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CASE STUDY

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Diagnostics difficulties in mycosis fungoides — a case report

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ABSTRACT

Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma (CTCL) accounting for more than 50% of all CTCL. Its diagnosis still poses great diagnostic difficulties. Because MF is a heterogeneous disease with a slow course and similarities to many benign cutaneous dermatoses, diagnosis can be particularly complicated in the early stages. Here, the authors would like to present a 31-year-old woman who was diagnosed with an erythrodermic form of MF 5 years after the onset of the first symptoms. During the diagnostic process, 5 skin biopsies were taken within 3 years, and their histopathological picture only presented features of chronic inflammatory conditions, such as atopic dermatitis, and pityriasis rubra pilaris (PRP). Due to the erythroderma, the ineffectiveness of previous treatment and lymphadenopathy, a lymph node biopsy was performed. Histopathological examination revealed the presence of Sezary cells, and a diagnosis of MF was eventually made. Interestingly, the assessments of skin biopsies were very inconclusive. Since the prognosis decreases dramatically with the progression of the disease, the importance of early diagnosing MF should be emphasized, however, it should also be stressed that in some patients the diagnosis is difficult to establish and can be delayed for many years.

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Key words: mycosis fungoides, Sezary syndrome, erythroderma

INTRODUCTION

Mycosis fungoides (MF) and Sezary syndrome belong to the group of primary cutaneous T-cell lymphomas (CTCL) derived from a cluster of differentiation 4 (CD4+), CD45RO+ memory cells. The peak incidence of MF is between the ages of 55 and 60 years, but it can be even observed in children and adolescents. The annual incidence in Europe is estimated to be about 0.2–0.37 cases per 100,000 inhabitants, but the number of cases may be underestimated [1]. MF is a low-grade lymphoma characterized by the clonal proliferation of skin-resident epidermotropic T-cells. The aetiology remains not fully understood, but it is suggested that it results from chronic antigenic stimulation, which may lead to the accumulation and proliferation of abnormal T-cells in the skin. According to previous studies, the cells involved in the pathogenesis of MF are mainly CD4+ lymphocytes and demonstrate the reduction or absence of several antigens, such as CD5, CD7 and CD26, but other phenotypes are also possible [2].

Mycosis fungoides, despite significant advances and wider diagnostic possibilities, remain a great diagnostic difficulty. Delayed diagnosis results from the heterogeneity of its variants, the slow, often hidden course and the diversity of its histopathological features. Skin lesions in MF can be difficult to differentiate from benign dermatological skin conditions. In the initial stage, the disease usually manifests as erythematous skin patches and plaques without signs of subcutaneous involvement, located mainly in areas of the skin protected from the sun [3, 4]. In the more advanced stages, skin tumours and/or erythroderma with possible involvement of extracutaneous tissues are observed (stage IIB–IVB) [5, 6]. Lymphoma cells may also spread to lymph nodes, blood, bone marrow and internal organs [7]. In addition, erythrodermic MF can also be undistinguishable from Sezary syndrome, another variant of CTCL. As MF remains a disease characterized by localized growth in the early stages and an aggressive course with a poor prognosis in the advanced stages, prompt diagnosis is important. This report presents a case of a 31-year-old woman who was diagnosed with an erythrodermic form of MF as late as 5 years after the onset of the first symptoms to emphasize the difficulties of MF diagnosis, because of the similarity to other benign dermatoses.

CASE STUDY

A 31-year-old woman was admitted for the first time to the Dermatology Clinic in Italy in February 2020 because of disseminated erythematous skin lesions. Based on the

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medical history, the first erythematous papules appeared 2 years earlier, i.e. in 2018, on the lower limbs, and over time they covered the trunk, upper limbs, hands and feet. Based on the clinical course and skin manifestation of the disease, the diagnosis of atopic dermatitis was suggested. The systemic treatment with prednisone (initially 50 mg/d, then 25 mg/d), as well as local treatment with betamethasone and mometasone were implemented between February and October 2020 (Fig. 1). In April 2020, due to a rather poor improvement after the applied treatment, the first skin biopsy was performed. The histopathological examination showed features corresponding to atopic dermatitis. The second skin biopsy was conducted in July 2020 and the image of the skin sample confirmed the previously established diagnosis of AD. The immunophenotype of the lymphocytes in the infiltrate was as follows: CD4+, CD2+, CD3+, CD5+, CD7+, TCRAB+/TCRGD–. In addition, a bone marrow biopsy, positron emission tomography/computed tomography (PET/CT), as well as immunophenotyping of peripheral blood, were performed to exclude lymphoma, but these investigations did not confirm a proliferative aetiology of the disease. In August 2020, treatment with cyclosporine at a dose of 300 mg/d has been implemented. The drug was discontinued a month later due to side effects reported by the patient such as stomach pain and nausea. The dermatological therapy also included 5 cycles of ultraviolet B (UVB) phototherapy, still without clinical improvement. Due to the lack of a therapeutic effect, it was decided to start the biological treatment; in September 2020 the first dose (300 mg) of dupilumab was applied and, in total, the patient received 7 doses of the drug with moderate clinical improvement.

In January 2021, the patient moved to Poland and was admitted to the Department of Dermatology in Rzeszow. On admission, erythroderma was observed (Fig. 2), with the presence of erosions in the intertriginous areas, erythema on the face and hyperkeratosis of the hands and feet. A skin biopsy was performed, which revealed lymphocytic infiltrates without atypia (T-cell phenotype: CD3+, CD4–, CD5+, CD7+, few CD9+, CD20–, CD30–) with the presence of

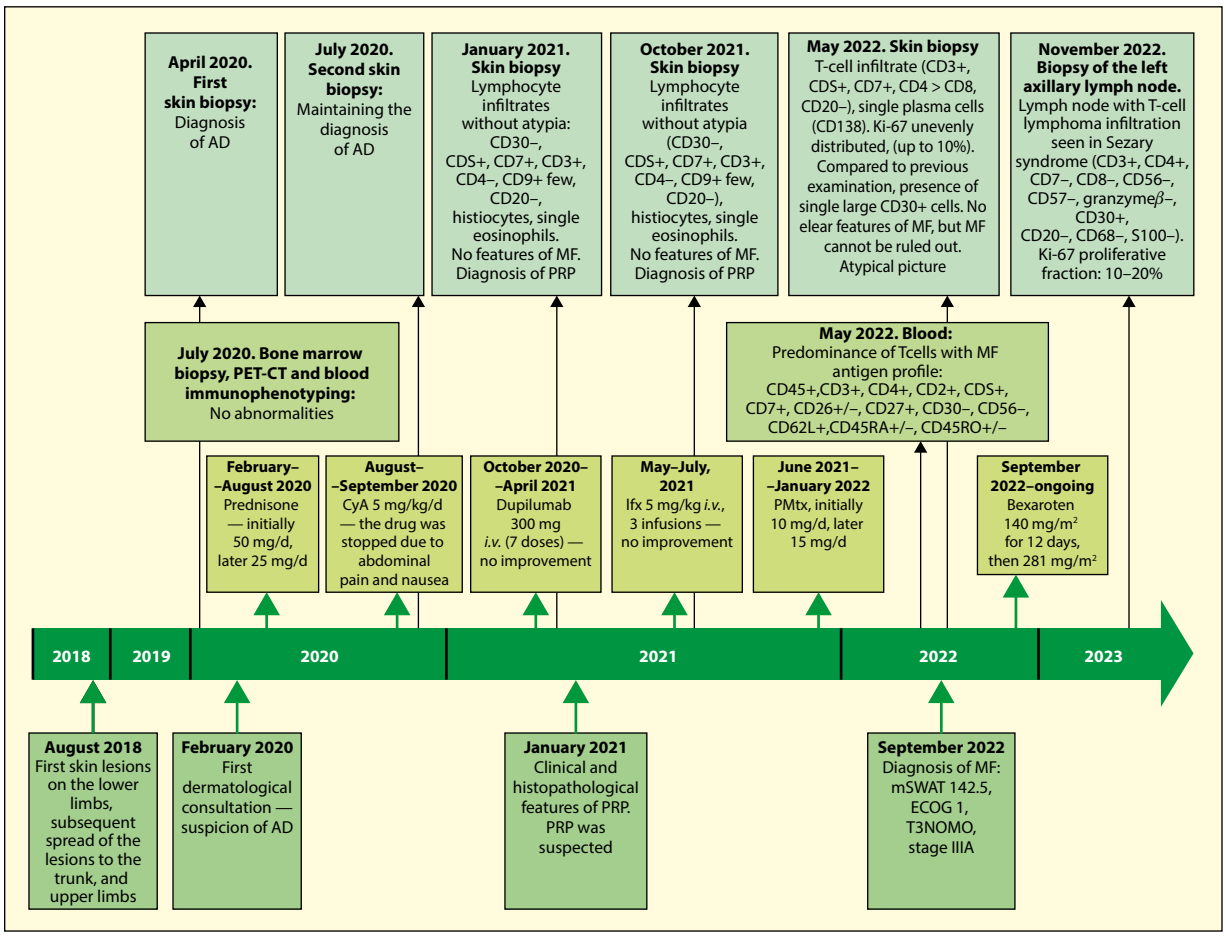

Figure 1. The graphic presentation of the medical history of the presented patient; AD — atopic dermatitis, CyA — cyclosporine A; ECOG — Eastern Cooperative Oncology Group; Ifx — infliximab, mSWAT — Modified Severity-Weighted Assessment Tool; Mtx — methotrexate, PRP — pityriasis rubra pilaris)

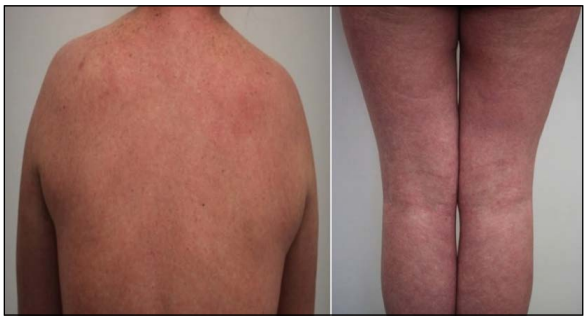

Figure 2. Erythroderma. Clinical presentation of classical early mycosis fungoides. Based on performed skin biopsy a diagnosis of ityriasis rubra pilaris was made

histiocytes and single eosinophils (Fig. 3A, 3B). No histological features of MF were noted. Chest X-ray and sonography of the abdominal cavity showed no abnormalities. Based on the conducted examinations and the clinical presentation, a diagnosis of pityriasis rubra pilaris (PRP) was proposed. Due to the severity of the disease, the lack of improvement after previous treatments and contraindications to acitretin (the patient planned to become pregnant) dupilumab was discontinued and infliximab, a tumour necrosis factor (TNF) inhibitor was implemented in a dose of 300 mg *i.v.*/d, which the patient used from May 2021 to July 2021, in combination with methotrexate at a dose of 10 mg/d initially, and then

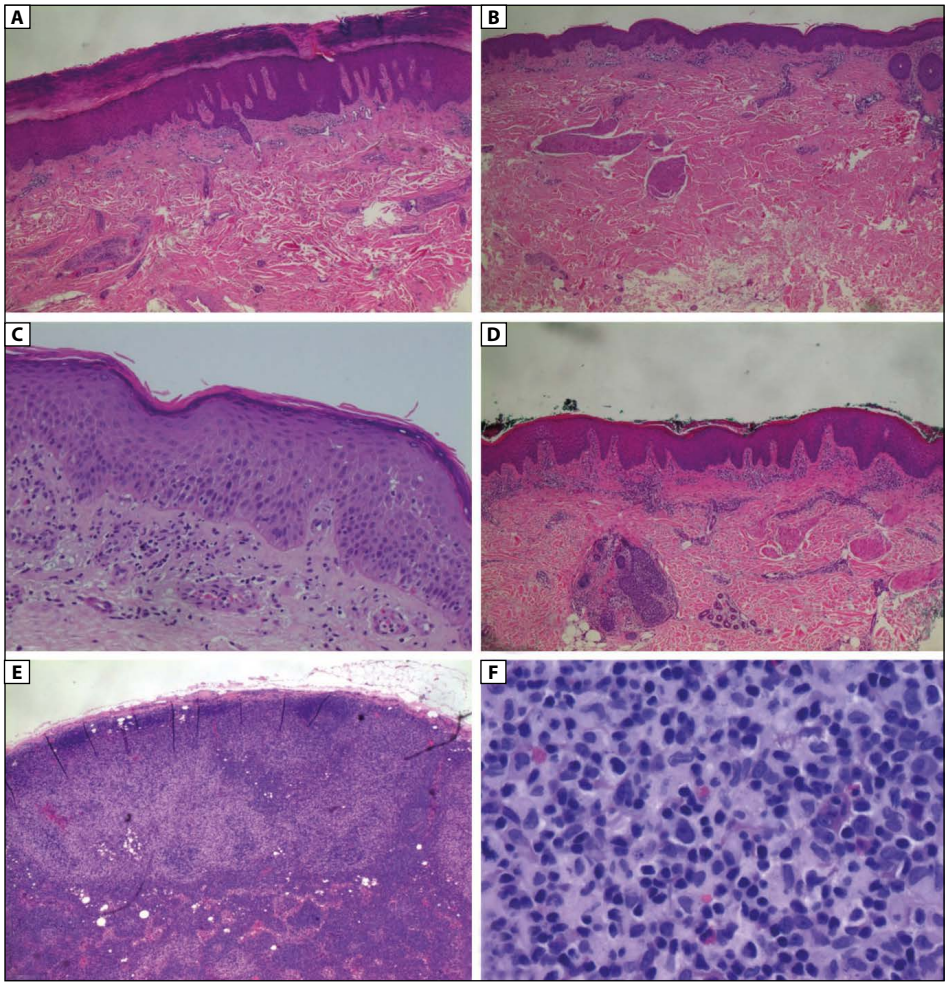

Figure 3. Histopathological picture of the performed skin biopsies; **A. Skin biopsy from January 2021**. The acanthotic epidermis, hyperkeratosis, expanded granular layer. Within the dermis, mainly in the papillary layer and the superficial layer of the reticular layer, sparse inflammatory infiltrates composed of lymphocytes without atypia and few plasmocytes. The infiltrates are arranged mainly around small vessels with a dilated lumen and do not penetrate deep into the epidermis (original magnification ×10); **B. Skin biopsy from January 2021**. Epidermis with irregular, mild acanthosis, keratosis and irregular parakeratosis. Perivascular and diffuse inflammatory infiltrates composed of lymphocytes without atypia, few histiocytes and plasma cells in the upper layers of the dermis and around the skin appendages (original magnification ×10); **C**. **Skin biopsy from October 2021**. A fragment of the skin covered with poorly developed acanthotic epidermis, with slight keratosis and focal parakeratosis. In the dermis, mainly in the superficial layer, sparse inflammatory infiltrates, scattered and arranged around the vessels, composed of lymphocytes without atypia, histiocytes, and few eosinophilia. Single lymphocytes, also without atypia, penetrate the epidermis, which is accompanied by intercellular oedema (original magnification ×20); **D**. Skin biopsy from May 2022: Epidermis with features of spongiosis. In the dermis, the subepithelial inflammatory infiltrate is composed of mononuclear cells (T-cells, single plasma cells) without epidermotropism. Atypical picture, cannot exclude mycosis fungoides (original magnification ×10); **E**. **Lymph node biopsy from November 2022**: Lymph node with T-cell lymphoma infiltration (original magnification ×10); **F**. **Lymph node biopsy from November 2022:** Evident Sezary cells in the analysed lymph node (original magnification ×40)

15 mg/d from June 2021 to January 2022, with a moderated therapeutic effect. The fourth skin biopsy was performed in October 2021. At that time, the histopathological examination of the skin of the lower limb again showed dispersed lymphocyte infiltrates without atypia (CD3+, CD4–, CD5+, CD7+, few CD9+, CD20–, CD30–) around the vessels in the dermis, histiocytes, and single eosinophils (Fig. 3C). The histopathological picture did not allow to make the diagnosis of MF despite the clear suggestion from the treating physicians. The previous diagnosis of PRP was maintained. In May 2022, the fifth skin biopsy was performed. The examination of a skin biopsy showed a moderately abundant infiltration of T-cells with the phenotype of CD3+, CD5+, CD7+, CD4+>CD8+, CD20– and single plasma cells CD138+ (Fig. 3D). Ki-67 antigen was unevenly distributed and present in up to 10% of cells. Compared to previous examinations, single larger CD30+ cells were evident. Immunophenotyping of the blood was also performed and showed a predominance of T lymphocytes with an antigen profile corresponding to MF cells: CD45+, CD3+, CD4+, CD2+, CD5+, CD7+, CD26+/–, CD27+, CD30–, CD56–, CD62L+,CD45RA+/–, CD45RO+/. In September 2022, it was decided to perform a biopsy of the left axillary lymph node for histopathological examination. T-cell lymphoma infiltrate within the lymph nodes was described (Fig. 2E, 2F). The T-cells presented the CD3+, CD4+, CD7–, CD8–, CD56–, granzyme B–, CD30+, CD68–, S100– phenotype. Ki-67+ proliferative fraction was 10–20%. Finally, CTCL (an erythrodermic form of MF) was diagnosed in stage IVA, T3N3M0B2, MSWAT (Modified Severity-Weighted Assessment Tool) 142.5. In September 2022, bexarotene treatment was started, initially at a dose of 140 mg/m^2 for 12 days, and then 281 mg/m^2. Currently, the patient is being planned to undergo allo-PBMSC (allo-peripheral blood mononuclear cell).

DISCUSSION

MF is the most common primary cutaneous lymphoma rated as more than 50% of total CTCL cases in the United States between 2000 and 2017 [4]. Although it appears relatively often in comparison to other cutaneous lymphomas, its diagnosis may be difficult in the early stages. MF is a heterogenic disease characterized by a slow course, which often demonstrates similarity to many benign skin dermatoses, particularly, in the early stages. According to the literature, MF can be differentiated from at least 50 different disease entities [8]. Typically, MF begins with patches, which, after months to years, can develop into thick plaques and tumours [9]. Erythrodermic MF (eMF) has also been reported, which is considered a progression of MF and is characterized by concomitant erythroderma and the absence or very low number of atypical T-lymphocyte characteristic for Sezary syndrome. Both SS and eMF may be accompanied by symptoms such as hair loss or ectropion, which may help the clinicians to make the correct diagnosis, but other features, such as pruritus or dry skin, may be ambiguous due to their frequent occurrence in other chronic dermatoses or the elderly people [10].

As the prognosis and estimated life expectancy decrease dramatically with the advancement of the MF, early diagnosis is an important prognostic factor and has a great impact on the patient's quality of life. One study showed that the risk for disease progression within 5 years was 10% in T1, 22% in T2, and 48% to 56% in T3 to T4 stages according to TNM classification [11]. Based on various studies, MF in its initial stage is often misdiagnosed with inflammatory skin diseases, such as atopic dermatitis or eczema. There have also been reports of cases where MF was initially diagnosed as lichen sclerosus, pyoderma gangrenosum, granulomatous rosacea, pityriasis rubra pilaris, keratosis punctata palmaris, seborrheic dermatosis, psoriasis inversa or plaque-type psoriasis [8, 12].

Diagnostic difficulties are not only created by its clinical course and manifestation but also in histopathological examinations, as the current case presents. Skin biopsy is not always a determinant of disease diagnosis, although it may present some features that could lead us to correct disease recognition. The specific histopathological features of MF include malignant infiltrate composed of small or medium-sized atypical lymphocytes with cerebriform nuclei and associated clear cytoplasm, called "halo effect", and the presence of clusters of malignant lymphocytes called Pautrier's microabscesses within epidermis [13]. However, in previously conducted studies, it was found, that despite numerous skin biopsies, the results are often ambiguous, and it is hardly possible to establish an unequivocal diagnosis [14, 15]. One study reported a delay in making the diagnosis in 86% of enrolled patients, with a median delay of 3 years (range 1–7.5 years) [6]. In addition, Skov et al. [15] in their retrospective study described the results of biopsies in patients with MF, in which the final histological diagnosis was made only in 25% of cases after the first biopsy, while in 29% of patients, the histological diagnosis of MF was never established despite more than one biopsy [7]. Another study revealed that two forms of MF (psoriasiform and palmoplantar) were misdiagnosed and treated as psoriasis or eczema for an average of 10.5 years [9]. Massone et al. [16] described in their study, that in 28 patients two or more biopsies conducted on the same day at different body sites were characterized by different histopathological features. Moreover, among 745 biopsies taken from 427 patients with MF, only 9% revealed atypical lymphocytes and 19% showed Pautrier's microabscesses, which are thought to be pathognomic histopathological features for MF. An additional impediment was the presence of features of interface

dermatitis, such as spongiosis in 59%, which could weaken the oncological vigilance [16]. In some cases, pathologic criteria alone may be not sufficient to diagnose the early stage of MF suspected based on morphologic findings.

To sum up, the early diagnosis of MF is a significant diagnostic problem, both due to the uncharacteristic clinical picture in the early stage of the disease and the often ambiguous results of diagnostic examinations, including skin biopsy, which is not always unequivocal. As the prognosis decreases dramatically with the progression of the disease, a multidisciplinary approach to the patient is important. In addition, one has to take into account the indications that may suggest the diagnosis of MF, especially in the case when classic dermatological therapy is ineffective.

Conflict of interest

The authors report no competing interests.

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