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Poikilodermatous Mycosis Fungoides – Rare Entity, Different Treatment Modalities

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ABSTRACT Poikilodermatous mycosis fungoides (PMF) is a rare clinical variant of early-stage MF with peculiar histological features. Poikiloderma occurs in many different clinical conditions, which makes a diagnostic procedure more complicated. PMF belongs to a group of MF variants with low risk of disease progression. We report a case of a 64-year-old woman, who presented with mottled skin aspect of erythema, poikilodermatous patches (hypopigmentation, hyperpigmentation, atrophy, and telangiectasia) on more than 80% of the body. Based on clinical, histopathological, and immunohistochemical findings, we established the diagnosis of PMF. Staging procedure determined stage IIA. As skin-directed therapy was the treatment of choice, the patient was successfully treated with psoralen-UVA (PUVA), nbUVB plus retinoid (Re-nbUVB), and PUVA plus retinoid (Re-PUVA), however, with rapid recurrence.

KEY WORDS: cutaneous T-cell lymphoma, poikilodermatous mycosis fungoides, *poikiloderma vasculare atrophicans*, poikiloderma

INTRODUCTION

Mycosis fungoides (MF) is the most common type of cutaneous lymphoma. MF shows varieties in both its clinicopathological presentation and immunophenotype. Poikilodermatous mycosis fungoides (PMF), also called *poikiloderma vasculare atrophicans* (PVA), is a rare clinical variant of early-stage MF, characterized by localized or diffuse large macules and patches of mottled hypopigmentation and hyperpigmentation with atrophy and prominent telangiectasia (poikiloderma). Lesions have a predilection for the trunk (especially breasts) and buttocks, but they may be generalized (1,2). Rarely, the retiform pattern of atrophic patches occurs, which was previously termed *parakeratosis variegata* (3). Some authors define PVA as a clinicopathological entity distinct from PMF because PVA has CD8+ T-cell infiltrate and a long benign course (4). PMF usually presents at a younger age than classic MF and is more frequently associated with lymphomatoid papulosis (5). The lesions may be asymptomatic, rarely mildly pruritic, or with a stinging sensation. Histological findings in PMF are: atrophic epidermis, loss of rete ridges, band-like infiltrate of lymphocytes, epidermotropism, dilated capillaries, necrotic keratinocytes, pigment incontinence, and a thickened papillary dermis (2). Histopathological and immunological features of PMF are similar to those of

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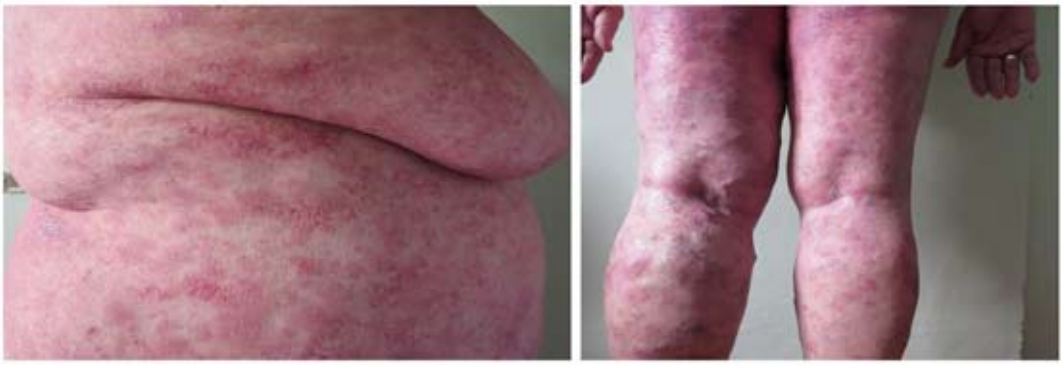

Figure 1. Clinical findings: mottled skin aspect of erythema, patches with hypopigmentation, hyperpigmentation, atrophy, and telangiectasia (poikiloderma) involving more than 80% of the body surface.

classic MF in early stages with $CD2^+$, $CD3^+$, $CD4^+$, CD7, $CD45RO^+$, $CD8^-$ T-cell immunophenotype, although some recent studies and case reports suggest a cytotoxic phenotype ($CD8^+$, $CD4^-$, $CD56^+$) (5). Poikiloderma occurs in many clinical conditions that should be considered in differential diagnosis: dermatomyositis, lupus erythematosus, systemic sclerosis, pigmented atrophic lichen planus, poikiloderma of Civatte, xeroderma pigmentosum, Kindler syndrome, etc.(4). Treatment of PMF depends on disease stage, patient age, and general health, and includes both skin-directed and systemic treatments. PMF has a lower risk of disease progression and better survival, just like hypopigmented MF, when compared with other clinical variants of MF (6).

CASE PRESENTATION

We report a case of a 64-year-old woman who presented to our Dermatology Department with mottled skin aspect of erythema, patches with hypopigmentation, hyperpigmentation, atrophy, and telangiectasia localized on the trunk and upper and lower extremities involving more than 80% of the body surface (Figure 1). She complained of itching and reported first lesion onset at age 59 on her right breast followed by similar lesions on the abdomen, with periods of almost complete remission after sun exposure. Her personal and family medical history was without significance for diagnosis. Two biopsy specimens were taken from lesions in the gluteal and presternal region. Histopathology revealed epidermotropism with Pautrier's microabscesses (PMAs), basal alignment of atypical lymphocytes, and lichenoid dermal infiltrate of atypical lymphocytes (Figure 2). Immunohistochemical evaluation showed small atypical $CD3^+$, $CD4^+$, $CD2^+$, $CD5^-$, $CD7^-$ T-lymphocytes in the dermis and epidermis and scattered $CD8^+$ lymphocytes within the epidermis (Figure 3). The diagnosis of PMF was established according to clinical findings, histology, and immunohistochemistry. Computed tomography (CT) scans of the thorax, abdomen, and pelvis, as well as aspiration of the sternal bone marrow for cytological assessment were performed to determine the stage of the disease. Laboratory data: C-reactive protein (CRP) 11.1 (normal range 0.0-5.0mg/L), lactate dehydrogenase (LDH) 173 (normal <240 U/L), triglycerides 3.8 (<1.7 mmol/L). Only reactive lymphadenopathy was found (axillary lymph nodes and inguinal up to 1.3 cm × 1cm, histologically uninvolved). As investigations excluded extracutaneous disease involvement, PMF stage IIA (T2N1M0) was determined. We decided to start PUVA therapy: UVA irradiation two hours after oral administration of 8-methoxypsoralen (8-MOP) 40 mg/daily. The patient received a cumulative UVA dose of 21.5 J/cm^2 during a course of 13 exposures that resulted in only partial regression of erythema and induration.

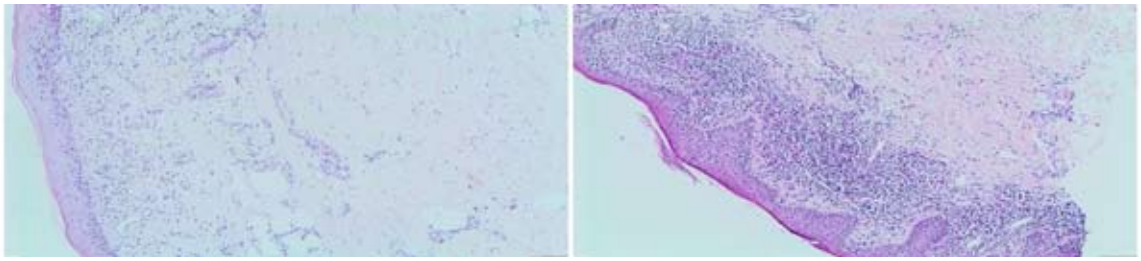

Figure 2. Histological features: atrophic and flattened epidermis, dilated blood vessels, epidermotropism, basal alignment of atypical lymphocytes, and lichenoid dermal infiltrate of atypical lymphocytes (hematoxylin and eosin, ×10).

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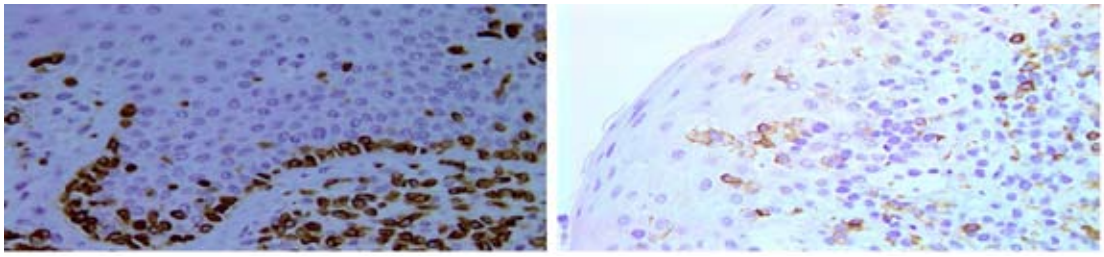

Figure 3. Immunohistochemical features: tumor cells show epidermotropism with diffuse expression of a) CD3, b) CD4 (immunohistochemistry CD3 and CD4, ×40).

Subsequently, we decided to add oral retinoid (acitretin 30 mg/daily) and perform Re-PUVA with the additional local application of betamethasone cream twice daily for two weeks. The patient received an additional cumulative UVA dose of 7.5 J/cm^2 during a course of another nine exposures that resulted in complete regression of erythema and loss of induration.

The patient was readmitted to the hospital due to recurrence of skin lesions after five months. This time she was treated with PUVA therapy and received a cumulative UVA dose of 8.5 J/cm^2 during a course of eight exposures, but the therapy was discontinued due to unavailability of 8-MOP on the market. Therefore, combined treatment with acitretin (initial dose of 50 mg/daily) and nbUVB phototherapy (Re-nbUVB) was started. Betamethasone cream was applied twice daily for two weeks. The patient received a cumulative nbUVB dose of 5.8 J/cm^2 during a course of eleven exposures that resulted in complete regression of erythema and partial loss of induration.

Due to worsening of the disease in the form of erythema, poikilodermatous patches, and plaques, pityriasiform desquamation on the upper eyelid and scalp, and clinically enlarged submandibular lymph nodes, the patient was admitted for the third time to the hospital after eleven months. Laboratory data showed CRP 13.1 (normal range 0.0-5.0 mg/L), LDH 208 (normal <240 U/L), leukocytes 10.9 (3.4-9.7 10e9/L), triglycerides 2.92 (<1.7 mmol/L). The whole staging procedure was performed again. CT scans revealed reactive inguinal and axillary lymphadenopathy (right axillary lymph nodes up to 1.9 cm × 1.3 cm, left axillary lymph nodes 1.8 cm × 1.1cm, left inguinal lymph nodes up to 1.8 cm × 1.4 cm, histologically uninvolved). PMF stage IIA (T2N1M0) was determined. The patient was referred to a hematologist for consultation. Due to a lack of signs of extracutaneous disease propagation, the hematologist recommended PUVA therapy. The patient underwent PUVA therapy over the course of twenty exposures (cumulative UVA dose 33.5 J/cm^2) and local betamethasone therapy that resulted in complete disappearance of erythema, scaling, and induration, leaving only poikiloderma. The patient was recommended regular check-ups.

DISCUSSION

Rare clinical variants of MF include hypopigmented MF, granulomatous slack skin, pagetoid reticulosis, and folliculotropic and poikilodermatous MF. It is still debatable whether PMF is a clinical variant of early-stage MF or special entity. We must also bear in mind the fact that is has been reported that poikiloderma can coexist with classical MF lesions, so PMF can only be considered when poikilodermatous lesions are predominant (>50% of lesions), as in our case where poikilodermatous lesions covered almost 80% of the body surface (5).

Histology and immunohistochemistry revealed MF, but due to specific clinical findings (poikiloderma), we established the diagnosis of very rare clinical variant – PMF. The most commonly found immunophenotype in PMF is predominantly CD4$^+$ (5), as in our case, although the predominance of CD8$^+$ and double negative (CD4$^-$ and CD8$^-$) was found infrequently. Recent data suggest that the CD4$^+$CD8$^-$ immunophenotype and CD8$^+$CD4$^-$ immunophenotype in PMF do not differ in prognosis (5).

T-cell receptor (TCR) gene rearrangement by using PCR is not lymphoma-specific; in other words, monoclonality does not necessarily mean malignancy (7), and positive TCR gene rearrangement (monoclonality of T-cell infiltrate) is not required for the diagnosis (5). Furthermore, monoclonality may be lacking in lymphomas and may be found in a distinct proportion of pseudolymphomas (3). Some authors propose that undetectable monoclonality should be considered pre-mycosis (8). A TCR gene rearrangement study was not performed in our case.

Lymphadenopathy is a frequent finding in patients with MF, but it does not necessarily correlate with histological lymphomatous involvement. Dermatopathic lymphadenitis is often observed in such patients, as in our case, where the axillary and inguinal lymph nodes were slightly enlarged but still only

up to 2 cm in diameter without histological involvement (9).

Choice of treatment for PMF, as for classic MF, is based on staging and includes skin-directed therapies (topical corticosteroids, bexarotene, carmustine, mechlorethamine, nbUVB, PUVA, radiation) and systemic therapies. PUVA and nbUVB were found to be equally effective (with complete response to treatment in approximately 60% of patients) in retrospective studies with early-stage MF (10,11). Narrowband UVB therapy should be included in first-line treatment options of MF given its efficacy, convenience, and the likelihood of fewer long-term adverse effects only for the patch stage (11). New treatment options for MF have recently expanded to include UVA1 and excimer laser (12). A combination of PUVA with systemic therapy is used to diminish the total UVA exposure and therefore minimize the long-term side-effects. The most common systemic drugs for use with PUVA in MF are either retinoids (acitretin, isotretinoin, and bexarotene) or interferon-alfa. However, it is still an open question whether combination treatments are more efficacious than PUVA alone in early disease (12). PUVA is more effective than UVB for thicker lesions – plaques – or in individuals with dark skin because UVA penetrates deeper than UVB (12). PUVA therapy is associated with an increased risk of non-melanoma skin cancer, and maintenance therapy is not recommended because prolonged disease-free intervals are possible. Combined PUVA and retinoid therapy may be considered in patients who rapidly relapse after PUVA treatment, as was the case with our patient. Also, hyper- and hypopigmentation will not resolve after treatment, in contrast to erythema, itching, desquamation, and induration that are treatable (5). PUVA, Re-PUVA, and Re-nbUVB therapy in our patient resulted in residual hyper- and hypopigmentations. A case of treatment failure of PMF presenting with erythroderma has also been reported in the literature (13).

The overall prognosis for PMF is favorable (most patients will have non-progressive disease), although recent study revealed PMF cases with progression to lymphomatoid papulosis stage III (LyP) and PMF stage IVB (5).

CONCLUSION

PMF is a rare clinical entity with little data in the literature on its clinical, histopathological, immunophenotypic, molecular, and prognostic features. We can conclude from published data that first-line treatment for PMF (stages IA, IB, IIA) in the patch-stage could be nbUVB and for plaque-stage PUVA. In our case, Re-PUVA had very good treatment results, and this combined therapy probably resulted in fewer treatment sessions and lower cumulative UVA dose. An individual approach is obligatory as different treatment modalities could be successful in the case of early-stage PMF. PMF must be considered a malignant disease that may stay at the same stage with many rapid/non-rapid recurrences or may progress. Although overall prognosis is good, careful monitoring and appropriate treatment of PMF is necessary.

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