PUVA Induced PLC-Like Lesions in Patients with Mycosis Fungoides: A clinical, Pathological and Immunohistochemical Study

Thesis

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Abstracts

Background: The nature of pityriasis lichenoides chronica (PLC) like lesions arising in mycosis fungoides (MF) patients during treatment with PUVA is not fully understood. PLC like lesions has been observed in MF patients during treatment with PUVA. It has been of interest whether PLC like lesions is upgrading or downgrading of the disease.

Objective: Is to investigate the nature of PLC-like lesions arising in MF patients receiving PUVA therapy both clinically, pathologically and immunohistochemically and to compare them with classic PLC lesions .

Methods: The study included 15 MF patients who developed PLC like lesions during treatment with PUVA (group A) and 15 patients with classic PLC (group B) were included and served as controls. Thorough clinical examination was done for each patient. A 5mm punch biopsy was obtained and examined histopathologically and immunohistochemically.

Results: In the present study no statistically significant difference was noted between group A and group B on the histopathological and immunohistochemical aspects **(P > 0.05)** .

A statistically significant difference was noted between group A and group B as regards age **(P < 0.00001)**, Onset **(P= 0.003)** and duration of the disease **(P < 0.00001)**, There was no statistically significant difference as regards course .

In group A there was a significant correlation between extent of PLC like lesions and duration **(P < 0.05)**. The extent of PLC like lesions showed non significant correlations with stage of MF, number of PUVA sessions received at time of its appearance, status of MF (clinically improved or showed persistent lesions) and with cumulative dose of PUVA at time of its appearance **(P > 0.05)** .

Conclusion: The papular lesions appearing in patients receiving PUVA showed no evidence of papular MF both histopathologically and immunohistochemically which may denote upgrading and good prognosis of the disease .

Keywords: Pityriasis lichenoides chronica (PLC), Pityriasis lichenoides chronica like lesions (PLC like lesions), Mycosis fungoides (MF), Psoralen UVA (PUVA).

List of Abbreviations

AIH	:	Autoimmune hepatitis
ANOVA	:	Analysis of variance
APC	:	Antigen presenting cell
BCNU	:	Topical carmustine
CDKs	:	Cyclin-dependent kinases
CHOP	:	Cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisolone
CKIs	:	Cyclin-dependent kinase inhibitors
CLA	:	Cutaneous lymphocyte associated antigen
CMV	:	Cytomegalovirus
CT	:	Computed tomography
CTCL	:	Cutaneous T-cell lymphomas
DAB	:	Di-amino-bezidine tetrahydrochloride
DC	:	Dendritic cell
DDS	:	Diaminodiphenyl sulfone
DHFR	:	Dihydrofolate reductase
EBV	:	Epstein-Barr virus (EBV)
EBV	:	Epstein-Barr virus
ECP	:	Extracorporeal photopheresis
EPOCH	:	A combination of etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide
FasL	:	Surface molecule Fas with its ligand
FDA	:	Food and Drug Administration
GM-CSF	:	Granulocyte macrophage colony stimulating factor
HDACs	:	histone deacetylase inhibitors
HIV	:	Human immunodeficiency virus (HIV)
HIV	:	Human immunodeficiency virus
HLA-DR1	:	Human leukocyte antigen D -related subtype positive
HN2	:	Nitrogen mustard (mechlorethamine)
HTLV	:	Human T-cell lymphotropic virus
IFA	:	Immunofluorescence antibody

IFN	:	Interferon
IHA	:	Indirect hemagglutination
IL	:	Interleukin
ISCL	:	The International Society of Cutaneous Lymphoma
LC	:	Epidermal Langerhans cell
MF	:	Mycosis fungoides
MMP	:	Matrix metalloproteinase
MOP	:	Methoxypsoralen
mRNA	:	Messenger-RNA
MTX	:	Methotrexate
nbUVB	:	Narrow-band UVB (nbUVB)
NF-AT	:	Nuclear factor of activated T cells
NK	:	Natural killer .
P value	:	Probability value
PBS	:	Phoshate buffer saline
PCR	:	Polymerase chain reaction
PDT	:	Photodynamic therapy
PL	:	Pityriasis lichenoides
PLC	:	Pityriasis lichenoides chronica
PLEVA	:	Pityriasis lichenoides et varioliformis acuta
PTEN	:	Phosphatase and tensin homolog gene mutation
PUVA	:	Psoralen and ultraviolet A
Rb	:	Retinoblastoma protein
REC	:	Research ethical committee
RXR	:	Retinoid X receptor
SAHA	:	Suberoylanilide hydroxamic acid
Scoring system	:	The TNMB system scores involvement in the skin (T), lymph nodes (N), viscera (M), and peripheral blood (B) .
SD	:	Standard deviation
SPSS	:	Statistical Package for the Social Science
T regs	:	Regulatory T cells
T. gondii	:	Toxoplasma gondii
TCR	:	T-cell receptor

TCRGR	:	T-cell receptor gene rearrangement
TIA1	:	T-cell intracellular antigen-1
TNF-alpha	:	Tumor necrosis factor alpha
TSEB	:	Total skin electron-beam radiation
VZV	:	Varicella zoster virus
XP	:	Xeroderma pigmentosum

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INTRODUCTION AND AIM OF WORK

Pityriasis Lichenoides was first described ***in 1894 by Zur***, who reported cases of acute and chronic forms, respectively. Initially it was included in the parapsoriasis group by ***Brocq in 1902***. ***In 1916, Mucha et al.*** distinguished the acute form and chronic form.

Pityriasis Lichenoides is an uncommon and benign disease. Although commonly considered being more prevalent in males, some reviews show no solid predisposition in either sex in the general population ***(Bowers and Warshaw, 2006).*** Usually children ***(Romani et al, 1998)*** and young adults predominate ***(Marks et al, 1972).***

Pathogenesis remains unknown with three major theories including infectious etiology, lymphoproliferative etiology, and immune complex mediated vasculitis theory ***(Khachemoune and Blyumin, 2007).***

Some studies demonstrating T-cell clonality support the lymphoproliferative theory, probably triggered by an unknown antigenic stimulus ***(Magro et al, 2002 and Weinberg et al, 2002).***

Pityriasis lichenoides is often a benign disorder but, because of the presence of a clonal T cell population detected both in the chronic and acute forms, some authors have suggested that it may belong to the group of primary cutaneous T cell lymphomas. Although various studies have clearly documented no significant association between pityriasis lichenoides and malignant lymphomas, cases of longstanding pityriasis lichenoides evolving into mycosis fungoides have been described ***(Tomasini et al, 2002).***

Pityriasis lichenoides chronica has an indolent clinical course. The initial Lesion is an erythematous papule with a micaceous scale and a reddish hue that spontaneously regresses, without necrosis, over a period of weeks. Lesions usually predominate on trunk and proximal extremities with multiple exacerbations and remissions ***(Labarthe et al, 1996).***

The pathologic hallmarks of PLC are variable psoriasiform hyperplasia, focal dyskeratosis, parakeratosis, prominent lymphocytic infiltration into the upper spinous layer and a perivascular lymphocytic infiltrate in the superficial and mid-dermis accompanied by hemorrhage but without other inflammatory cell elements such as eosinophils and plasma cells. Intraepidermal collections of atypical lymphocytes reminiscent of Pautrier's microabscesses, characteristically showing localization to the upper layers of the epidermis, were noted in some cases ***(Solomon and Magro, 2008).***

Pityriasis lichenoides-like mycosis fungoides present with clinical features of Pityriasis lichenoides (scaly red to brown papules and macules) in which there are histopathological findings of mycosis fungoides (disproportionate epidermotropism, pautrier's microabscesses, and wiry and coarse collagen bundles). Immunohistochemical staining revealed a prevalence of T lymphocytes in the infiltrate. T-cell receptor gene rearrangement analysis in lesional skin demonstrated rearrangement of gamma chain in all cases ***(Ko et al, 2000).***

CD4, CD8, and CD1a immunostains are used in distinguishing Mycosis Fungoides from its inflammatory mimics (Pityriasis lichenoides chronica, actinic reticuloid, lichenoid purpura, and various psoriasiform dermatoses) in the form of an elevated CD4:CD8 ratio, together with an

increase in the expression of CD1a+Langerhans/dermal dendritic cells ***(Tirumala and Panjwani, 2012)***.

CD4+ T cells predominate in PLC ***(Giannetti et al., 1988 and Rogers et al., 1992)***.

CD1a expression emerged as an important discriminator between mycosis fungoides and inflammatory dermatoses ***(Tirumala and Panjwani, 2012)***.

It was remarkably increased in MF in both the epidermal and dermal compartments. Even in those cases where CD4:CD8 ratio overlapped, the difference in CD1a pattern was maintained, except for a single case of PLC. The continuous or confluent pattern was never seen in inflammatory lesions ***(Tirumala and Panjwani, 2012)***.

We observed the appearance of PLC- like lesions in MF patients receiving PUVA therapy and this prompted us to carry out this study to investigate the nature of these PLC-like lesions arising in MF patients receiving PUVA therapy both clinically, pathologically and immunohistochemically and to compare them with classic PLC lesions.

CHAPTER I

Mycosis Fungoides

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of malignancies derived from skin-homing T cells. The most common forms of CTCL are mycosis fungoides (MF) ***(Wong et al., 2011)***.

Epidemiology:

Mycosis fungoides is the most common form of CTCL and accounts for around 60% of new cases. It accounts for 3% to 5% of non-Hodgkin's lymphoma ***(Trautinger et al., 2006)***.

Mycosis fungoides particularly affects male and female adults, with a male to female ratio between 1.6: 2.1. These individuals are usually older than 50 years, but incidence has increased in children and adolescents ***(Cerroni et al., 2009)***. The survival percentage in the fifth year of follow-up ranges from 80% to 100% ***(Cerroni et al., 2009)***.

Clinical Presentations:

Three classical cutaneous phases of MF are present including patches, infiltrated plaques, and tumors ***(Keehn et al., 2007)***.

Patch-stage lesions are erythematous patches or slightly raised plaques with a fine scale. The lesions may be single or multiple and are often located on the buttocks, thighs, and abdomen. Patch lesions may be intensely pruritic or entirely asymptomatic ***(Keehn et al., 2007)*** (Fig.1).