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Folliculotropic Mycosis Fungoides with Follicular Mucinosis – Case Report

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SUMMARY Reports on clinical and histologic follicular alterations in patients previously diagnosed with mycosis fungoides (MF) or at the time of MF diagnosis are rare. The clinical and histologic criteria to distinguish MF associated with follicular mucinosis from follicular MF are a matter of debate. A patient is described with advanced clinical and histologic alterations predominated by follicular lesions and presence of mucin. In the early stage of the disease, folliculotropism was clinically and histologically present but less pronounced than epidermotropism and classic plaque-like lesions. The patient died four years after the diagnosis. As the term 'folliculotropic' describes a particular histopathologic finding, we consider it correct to use the term "folliculotropic MF" to denote atypical lymphocyte folliculotropism in the absence or presence of mild epidermotropism, presence of mucin, or no evidence for intrafollicular mucin. Folliculotropic MF seems to represent a specific clinicopathologic entity which may have a poorer prognosis than classic MF.

KEY WORDS: mycosis fungoides; mycosis fungoides with follicular mucinosis; follicular mycosis fungoides; folliculotropic mycosis fungoides

INTRODUCTION

Follicular mucinosis can occur as a benign primary 'idiopathic' disorder or as a secondary sequel of various benign or malignant diseases. It mostly occurs in association with cutaneous T-cell lymphoma mycosis fungoides (MF). MF can precede, concur or develop decades after the occurrence of follicular mucinosis. In recent years, the term follicular MF (also folliculocentric or pilotropic MF) has been introduced to denote the rare clinical MF variants characterized by follicular papules, follicular keratosis, comedo-like lesions, and epidermal cysts. Histologically, perifollicular infiltrations with pronounced folliculotropism are found, generally without epidermotropism or follicular mucinosis (1).

We present a patient in whom the classic form of MF was diagnosed at age 67, whereas clinically and histopathologically overt follicular localization of the lesions with follicular mucinosis developed two years later. The patient died four years after the diagnosis.

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CASE REPORT

In a 67-year-old patient, the classic form of MF, stage I A (T1N0B0M0) was diagnosed on his first hospitalization at our Department in July 2000. Until the onset of cutaneous symptoms, the patient was mostly healthy, apart from allergic rhinitis and conjunctivitis in spring he had been suffering from his young age. The clinical picture was predominated by sparsely disseminated, poorly infiltrated and unsharply delineated erythematous plaques (Fig. 1a). Histology of the skin biopsy revealed dense infiltration with atypical lymphocytes, along with epidermotropism and Pautrier's microabscesses (Fig. 1b). Besides epidermotropism, the nuchal region skin biopsy (Fig. 2a) also showed folliculotropism without mucin formation (Fig. 2b). Upon examinations and staging of the disease, two-month therapy with peroral photosensitizer and UVA (PUVA) in combination with local corticosteroid was initiated, which resulted in almost complete disappearance of the lesions.

In June 2002, the patient was rehospitalized for intense pruritus, subtotal alopecia and disseminated follicular skin-colored papules with follicular keratosis and mucinorrhea. The follicular papules were densely grouped in the nuchal and lateral trunk regions (Fig. 3a and 3b). Physical examination revealed bilateral lymphadenopathy of the inguinal region and palpable liver by 2-3 cm in MCL. Routine biochemistry testing indicated mild leukocytosis (10.4-11.3), eosinophilia in differential blood count (23%-32%), lymphopenia (11%-17%) and an increased level of lactate dehydrogenase (LDH 615; normal <460), whereas other findings were within the normal limits. Histology of the nuchal skin biopsy showed large follicles with keratin, dense and mostly perifollicular infiltrates composed of atypical lymphocytes with folliculotropism (Fig. 4a) and numerous eosinophils in the infiltrate. Intrafollicularly, there were large areas of mucinous degeneration (Fig. 4b) that were alcian blue positive (Fig. 4c) and PAS negative. Immu-

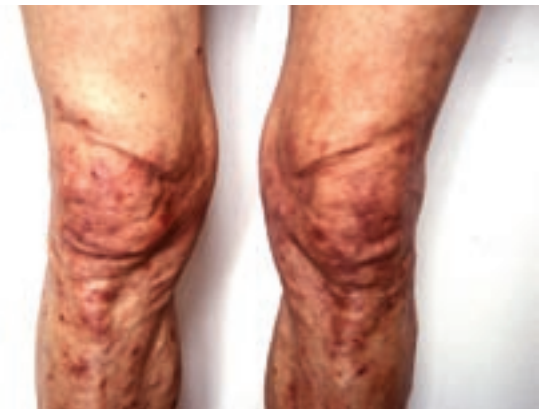

Figure 1a. Erythematous, sparsely infiltrated plaques on lower limbs, at the time of the "plaque stage" mycosis fungoides diagnosis.

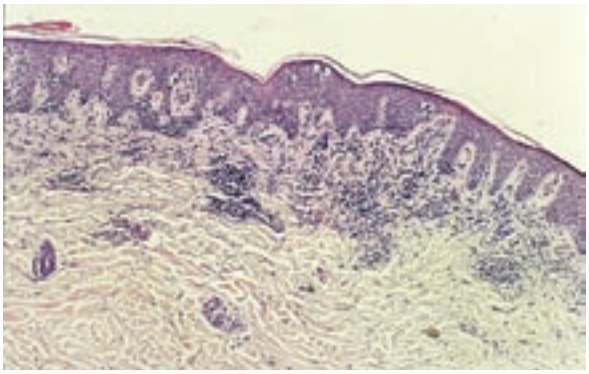

Figure 1b. Dense, almost thread-like infiltrate of atypical lymphocytes in the dermis, with Pautrier's microabscesses, at the time of diagnosis (H&E staining, original magnification x40).

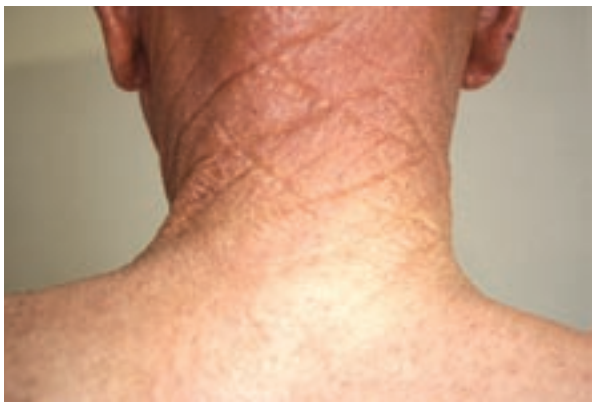

Figure 2a. Confluent follicular papules forming an occipital plaque, at the time of diagnosis.

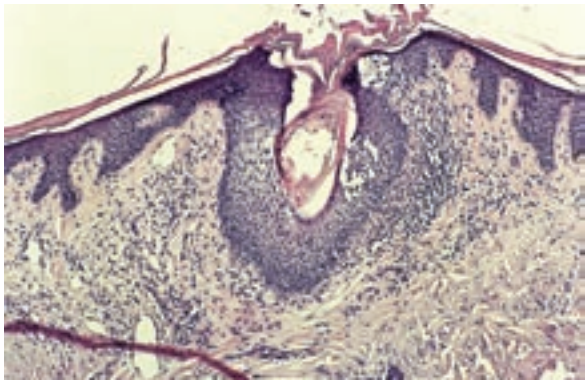

Figure 2b. Pautrier's microabscesses in the infundibular segment of hair epithelium, with dense perifollicular infiltration, at the time of diagnosis (H&E staining, original magnification x40).

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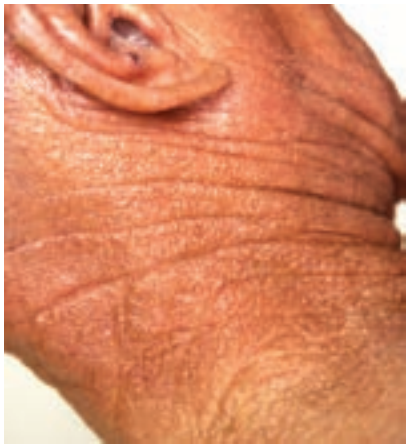

Figure 3a. Pronounced follicular localization of papules with clinically overt mucinorrhea on lateral aspects of the neck, two years of the diagnosis.

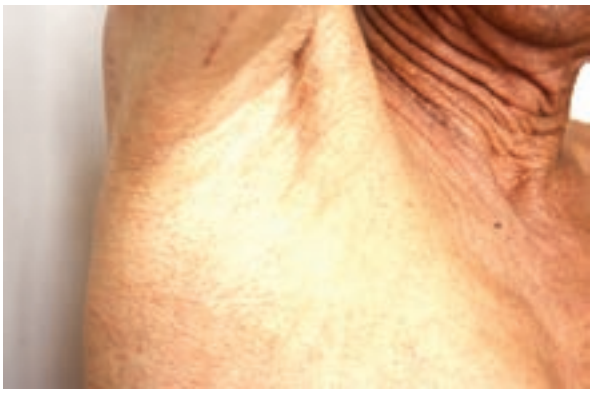

Figure 3b. Follicular pin-size papules, densely and uniformly distributed on lateral aspects of the trunk, two years of the diagnosis.

nohistochemistry pointed to the CD3+CD4+CD8- lymphocyte phenotype (Fig. 4d and 4e).

X-ray, ultrasonography and computed tomography of the chest, abdomen and pelvis showed no lymph node enlargement. Biopsy specimen of a clinically enlarged lymph node in the right inguinal region showed occasional lymphatic cells with polymorphic nuclei, thus extirpation and histopathologic examination of the lymph node were performed to reveal only architectural lymph node impairment in terms of paracortex expansion with no mycosis cells. There were no Sézary cells in peripheral blood smears. Bone marrow biopsy showed a more intense cellularity with regular relations and appearance of all three cell lines. The disease staging was IIA (T2N1B0M0) and therapy included retinoid (acitretin) with PUVA (RePUVA) with minimal effect. Remission of pruritus and flattening of the papules with partial hair growth occurred upon the introduction of peroral corticosteroids at a dose of 32 mg with dosage tapering, and methotrexate 2.5 mg daily, prescribed in consultation with a hematologist. As reported by his family members, the patient was treated for pneumonia at Department of Medicine – Hematology at the end of 2003. The patient died in mid-2004.

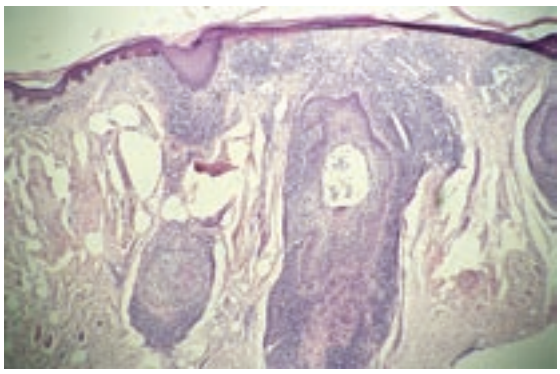

Figure 4a. Dense, deep, predominantly peri- and infrafollicularly localized infiltrates of atypical lymphocytes without epidermotropism, two years of the diagnosis (H&E staining, original magnification x40).

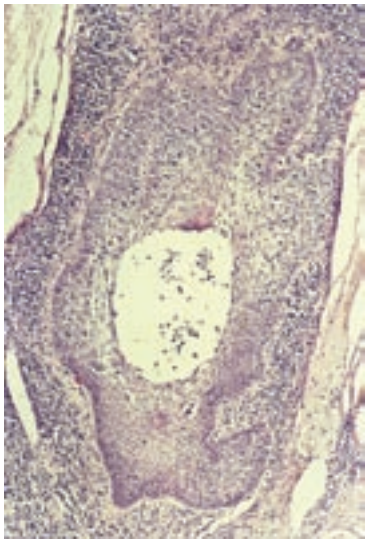

Figure 4b. Mucinous degeneration of hair epithelium, two years of the diagnosis (H&E staining, original magnification x80).

DISCUSSION

MF has a plethora of clinicopathologic manifestations. Many variants of this lymphoma differ substantially from the classic Alibert-Bazin disease and are therefore sometimes referred to as “atypical” forms of the disease (2) or may mimick other dermatoses (3). In spite of this heterogeneity,

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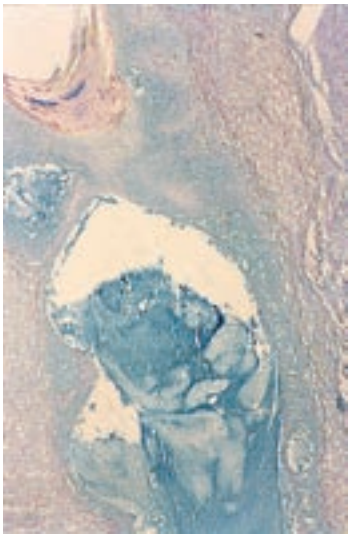
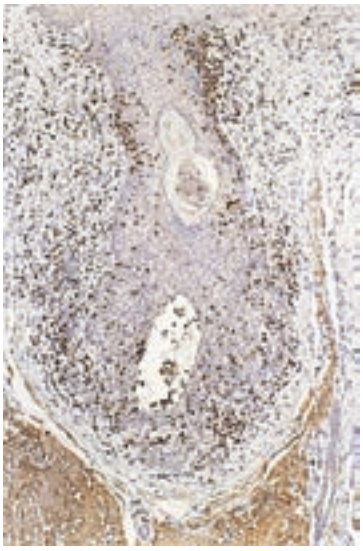
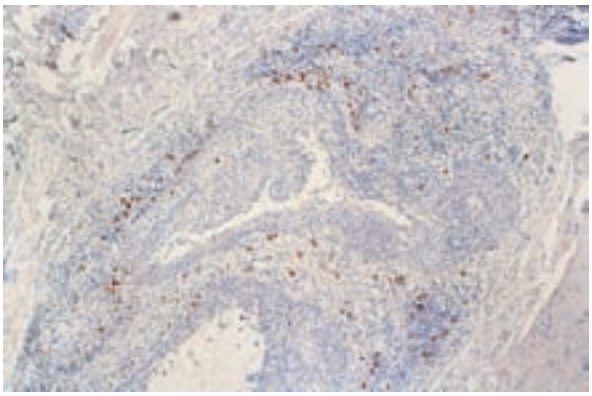


Figure 4c. Blue stained material represents positive reacting mucin (alcian blue staining, original magnification x80).



Figures 4d and 4e. Immunohistochemistry: the majority of atypical lymphocytes were CD4+ and CD8- (APAAP).



the clinical variants such as bullous MF, hypo- or hyperpigmented MF have the clinical course in common with classic MF, thus they are not considered specific MF variants. Unlike these forms, MF associated with follicular mucinosis and pagetoid reticulosis have specific clinicopathologic features with the course and prognosis different from classic MF, thus being categorized as specific MF variants according to the European Organization for Research and Treatment of Cancer (EORTC) classification (4).

Traditional descriptions of MF associated with follicular mucinosis are characterized by the presence of folliculotropic infiltrate and mucous degeneration of hair follicles (follicular mucinosis) with epidermotropism and Pautrier's microabscesses. Such cases of follicular mucinosis associated with MF should be distinguished from so-called idiopathic follicular mucinosis; however, there are different opinions about the issue (5-7). Additional studies are necessary to elucidate the relationship between MF associated follicular mucinosis and idiopathic follicular mucinosis. The relationship between follicular mucinosis and MF has not yet been fully clarified either. Cases of MF diagnosis with clinical and histologic (predominantly or exclusively) follicular involvement but without follicular mucinosis have been described as folliculocentric, pilotropic and follicular MF (8-19). The absence of mucin and complete lack of epidermal involvement with neoplastic infiltration were the specific criteria upon which some authors based the diagnosis of follicular MF (8-14,17,19), whereas others did not insist on these criteria, admitting the diagnosis of follicular MF also in the presence of mucin (15,16,18) and/or epidermotropism (8), and concurrent presence of classic MF lesions (9,10). Until the study performed by van Doorn *et al.* (20), these were mostly isolated reports or studies in small patient samples. Some authors used to emphasize the malignant and progressive course of follicular MF with rapid progression to lymph nodes (16) or transformation to high malignancy lymphoma (13). Recent studies have shown that there are no differences in the clinical picture and clinical course between folliculotropic MF with and without associated follicular mucinosis (21). In order to avoid terminological confusion, the new World Health Organization – European Organization for Research and Treatment of Cancer (WHO-EORTC) classification prefers the term folliculotropic MF for all MF variants characterized

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by the presence of folliculotropic infiltrate irrespective of mucin. Biologically, the presence of deep follicular and perifollicular infiltrates of neoplastic lymphocytes is of utmost importance, lowering the efficacy of traditional skin therapy such as PUVA and RePUVA. In contrast to classic MF, the clinical picture of folliculotropic MF is predominated by follicular localization of lesions, e.g., grouped follicular papules, follicular keratosis, epidermal cysts, acneiform lesions, indurated plaques, and occasionally tumors mostly involving the head and neck. Cutaneous lesions are associated with alopecia and occasionally with mucinorrhea. Unlike classic MF, pruritus is severe and may frequently serve as a good parameter to assess the disease progression. Histopathology reveals primarily perivascular and periadnexal localization with variable infiltration of follicular epithelium with small, medium and large hyperchromatic lymphocytes with cerebriform nuclei and sparing epidermis (folliculotropism instead of epidermotropism). Follicular mucinosis is found in most cases, which is demonstrated by alcian blue stain. In 70%-80% of patients with folliculotropic MF, the prognosis (disease specific 5-year survival) is comparable to the prognosis of classic tumor stage MF but is much worse in patients with classic "plaque stage" disease. The Netherlands Group for Lymphomas classifies patients with follicular MF as tumor stage disease irrespective of the clinical appearance of the lesions (20).

Due to therapeutic resistance, total skin electron beam irradiation (TSEB) is recommended as therapy of choice for follicular MF (20,21).

We are inclined to believe that it was a case of classic MF conversion to the folliculotropic form of MF with follicular mucinosis rather than follicular MF, which has defined clinical and histologic criteria. As reported by van Doorn *et al*., in follicular MF the lesions mostly involve the head and neck, but there are no (or very few) more or less infiltrated plaques on the trunk and thighs or atypical T-lymhocyte epidermotropism.

Although the exact cause of death remained unknown and could only be speculated (e.g., extracutaneous dissemination of the disease, transformation to lymphoma of high grade of malignancy, complications of immunosuppressive therapy), the fact is that the patient died four years after the diagnosis, suggesting a highly aggressive and progressive course of the disease with therapeutic complications, which is consistent with the known data on worse survival prognosis in patients with folliculotropic MF. We also consider that follicular MF (as defined according to van Doorn's criteria) and "MF associated follicular mucinosis" belong to the spectrum of MF with hair follicle as a predilection site, thus this type of MF should preferably be termed folliculotropic MF for practical reasons, primarily for patient follow up, proper choice of therapy, and prognosis.

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