lymphoma-associated" FM).<sup>3-13</sup> In addition, progression of idiopathic FM into cutaneous T-cell lymphoma (CTCL) has been well documented in several cases.<sup>14-18</sup>

neous T-cell lymphoma (CTCL) has been well documented in several cases.<sup>14-18</sup>

### *See also pages 191 and 244*

In this study, we reviewed data from a large group of patients with idiopathic and lymphoma-associated FM with respect to clinicopathologic presentation and molecular features.

## RESULTS

### IDIOPATHIC FM

Clinicopathologic and molecular features for patients with idiopathic FM are summarized in **Table 1**. Sixteen patients had FM without signs of CTCL or other cutaneous or extracutaneous diseases (M/F, 1.3:1;

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## PATIENTS AND METHODS

Data from 44 patients with FM were retrieved from the files of the Department of Dermatology of the University of Graz, in Austria. Patients were divided into 2 groups according to clinicopathologic features: 16 patients had no evidence of mycosis fungoides or Sézary syndrome at presentation and did not develop CTCL in the follow-up time (group 1, idiopathic FM); the other 28 had clinicopathologic evidence of mycosis fungoides or Sézary syndrome at presentation or developed CTCL in the follow-up time (group 2, lymphoma-associated FM). Diagnosis of mycosis fungoides and Sézary syndrome was made according to criteria published in the European Organization for Research and Treatment of Cancer (EORTC) classification for cutaneous lymphomas.<sup>19</sup>

### HISTOLOGIC CHARACTERISTICS

In all cases, one or more biopsy specimens were available for review of histopathologic features. Hematoxylin-eosin, periodic acid-Schiff, colloidal-iron, and Giemsa stains were available for histologic review of biopsy specimens.

### IMMUNOHISTOLOGIC CHARACTERISTICS

In 30 cases where enough material was available, complete immunophenotypical studies were performed using a standard 3-step immunoperoxidase technique.<sup>20</sup> Antigen retrieval was performed for most of the antibodies with a standard heat-retrieval technique.

## MOLECULAR BIOLOGIC CHARACTERISTICS

Analysis of the T-cell receptor  $\gamma$  (*TCR $\gamma$* ) gene rearrangement was performed on formalin-fixed, paraffin-embedded tissue sections in 30 cases where enough material was available. Isolation of DNA was performed with standard methods. Briefly, five 5- $\mu$ m sections were cut from each biopsy specimen and coated on slides. To avoid cross contamination, the blade of the microtome was changed after cutting each sample. Slides were subsequently deparaffinized by xylene and ethanol. After air drying, sections were scraped off the slides and resuspended in 50 to 100  $\mu$ L of digestion buffer (100mM of Tris-hydrochloride, pH 8.0; and 1  $\mu$ g/ $\mu$ L of Proteinase K [Boehringer Mannheim, Mannheim, Germany]), depending on the size of the specimen. After incubation at 55°C for 24 hours, samples were heated to 94° for 15 minutes and stored at -20°C.

The *TCR $\gamma$*  gene was analyzed using the polymerase chain reaction (PCR) technique as described by McCarthy et al,<sup>21</sup> with minor modifications. Briefly, 2% to 5% of total template DNA was used in a 50- $\mu$ L PCR reaction containing primers V $\gamma$ 11 (250 nM), V $\gamma$ 101 (250 nM), J $\gamma$ 11 (500 nM), J $\gamma$ 12 (500nM), dinucleotide triphosphate (200 $\mu$ M each), magnesium chloride (1.5mM), potassium chloride (50mM), Tris-hydrochloride at pH 8.3 (10mM), and AmpliTaq Gold DNA Polymerase (Perkin Elmer, Branchburg, NJ). After initial heating at 94°C for 10 minutes, 40 cycles of the reaction were carried out (denaturation, 94°C for 60 minutes; annealing, 50°C for 30 minutes; extension, 72°C for 30 min). A 10- $\mu$ L Aliquot of the PCR products was then run on a 3.5% MetaPhor agarose gel (FMC BioProducts, Rockland, Mass), stained with ethidium bromide, and viewed under UV light. The  $\beta$ -actin gene was analyzed as internal control in all cases.

mean age, 37.5 years; median age, 40 years; range, 13-61 years). Patients presented with solitary (n=11) or multiple (n=5) folliculotropic patches or plaques (**Figure 1**). Lesions were located on the face and neck in 15 patients and on the trunk in 1. No patient had generalized lesions. Histologic analysis revealed mucin deposits within the hair follicles in all cases. The amount of mucin varied in different cases, and in different hair follicles in the same case. A varying amount of eosinophils could be observed in 11 of 16 cases.

In 6 cases, there was a dense lymphoid infiltrate and great numbers of lymphocytes around and within affected hair follicles (**Figure 2**). Some lymphocytes had hyperchromatic, folded nuclei (small to medium-sized pleomorphic lymphocytes). Epidermotropism was not observed. These cases were not classified as lymphoma-associated FM because of the lack of clinicopathologic features of CTCL.

The other 10 cases showed only a mild lymphocytic infiltrate around hair follicles with scattered intrafollicular lymphocytes (**Figure 3**). Immunohistologic analysis performed in 11 cases revealed that the great majority of the lymphocytes had a T-helper phenotype. Molecular analysis showed the presence of a monoclonal rearrangement of the *TCR $\gamma$*  gene in 6 of 11 cases analyzed (**Figure 4**).

The mean follow-up time was 71.6 months (range, 5-242 months; median, 22 months). All patients were

**Table 1. Summary of Clinicopathologic Features and Follow-up Data for Patients With Idiopathic Follicular Mucinosis\***

| Patient No./ Sex/Age, y | Location | Distribution of Lesions | Lymphoid Infiltrate | PCR† of <i>TCR<math>\gamma</math></i> | Follow-up (No. of mo) |
|-------------------------|----------|-------------------------|---------------------|---------------------------------------|-----------------------|
| 1/F/54                  | HN       | S                       | Dense               | P                                     | A&D (25)              |
| 2/F/20                  | HN       | M                       | Dense               | P                                     | A&D (6)               |
| 3/M/16                  | HN       | S                       | Mild                | nd                                    | A&D (12)              |
| 4/M/48                  | HN       | S                       | Dense               | Mo                                    | A&W (215)             |
| 5/M/61                  | HN       | M                       | Dense               | P                                     | A&W (225)             |
| 6/M/53                  | HN       | S                       | Mild                | Mo                                    | A&D (19)              |
| 7/M/21                  | HN       | S                       | Mild                | Mo                                    | A&W (242)             |
| 8/M/22                  | HN       | S                       | Mild                | P                                     | A&W (111)             |
| 9/F/61                  | HN       | S                       | Mild                | nd                                    | A&D (5)               |
| 10/M/27                 | HN       | S                       | Dense               | Mo                                    | A&W (29)              |
| 11/F/35                 | T        | M                       | Mild                | P                                     | A&D (6)               |
| 12/F/18                 | HN       | S                       | Mild                | Mo                                    | A&W (52)              |
| 13/F/13                 | HN       | S                       | Mild                | nd                                    | A&D (14)              |
| 14/F/50                 | HN       | M                       | Dense               | Mo                                    | A&D (12)              |
| 15/M/56                 | HN       | S                       | Mild                | nd                                    | A&W (166)             |
| 16/M/45                 | HN       | M                       | Mild                | nd                                    | A&D (6)               |

\*HN indicates head and neck; T, trunk; S, solitary lesion; M, multiple lesions; P, polyclonal pattern; nd, test not done; Mo, monoclonal pattern; A&D, alive with skin disease; and A&W, alive and well.

†Findings of polymerase chain reaction (PCR) analysis of T-cell receptor  $\gamma$  (*TCR $\gamma$* ) gene rearrangement.

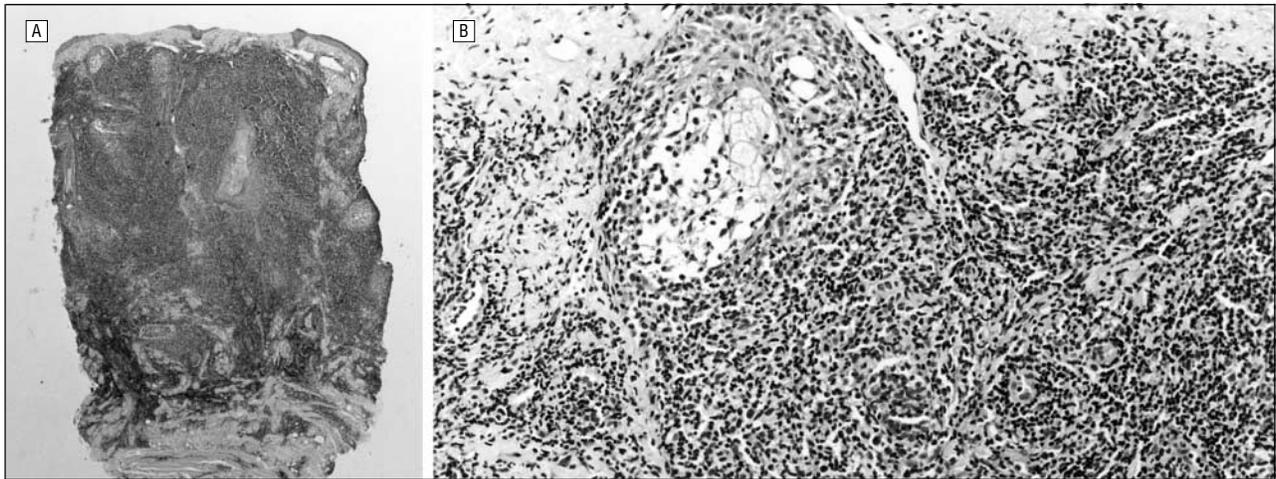
alive, and no one developed mycosis fungoides or other CTCLs by the last follow-up examination. Seven patients are currently in complete remission (mean follow-up, 148.6 months; range: 29-242 months), whereas the other 9 show residual disease (mean follow-up, 11.7 months; range 5-25 months).



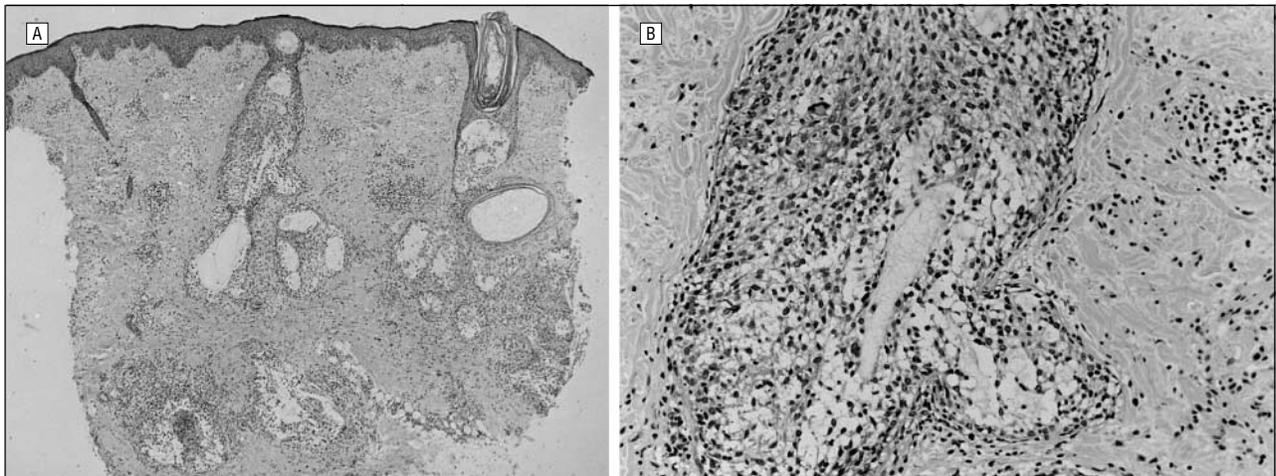
**Figure 1.** A solitary patch of idiopathic follicular mucinosis on the chin of patient 8.

## LYMPHOMA-ASSOCIATED FM

Twenty-eight patients had FM associated with mycosis fungoides (n=26) or Sézary syndrome (n=2) in different stages (M/F, 2.5:1; mean age, 52.2 years; median age, 53 years; age range, 32-74 years) (**Table 2**). At first presentation, patients had solitary (n=2) or multiple (n=20) patches or plaques covering less than 10% of the body surface (**Figure 5**). Two patients with Sézary syndrome had erythroderma, and 4 with mycosis fungoides had generalized patches and plaques covering more than 10% of the body surface. Histopathologically, all cases revealed varying amounts of mucin within 1 or more hair follicles. Varying numbers of eosinophils could be observed in 19 of 28 cases. Seventeen of 28 cases showed histopathologic features of CTCL, including the presence of focal epidermotropism of lymphocytes within the epidermis between the hair follicles (**Figure 6**). Clear-cut Pautrier microabscesses, however, were seen only in a minority of the cases. Some lymphocytes in the dermis had hyperchromatic, folded nuclei (small- to medium-sized pleomorphic lymphocytes), but atypical cells never represented the majority of the infiltrate.

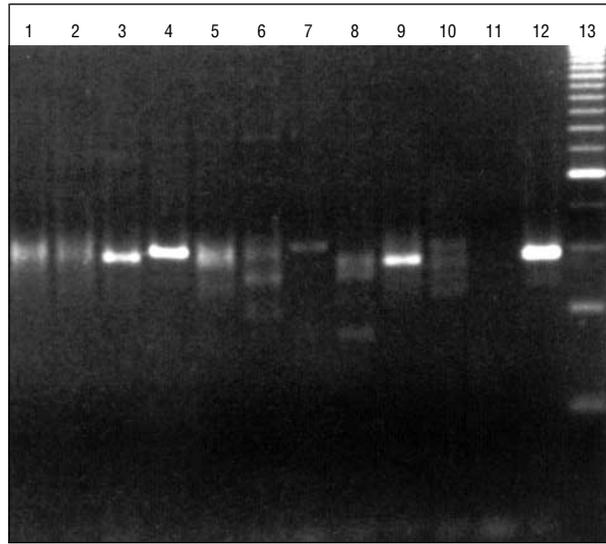


**Figure 2.** Idiopathic follicular mucinosis (FM) on patient 4. A, A dense infiltrate of lymphocytes is found within the entire dermis, but the epidermis is spared. B, An almost completely destroyed hair follicle shows remnants of FM with a dense perifollicular and intrafollicular lymphoid infiltrate.



**Figure 3.** A, Idiopathic follicular mucinosis (FM) in patient 12 with a mild lymphoid infiltrate. B, Detail of a hair follicle with FM and intrafollicular lymphocytes.

In 2 patients (patients 22 and 33), a biopsy specimen taken at presentation showed a dense lymphoid infiltrate around and within hair follicles, but no evidence of epidermotropism. In 1 of these 2 patients (patient 33)



**Figure 4.** Results of molecular analysis of T-cell receptor  $\gamma$  gene rearrangement in some of the cases. Lanes 1 through 5, lymphoma-associated follicular mucinosis (FM); note the monoclonal band in lanes 3 and 4. Lanes 6 through 10, idiopathic FM; note the monoclonal band in lanes 7 and 9. Lane 11, negative control (no DNA); lane 12, molecular ladder; lane 13, referent.

a second biopsy specimen taken at the same time showed features of mycosis fungoides without FM. The last 9 cases revealed a histopathologic picture characterized by mucin deposits in the hair follicles with only a mild lymphoid infiltrate (**Figure 7**). In 10 of the last 11 patients, the initial diagnosis was idiopathic FM (patients 18, 22, 25, 27, 28, 31, 35, 39, 42, and 44), and the diagnosis of CTCL was made only after analysis of specimens from repeated biopsies done over different periods of time (mostly within a few weeks or months; in patients 25 and 39, after 2 and 15 years, respectively).

Immunohistologic analysis performed in 19 cases showed the predominance of cells with a T-helper phenotype. Molecular analysis showed the presence of a monoclonal population of T lymphocytes in 9 of 19 cases analyzed (Figure 4). Seven patients died of their disease after a mean survival time of 125 months (range, 19-262 months). After a mean follow-up of 60.9 months (range, 2-221 months; median, 48 months), 19 patients are alive and in complete (n=2) or partial (n=11) remission or with progressive disease (n=6). Two further patients with progressive disease died of unrelated causes after 48 and 59 months, respectively.

#### COMMENT

Follicular mucinosis is an epithelial reaction pattern characterized by the accumulation of mucin within hair fol-

**Table 2. Summary of Clinicopathologic Features and Follow-up Data for Patients With Lymphoma-Associated Follicular Mucinosis**

| Patient No./Sex/Age, y | Location      | Distribution of Lesions | Lymphoma Type | Lymphoid Infiltrate | PCR† of <i>TCR</i> $\gamma$ | Follow-up (No. of mo) |
|------------------------|---------------|-------------------------|---------------|---------------------|-----------------------------|-----------------------|
| 17/M/36                | HN            | M                       | MF            | CTCL                | P                           | A&D (2)               |
| 18/F/36                | HN            | M                       | MF            | Mild                | Mo                          | A&D (6)               |
| 19/M/47                | T             | M                       | MF            | CTCL                | nd                          | A&D (51)              |
| 20/M/68                | T, LE         | M                       | MF            | CTCL                | nd                          | A&D (101)             |
| 21/M/51                | T             | M                       | MF            | CTCL                | P                           | A&W (92)              |
| 22/M/74                | HN, T         | M                       | MF            | Dense               | Mo                          | D-un (48)             |
| 23/M/59                | HN, T         | M                       | MF            | CTCL                | Mo                          | D (216)               |
| 24/F/39                | HN            | S                       | MF            | CTCL                | P                           | A&D (12)              |
| 25/M/48                | HN, T         | M                       | MF            | Mild                | nd                          | A&D (175)             |
| 26/M/61                | T             | M                       | MF            | CTCL                | Mo                          | A&D (6)               |
| 27/F/70                | T             | M                       | MF            | Mild                | P                           | A&W (11)              |
| 28/M/58                | HN, T         | M                       | MF            | Mild                | P                           | A&D (15)              |
| 29/M/50                | HN, T, UE, LE | G                       | MF            | CTCL                | Mo                          | D-un (59)             |
| 30/M/56                | T             | S                       | MF            | CTCL                | P                           | A&D (54)              |
| 31/F/47                | HN, T, UE     | M                       | MF            | Mild                | nd                          | A&D (48)              |
| 32/M/48                | HN, T, UE, LE | G                       | MF            | CTCL                | nd                          | A&D (6)               |
| 33/M/39                | HN, T         | M                       | MF            | Dense               | Mo                          | A&D (221)             |
| 34/M/60                | T             | M                       | MF            | CTCL                | nd                          | A&D (84)              |
| 35/F/55                | T             | M                       | MF            | Mild                | nd                          | D (27)                |
| 36/M/56                | HN, T         | M                       | MF            | CTCL                | Mo                          | A&D (25)              |
| 37/M/56                | HN, T, UE, LE | G                       | MF            | CTCL                | nd                          | A&D (159)             |
| 38/M/70                | T             | M                       | MF            | CTCL                | nd                          | D (262)               |
| 39/F/33                | T, UE         | M                       | MF            | Mild                | P                           | D (204)               |
| 40/M/68                | T, LE         | M                       | MF            | CTCL                | Mo                          | A&D (6)               |
| 41/M/34                | HN, T, UE, LE | G                       | MF            | CTCL                | P                           | D (98)                |
| 42/F/51                | T, UE         | M                       | MF            | Mild                | P                           | A&D (83)              |
| 43/F/60                | ED            | G                       | Sézary        | CTCL                | P                           | D (49)                |
| 44/M/32                | ED            | G                       | Sézary        | Mild                | Mo                          | D (19)                |

\*HN indicates head and neck; T, trunk; LE, lower extremities; UE, upper extremities; ED, erythroderma; M, multiple lesions; S, solitary lesion; G, generalized lesions; MF, mycosis fungoides; CTCL, cutaneous T-cell lymphoma; P, polyclonal pattern; Mo, monoclonal pattern; nd, test not done; A&D, alive with skin disease; A&W, alive and well; D-un, dead of unrelated causes; and D, dead of disease.

†Findings of polymerase chain reaction (PCR) analysis of the T-cell receptor  $\gamma$  (*TCR* $\gamma$ ) gene rearrangement.



**Figure 5.** Lymphoma-associated follicular mucinosis in patient 29. Patches, plaques, and flat tumors appear on the face and neck.

icles.<sup>22</sup> It occurs in a number of inflammatory, infectious, and neoplastic skin conditions, and in this context cannot be considered a specific skin disease.<sup>22-34</sup> Although it is generally accepted that the disease was first described by Pinkus<sup>1</sup> in 1957, in the same year Braun-Falco<sup>35</sup> reported an identical condition, and a patient with similar clinicopathologic features had already been observed by Lehner and Szodoray<sup>36</sup> in 1939.

After the report by Pinkus, several publications proposed the existence of 2 main types of FM.<sup>3-13,37-43</sup> The first type occurs in young patients in the absence of concomitant cutaneous or extracutaneous disorders and shows localized lesions with a tendency to resolve within a few years (idiopathic FM). The second type occurs in elderly patients and is associated with mycosis fungoides or Sézary syndrome.

A third type of FM presenting with clinicopathologic features of both of the other 2 groups has also been described (the so-called persistent or chronic benign FM).<sup>3,15</sup> The existence of this distinct third type is questionable. In fact, cases classified within this third group probably represent examples of lymphoma-associated FM. For example, one child described by Gibson et al<sup>44</sup> in 1988 had widespread lesions on the trunk and extremities recurring for 17 years in spite of various treatments including systemic chemotherapy, radiotherapy, topical nitrogen mustard, and psoralen plus UV-A therapy. Analysis of specimens from 2 biopsies taken at presentation led to a diagnosis of lymphosarcoma, and the clinical features were consistent with mycosis fungoides.

Classification of cases like this one as persistent FM has contributed to the confusion existing in this field.

Moreover, even the prognosis of idiopathic FM is not well elucidated, and several cases showing “transformation” into mycosis fungoides or other CTCLs have been reported.<sup>3,4-18</sup> We have demonstrated here that no clear-cut criteria allow the differentiation of idiopathic from lymphoma-associated FM, and we propose that idiopathic FM may belong to the variant forms of mycosis fungoides that show a prolonged, nonaggressive clinical course (**Table 3**).

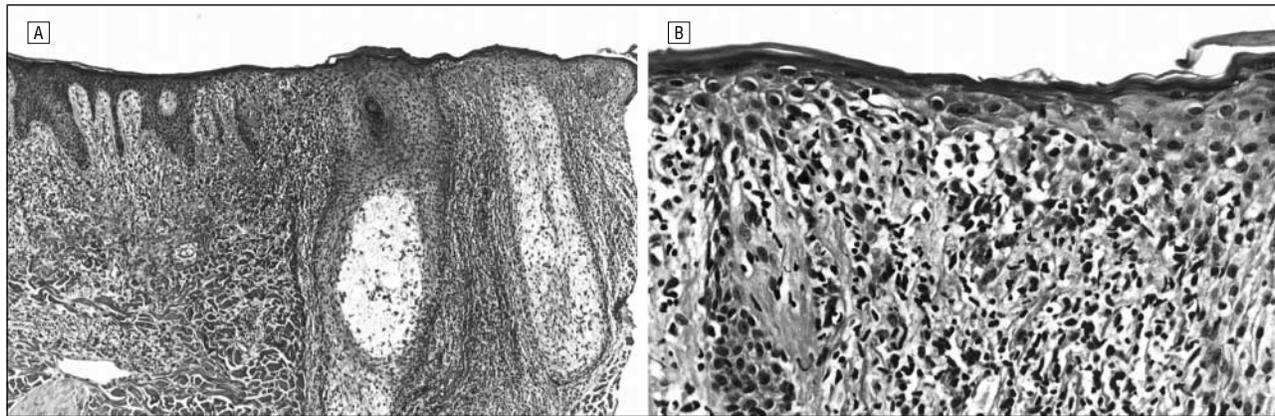
It has been suggested that the age of the patient, location of the lesion(s), and histopathologic features of the infiltrate may provide clues to help differentiate idiopathic from lymphoma-associated FM.<sup>3,8,9,45</sup> Another criterion proposed as helpful in the differential diagnosis is the molecular analysis of the *TCR $\gamma$*  gene rearrangement.<sup>46</sup> However, several authors have pointed out the difficulty, or even impossibility, of clearly distinguishing the 2 groups.<sup>4,6,47</sup>

We shall address these proposed distinguishing features one at a time, beginning with patient age. The mean age in our study was indeed lower in patients with idiopathic FM than in those with lymphoma-associated FM, but there was a considerable overlap between the 2 groups. Moreover, although mycosis fungoides is predominantly a disease of elderly patients, several cases have been reported in children, with or without FM.<sup>48-52</sup> Thus, it is not possible to exclude a diagnosis of mycosis fungoides solely on the basis of the age of the patient.

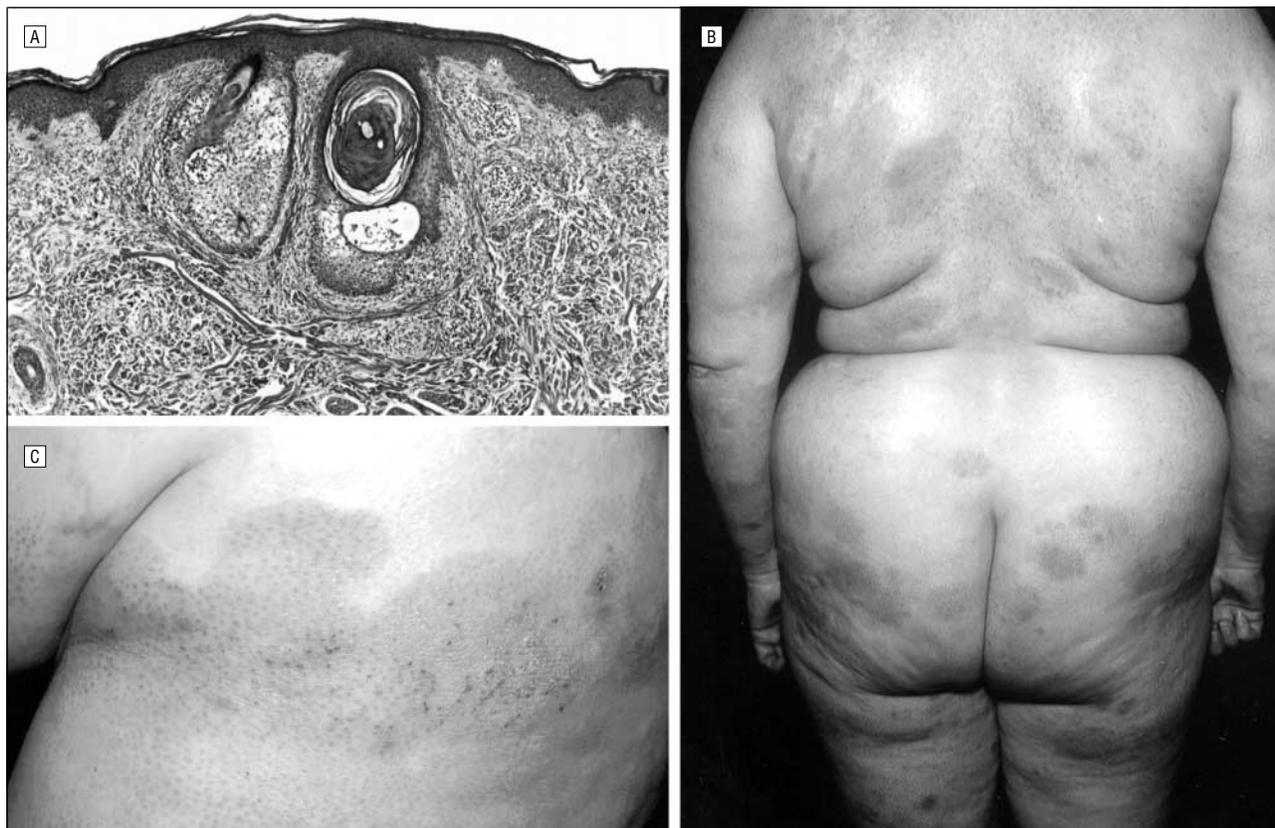
As for lesion location, lesions were present on the face and neck in most patients from both groups, but patients with lymphoma-associated FM showed often concomitant lesions on other areas of the body. In this context, it should be stressed that, contrary to previous suggestions, lymphoma-associated FM is commonly located on the face and neck region,<sup>17,19,53,54</sup> and some patients presenting with isolated lesions of FM on the face afterwards have developed clear-cut mycosis fungoides.<sup>53,55</sup> In short, location alone cannot be considered a valid discriminatory factor.

On the other hand, solitary vs multiple lesions might be a distinguishing characteristic. In our series, solitary lesions at presentation were common in patients with idiopathic FM (11 [68.8%] of 16 patients), but uncommon in those with lymphoma-associated FM (2 [7.1%] of 28 cases). The presence of solitary as opposed to multiple lesions, therefore, might be a distinguishing feature between the 2 groups. However, it should be noted that mycosis fungoides can present with solitary lesions.<sup>56-58</sup> Moreover, a case of folliculotropic mycosis fungoides (though without clear-cut FM) has also been documented with a solitary lesion,<sup>59</sup> and one of idiopathic FM with generalized lesions has been reported as well,<sup>60</sup> again underlying the overlapping clinical features of these 2 entities.

Remarkably, in our study histopathologic analysis did not provide useful clues to differentiate the 2 groups of patients, confirming previous observations.<sup>6,9</sup> In fact, in the group of lymphoma-associated FM, 9 (32.1%) of the 28 patients showed histopathologic features suggestive of idiopathic FM, and 2 more presented with dense lymphoid infiltrates but without epidermotropism of lymphocytes. Conversely, in the idiopathic FM group, 6 (37.5%) of 16 patients revealed skin



**Figure 6.** Lymphoma-associated follicular mucinosis (FM) in patient 40. A, Follicular mucinosis with bandlike infiltrate in the papillary dermis. B, Detail of the epidermis showing epidermotropic lymphocytes.



**Figure 7.** Lymphoma-associated follicular mucinosis (FM) in patient 39. This patient presented first in 1972 with multiple patches on the trunk and upper extremities. A, Histologic findings showed only FM with a mild lymphoid infiltrate and no feature of cutaneous lymphoma. In 1987, 15 years after the first biopsy, the patient presented with widespread patches and plaques with FM (B-C). The patient died in 1989 of widespread mycosis fungoides.

lesions with dense lymphoid infiltrates unusual for this type of FM and suggestive of a cutaneous lymphoproliferative process. Similar dense lymphoid infiltrates have been reported in patients with idiopathic FM, which underscores the overlapping histopathologic features between the 2 groups.<sup>1,6,22,47,61</sup>

The amount of mucin deposits within hair follicles and the presence of eosinophils within the infiltrate were similar in the 2 groups. It is also of interest to note that in 10 cases (35.7%) of lymphoma-associated FM, the diagnosis of CTCL was not made at presentation,

and skin lesions were originally classified as idiopathic FM before analysis of sequential biopsy specimens proved the nature of the infiltrate. A similar case was recently described by Bonta et al.<sup>62</sup> These cases would previously have been classified as idiopathic or persistent FM with transformation into CTCL, but we agree with Hempstead and Ackerman<sup>22</sup> that they most likely represent examples of cases where mycosis fungoides or Sézary syndrome was present from the beginning.

In our study, the immunophenotype was also similar in both groups, and even PCR analysis of the infil-

**Table 3. Clinicopathologic Criteria Used in the Literature for Differentiation of "Idiopathic" From "Lymphoma-Associated" FM and Corresponding Findings in Our 2 Groups of Patients\***

| Criterion                 | Idiopathic FM | Lymphoma-Associated FM |
|---------------------------|---------------|------------------------|
| Mean age, y               | 37.5          | 52.2                   |
| Location on head and neck | 15/16 (93.8)  | 15/28 (53.6)           |
| Solitary lesion           | 11/16 (68.8)  | 2/28 (7.1)             |
| Mild lymphoid infiltrate  | 10/16 (62.5)  | 9/28 (32.1)            |
| Monoclonality             | 6/11 (54.5)   | 9/19 (47.4)            |

\*Unless otherwise indicated, findings are expressed as number (percentage) of patients from each group presenting the given feature. FM indicates follicular mucinosis.

trate could not help differentiate the 2 types. In fact, a monoclonal rearrangement of the *TCR $\gamma$*  gene could be identified in 6 (54.5%) of 11 and 9 (47.4%) of 19 cases of idiopathic and lymphoma-associated FM, respectively, indicating that a monoclonal population of T lymphocytes can be detected in about half of the cases in both groups. These data are in contrast to those reported by Meehan et al.<sup>46</sup> who found no monoclonality in 5 patients with idiopathic FM, but confirm previous observations describing a monoclonal population of T lymphocytes in cases of idiopathic FM.<sup>46,61,63,64</sup>

Besides mycosis fungoides and Sézary syndrome, Hodgkin disease has also been observed in association with FM in several patients.<sup>8,44,65-67</sup> However, the association of Hodgkin disease with mycosis fungoides is well known,<sup>68</sup> and it might be that in at least some of these patients, cutaneous changes represented lesions of mycosis fungoides-associated FM. Indeed, most patients showed clinical presentations uncommon for idiopathic FM: One child described by Gibson et al<sup>44</sup> had a widespread skin eruption involving the upper and lower extremities as well as the face; the child described by Kim and Winkelmann<sup>8</sup> had multiple lesions on the arms and legs; the patient described by Stewart and Smoller<sup>67</sup> had lesions on both legs; and the one described by Ramon et al<sup>65</sup> had multiple lesions on the chest.

One of the main problems in studying patients with FM is the bias introduced by classifying them into one of the 2 main diagnostic groups. In fact, depending on the definition of idiopathic and lymphoma-associated FM in the given case, some patients may be classified into either of the groups, thus causing diagnostic confusion. We used clinicopathologic evidence of CTCL at presentation or during follow-up as the only distinguishing criterion to try to identify a group of patients with benign as opposed to malignant disease. Nevertheless, there was a considerable overlap in clinical presentation, histopathologic features, and molecular data between the 2 groups.

It may be argued that our follow-up for some of the patients with idiopathic FM was too short to rule out lymphoma-associated FM. However, even considering only the 5 patients with more than 9 years of follow-up in the idiopathic FM group (patients 4, 5, 7, 8, and 15; mean follow-up: 191.8 months; range: 111-242 months), a similar overlapping of clinicopathologic features was ob-

served (mean age at onset, 41.6 years; age at onset range, 21-61 years; histologic findings suggestive of CTCL in 2 [40.0%] of 5 cases; monoclonality found in 2 [50%] of 4 tested cases).

At this point, one must question whether idiopathic and lymphoma-associated FM are unrelated diseases (ie, represent 2 completely distinct clinicopathologic entities) or rather different names for a single disease with a variable spectrum of clinicopathologic presentations and outcomes. In this context, it should be noted that several variants of mycosis fungoides with prolonged, nonaggressive clinical course have been described, such as unilesional (solitary) mycosis fungoides, localized pagetoid reticulosis (Woringer-Kolopp disease), and parapsoriasis en plaques.<sup>54,56-58</sup> Moreover, it has also been recognized that most patients with mycosis fungoides experience a chronic disease with prolonged survival.<sup>19,54,69,70</sup> Our results, and findings from review of the literature, suggest that idiopathic FM may represent a variant of mycosis fungoides with localized disease and excellent prognosis, conceptually similar to the localized variant of pagetoid reticulosis (Woringer-Kolopp disease). Regardless of the classification of these cases as "indolent" CTCL or benign inflammatory dermatitis, patients with so-called idiopathic FM should be observed carefully for long periods of time.

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