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ORIGINAL PAPER

PUVA-induced pityriasis lichenoides chronica-like papular lesions in patients with mycosis fungoides: a clinical, histopathological and immunohistochemical study

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Abstract

Mycosis fungoides (MF) is the most common form of cutaneous T cell lymphoma (CTCL) with many clinical variants including papular and pityriasis lichenoides chronica (PLC)-like variants. During psoralen and ultraviolet A (PUVA) treatment of MF, PLC-like papular lesions were observed to appear. The exact nature of these lesions is not fully understood. This work aimed to study PLC-like papular lesions arising in MF patients receiving PUVA therapy clinically, histopathologically and immunohistochemically (using monoclonal antibodies against CD4 and CD8) and to compare them with lesions in classic PLC patients. Fifteen MF patients with PLC-like papular lesions arising during PUVA treatment were included and 15 patients with classic PLC served as controls. While the extent of these lesions significantly correlated with their duration ($p < 0.05$), it showed no significant correlation with the TNMB stage of MF, number of phototherapy sessions or cumulative UVA dose at which they started to appear. The response status of MF to PUVA did not affect their development. Compared to classic PLC, these lesions showed significantly more acute onset ($p = 0.003$). None of these lesions showed histopathological features essential to diagnose papular/PLC-like MF and no significant difference existed with regard to their histopathological and CD4/CD8 phenotypic features compared to classic PLC. Papular lesions mimicking PLC in MF patients receiving PUVA mostly represent an upgrading reaction with possible good prognostic implication.

Keywords Pityriasis lichenoides chronica (PLC) · Pityriasis lichenoides chronica-like lesions (PLC-like lesions) · Mycosis fungoides (MF) · Psoralen and ultraviolet A (PUVA)

Introduction

Mycosis fungoides (MF) is the most common form of cutaneous T cell lymphoma (CTCL) which accounts for around 60% of new cases. It accounts for 3–5% of non-Hodgkin's lymphoma [8]. It is known that MF has many clinical variants including the papular and pityriasis lichenoides chronica (PLC)-like variants [7]. Although it is generally thought that papular MF has good prognosis as other early forms of the disease, patients with this variant who progressed to erythroderma or tumour stage within relatively short period of time have been observed [2].

Pityriasis lichenoides (PL) is a benign condition with unknown exact cause. Three major theories are claimed to be of influence in the pathogenesis of PL; infectious theory, lymphoproliferative theory and immune complex-mediated vasculitis theory [6]. Pityriasis lichenoides include two forms; acute and chronic. The chronic form known as pityriasis lichenoides chronica (PLC) is characterized by an eruption of scaly erythematous papules with characteristic mica-like scale [1].

Although phototherapy is a classic line of treatment of PLC, we have observed the development of papular lesions clinically mimicking PLC in some patients with MF receiving psoralen and ultraviolet A (PUVA) treatment which disappeared, at least partially with the continuation of PUVA

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therapy. Whether these papular lesions are actual lesions of MF (indicating disease progression) or a form of upgrading of MF due to phototherapy treatment was the question behind this study. The study aimed to characterize these papular lesions, verify whether they represent papular/PLC-like variant of MF or not and to compare them with classic PLC. To the best of our knowledge, this phenomenon was not previously studied.

Materials and methods

Following approval by the Dermatology Research Ethical Committee and signing of an informed consent by the patient or their guardians, this cross-sectional study was conducted. Two groups of patients were recruited from the Out-Patient Clinic and the Phototherapy Unit of the Dermatology Department, Kasr AlAini University Hospital, Cairo University. Group (A) included: 15 MF patients [5 women (33.3%) and 10 men (66.7%); mean ± SD age 40.8 ± 8.8 years, range 27–57 years] who developed PLC-like papular lesions during treatment with PUVA. Any clinicopathological type of MF was included except papular MF. Group (B) included: 15 patients with classic PLC who served as controls [7 women (46.7%) and 8 men (53.3%); mean ± SD age 19.8 ± 2.29 years, range 15–23 years]. Both groups were sex matched ($p = 0.36$). Group B included patients with significantly younger age ($p < 0.0001$).

Clinical evaluation

For all cases, lesions were evaluated with regard to onset, course, percentage of body involvement (determined by the rule of nine) and the anatomical distribution of the lesions. For MF cases, additional data were collected; type of MF, tumour-node-metastasis-blood (TNMB) stage, number of PUVA sessions and cumulative dose of UVA at time of onset of the PLC-like papular lesions and the status of response to PUVA at that time whether improving, stationary or progressing.

Histopathological and immunohistochemical evaluation

Four millimetres punch biopsies were taken from the PLC-like papular lesions (group A) and the classic PLC lesions (group B). Skin biopsies were fixed in 10% neutral buffered formalin, and then processed and embedded in paraffin blocks. Four micrometres thickness sections were prepared for both routine H&E staining and automated immunohistochemical staining (using BenchMark XT autostainer, Ventana Medical Systems, Inc. Tucson, Arizona, USA). Automated staining was carried out according to the protocol described by BenchMark XT Reference Manual, Ventana Medical Systems, Part Number 2000100 Revision A. For immunohistochemical staining, the following antibodies were used: [CD4 mouse monoclonal antibody (catalogue number MS-1528 R7) and CD8 mouse monoclonal antibody (catalogue number MS-457-R7), Labvision Vermont, Rockford USA].

Routinely stained H&E slides prepared from group A patients were examined and all histopathological features were described. Diagnostic criteria of MF [5] were searched in every case. CD4 and CD8 positivity was interpreted both in the epidermal and dermal compartments as predominantly CD4 positive, predominantly CD8 positive or mixed CD4 and CD8 positivity. Histopathological and immunohistochemical features were compared with those in the classic PLC group (group B). All sections were examined using Zeiss Primostar microscope (Zeiss, Germany) with integrated camera by which photomicrographs depicting all histopathological and immunohistochemical features were taken. All photomicrographs presented are according to their original magnification.

Statistical methods

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Mann–Whitney U test for independent samples. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than five. Correlation between various variables was done using Spearman rank correlation equation. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programme SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

Clinical characteristics of group A patients are illustrated in Table 1. Trunk and extremities were involved by the PLC-like papular lesions in 40% of the cases (Fig. 1). The extent of these lesions showed no significant correlation with the TNMB stage of MF ($r = 0.02$, p value = 0.94), number of sessions of PUVA at which they started to appear ($r = 0.47$, p value = 0.07), or cumulative dose of PUVA at onset of lesions ($r = 0.15$, p value = 0.59). On the other hand, a significant positive correlation existed between the duration of the PLC-like papular lesions and their extent ($r = 0.86$, p value < 0.05). The response status of MF to PUVA whether

Table 1 Clinical characteristics of the MF patients and the PLC-like papular lesions that developed in them during PUVA therapy (group A)

Type of MF	Classic MF: 10 (66.7%) Hypopigmented MF: 5 (33.3%)
TNMB staging	Stage Ia: 2 (13.3%) Stage Ib: 13 (86.7%)
Number of PUVA session at which the PLC-like papular lesions developed	57 ± 13.59 (42–89)
Cumulative dose of UVA at onset of the PLC-like papular lesions	242.98 ± 118.71 J/cm^2 (133–509)
Status of response to PUVA at the time of onset of the PLC-like papular lesions	Improving: 13 (86.7%) Stationary: 2 (13.3%)
Onset of the PLC-like papular lesions	Acute: 11 (73.3%) Gradual: 4 (26.7%)
Course of the PLC-like papular lesions	Progressive: 13 (86.7%) Regressive: 2 (13.3%)
Duration of the PLC-like papular lesions	5 ± 2 months (1–9)
Percentage of body surface area involved	32.3 ± 25.1% (10–80)
Anatomical distribution of lesions	
Trunk	5 (33.3%)
Extremities	4 (26.7%)
Both	6 (40%)

Data are expressed as number (percent) or as mean ± standard deviation (range)

MF mycosis fungoides, *TNMB* tumour-node-metastasis-blood, *PUVA* psoralen and ultraviolet A, *PLC* pityriasis lichenoides chronica

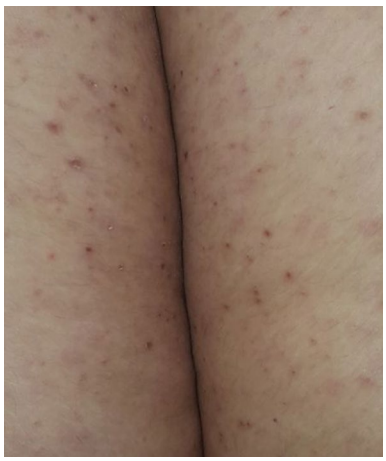

Fig. 1 A close-up view of PLC-like lesions developing in a patient with mycosis fungoides during PUVA therapy

improving or stationary, did not affect the development of the PLC-like lesions (p value = 0.21). Compared to classic PLC, lesions mimicking PLC arising in MF patients during PUVA therapy showed significantly more acute onset ($p = 0.003$), while no significant difference existed with regard to course, percentage of body involvement or anatomical distribution of the lesions (Table 2).

Histopathological features essential to diagnose papular/PLC-like MF were not detected in any lesion in group A. Stratum corneum changes included: orthokeratosis in 2 (13%) cases, focal parakeratosis in 11 (73%) cases and confluent parakeratosis in 2 (13%) cases. The epidermis was hyperplastic in 9 (60%) cases with spongiosis and lymphocyte exocytosis in 12 (80%) cases. All cases (100%) showed vacuolar degeneration along the dermoepidermal junction (DEJ). Necrotic keratinocytes along the DEJ was seen in ten (67%) and were scattered within the epidermis (including necrotic keratinocytes present high up in the epidermis) in six (40%) of the cases. The dermal infiltrate was limited to the superficial plexus in 13 (87%) cases and extended around superficial and deep plexuses in 2 (13%) of the cases. Extravasated erythrocytes/erythrocytes within the epidermis were found in 12 (80%) cases (Fig. 2). The epidermal compartment was CD4 predominant in six (40%) cases, CD8 predominant in four (26.7%) cases and showed mixed phenotype in five (33.3%) of the cases. On the other hand, the dermal compartment was CD4 predominant in seven (46.7%) cases, CD8 predominant in six (40%) cases and showed mixed phenotype in two (13.3%) of the cases (Fig. 3). No significant difference existed with regard to histopathological and CD4/CD8 phenotypic features of the PLC-like papular lesions arising in MF patients treated with PUVA when compared with classic PLC (Table 3).

Discussion

All PLC-like papular lesions appearing in MF patients receiving PUVA in the current study lacked criteria required to diagnose MF such as: epidermotropism of small/medium pleomorphic cerebriform lymphocytes (either as disproportionate epidermotropism, basilar epidermotropism or

Table 2 Comparison between the PLC-like papular lesions arising in MF during PUVA therapy (group A) and classic PLC (group B) with regard to their clinical characteristics

	Group A ($n=15$)	Group B ($n=15$)	p value*
Onset			
Acute	11 (73.3%)	3 (20%)	0.003*
Gradual	4 (26.7%)	12 (80%)	
Course			
Progressive	13 (86.7%)	11 (73.3%)	0.651
Regressive	2 (13.3%)	4 (26.7%)	
Percentage of body surface area involved	32.3 ± 25.1% (10–80)	36.3 ± 21.1% (10–70)	0.48
Anatomical distribution of lesions			
Trunk	5 (33.3%)	6 (40%)	1
Extremities	4 (26.6%)	3 (20%)	1
Both	6 (40%)	6 (40%)	1

Data are expressed as number (percent) or as mean ± standard deviation (range)

*$p \leq 0.05$ is considered as significant

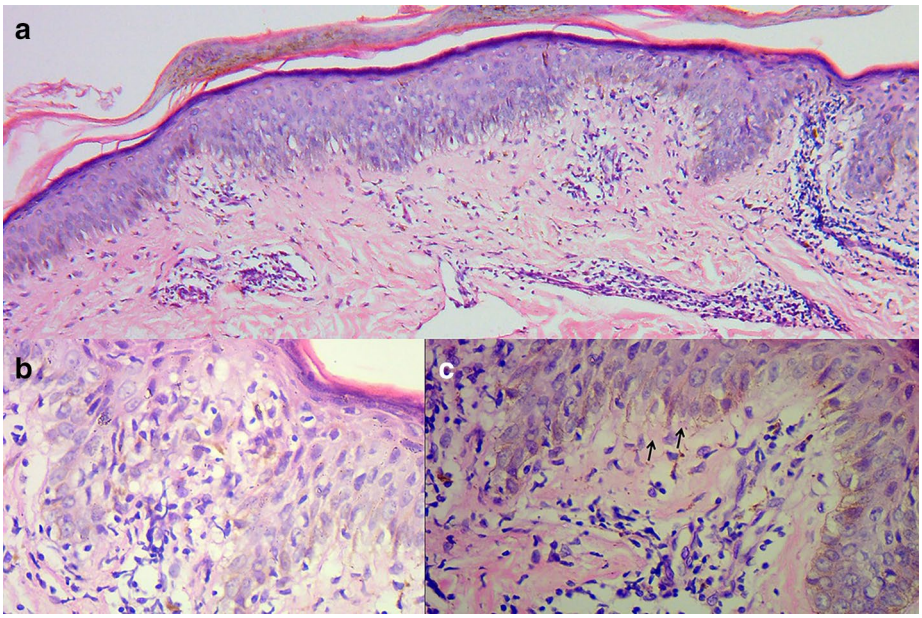

Fig. 2 Photomicrographs representing histopathological features of a PLC-like papular lesion arising during PUVA therapy in a patient with MF. **a** Parakeratotic stratum corneum, mild epidermal hyperplasia with evident interface changes and a superficial perivascular lymphohistiocytic infiltrate (H&E, ×100). **b** Vacuolar degeneration along the DEJ with interface lymphocytes as well as epidermal spongiosis and lymphocyte exocytosis (H&E, ×400). **c** Necrotic keratinocytes (black arrows) along the DEJ (H&E, ×400)

Paurtier's microabscesses), patchy band/band-like infiltrate, dermal lymphoid atypia and wiry fibroplasia of papillary dermal collagen [5]. Apart from having a more acute onset, these lesions showed no significant difference when compared with classic PLC neither histopathologically nor immunohistochemically. Since PLC is considered as a benign condition, the appearance of these lesions in MF patients during PUVA may indicate an upgrading reaction of the immune system to treatment.

The mechanism of action of PUVA in mycosis fungoides and other lymphoproliferative diseases includes the interaction of psoralens with DNA, proteins and other cellular components leading to singlet oxygen-mediated reactions or generation of free radicals. Infiltrating lymphocytes are strongly suppressed by PUVA, with variable effects on different T cell subsets. PUVA is far more potent in induction of apoptosis in T lymphocytes and antigen-presenting cells than in keratinocytes, which may explain its efficacy in cutaneous lymphomas [3]. In addition, PUVA also downregulates the expression of homing receptors of epidermotropic malignant T cells, thus serving as an effective treatment modality in early stages of cutaneous T cell lymphoma [4]. Accordingly, the downregulating effect of PUVA therapy on the malignant T cells may explain the eruption of lesions with the nature of the benign end of the lymphoproliferative spectrum.

The acute onset of the PLC-like papular lesions in MF patients during PUVA therapy could be related to a sudden or a dramatic change in the immune response. However, this

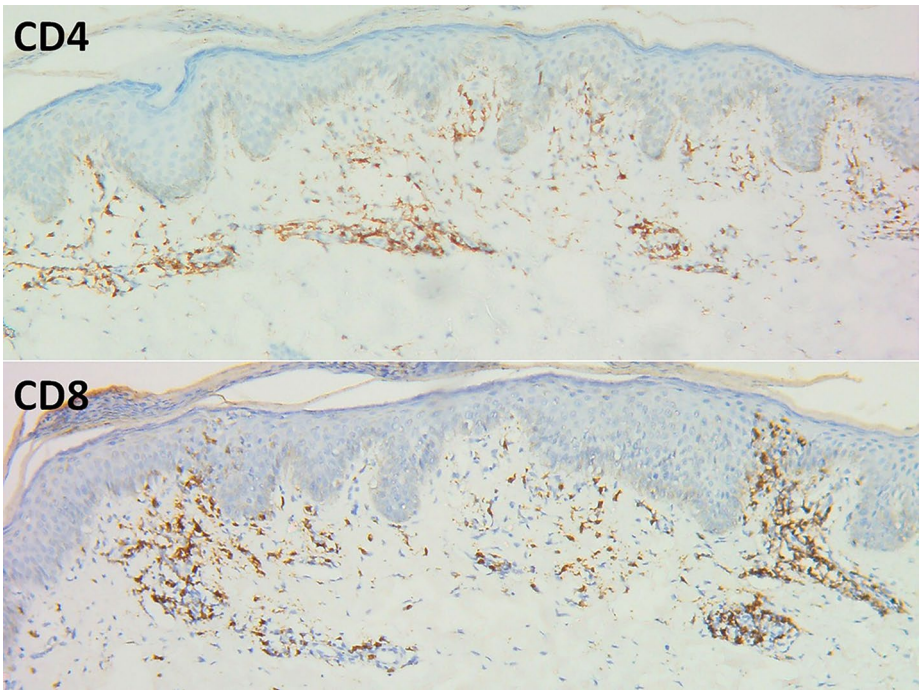

Fig. 3 Photomicrographs representing immunohistochemical features of the previous case. Although the dermal infiltrate showed both CD4 and CD8 positive cells, the epidermal compartment appeared to be CD8 predominant (CD4 and CD8 immunostain, ×100)

Table 3 Comparison between the PLC-like papular lesions arising in MF during PUVA therapy (group A) and classic PLC (group B) with regard to their histopathological and immunohistochemical features

Histopathological features	Group A ($n=15$)	Group B ($n=15$)	p value*
Orthokeratosis	2 (13%)	1 (7%)	0.5
Focal parakeratosis	11 (73%)	8 (53%)	0.32
Confluent parakeratosis	2 (13%)	6 (40%)	0.12
Epidermal hyperplasia	9 (60%)	11 (73%)	0.12
Spongiosis	12 (80%)	15 (100%)	0.11
Exocytosis	12 (80%)	15 (100%)	0.11
Vacuolar degeneration at DEJ	15 (100%)	15 (100%)	0
Necrotic KCs at DEJ	10 (67%)	12 (80%)	0.34
Necrotic KCs (Scattered and or high up within the epidermis)	6 (40%)	11 (73%)	0.07
Superficial perivascular infiltrate	13 (87%)	9 (60%)	0.11
Superficial and deep perivascular infiltrate	2 (13%)	5 (33%)	0.2
Extravasated erythrocytes or erythrocytes within the epidermis	12 (80%)	8 (53%)	0.12
Immunohistochemical features	**Group A ($n=15$)**	**Group B ($n=15$)**	**p value***
Epidermal compartment			
CD4 predominant	6 (40%)	9 (60%)	0.16
CD8 predominant	4 (26.7%)	5 (33.3%)	
Mixed phenotype	5 (33.3%)	1 (6.7%)	
Dermal compartment			
CD4 predominant	7 (46.7%)	3 (20%)	0.22
CD8 predominant	6 (40%)	7 (46.7%)	
Mixed phenotype	2 (13.3%)	5 (33.3%)	

Data are expressed as number (percent)

DEJ dermoepidermal junction, *KCs* keratinocytes

*$p \leq 0.05$ is considered as significant

needs further studies. The significant correlation between the duration of these lesions and their extent may denote a continuous active process of change of the immune system related to PUVA therapy with a continuous upregulation of the immune system. The small number of cases in the current study may explain the lack of significant effect of other studied parameters on the extent of these lesions.

In conclusion, PUVA-induced PLC-like papular lesions are similar to classic PLC lesions on histopathological and immunohistochemical basis indicating their benign nature. They mostly denote an upgrading reaction and are hypothesized to be an indication of good prognosis of the disease. However, this point needs further verification by long-term prospective studies comparing MF patients who developed PLC-like lesions during treatment with PUVA with those who did not develop.

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Compliance with ethical standards

Conflict of interest All the authors have no conflict of interest to declare.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the Dermatology Research Ethical Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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