THERAPEUTIC MODALITIES OF MYCOSIS FUNGOIDES

ESSAY

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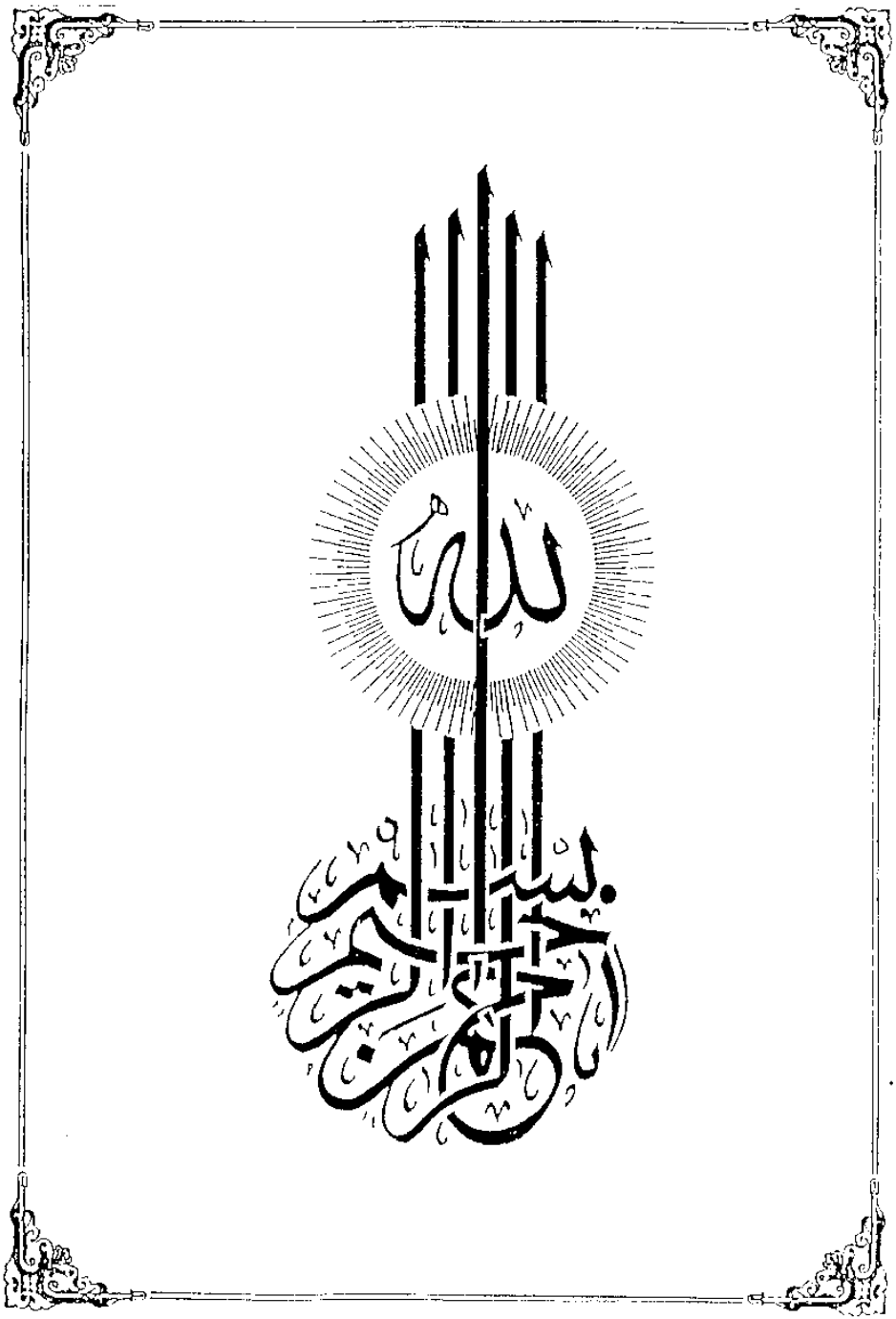

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List Of Abbreviations

AIA	Automated Image Analysis
ATL	Atypical lymphoma
BCNU	Bischloroethyl nitrosourea
cGy	Centigray
CTCL	Cutaneous T-cell lymphoma
DTTP	Deoxycitidine- 5 triphosphate
EB	Electron Beam
Gy	Gray
HTLVs	Human T-lymphoma-Leukemia viruses
IFNα	Interferon alpha
IL1-IL2	Interleukin 1 - Interleukin 2
IU	International unit
J/Cm2	Joule per cubic centimeter
KV	Kilo volt
LCs	Langerhan's Cells
L.N.	Lymph Node
LPAP	Large plaque Atrophic Parapsoriasis
MAbs	Monoclonal Antibodies
Me V	Megavolt
MF	Mycosis Fungoides
MFCG	Mycosis Fungoides Cooperative Group
8-MOP	8-Methoxy psoralen
PUVA	Psoralen + Ultraviolet A
rIFNα2a	recombined interferon alpha 2a
S.S.	Sezary Syndrome
TNM	Tumor- Node- Metastasis
UVA	Ultraviolet A

Introduction

Mycosis fungoides (MF) is a generally indolent cutaneous T-cell lymphoma characterized by a neoplastic proliferation of mature helper T-cells. *(Kaye et al., 1989).*

MF is a number of cutaneous T-cell lymphomas (CTCL) which includes also sezary syndrome (SS) and atypical adult T-cell lymphomas. *(Campbell et al., 1991).*

Clinically, the presentation of MF mainly includes limited or widespread cutaneous plaques, cutaneous tumors, or erythroderma. In late stages, the lymph nodes, blood, and viscera may be involved. *(Epstein, 1980).*

Many therapeutic modalities to treat MF are already stablished and others are still under trial. The choice of the therapeutic modality must be based on the biological expression of the disease in the individual patient *(Haynes& Van Scott, 1979).*

Appropriate treatment of malignant T-cell lymphomas depends apon the stage of the disease, the natural history of the disease left untreated, and whether the induction of a complete remission will

lead to prolongation of survival or cure of the disease *(Olsen, 1992)*. Main therapeutic methods include local, systemic and combination therapy.

Aim of work

To theough a light on different therapeutic modalities of Mycosis Fungoides which are already stablished and those which are still under trial.

And to determine the optimum therapeutic approach for various stages of the disease.

HISTORICAL ASPECTS

Mycosis Fungoides was first described by the french dermatologist Jean Louis Albert in 1806, (*Epstein, 1980*). He stated that the tumors resembled "mush rooms" or thus named is "agariscs" but, did not state whether this similarity was in size, colour, shape, consistency, or rapidity of growth. In 1814, Albert regarded the condition as a form of yaws and named it "pain fungoide" with the latin synonym "Frambesia Mycoides". However in 1832, Albert renamed the disease "Mycosis Fungoides" because of the "mushroom-like" appearance of the tumor, but did not intend to suggest fungi as the causative agent (*Bluefarb, 1959*) .

In 1938, Sezary and Bouvrain reported the triad of erythroderma, leukemia composed of large mononuclear cells with convoluted nuclei, and enlarged peripheral lymph nodes infilterated by the same characteristic cells as those found in the blood. (*Patterson & Edelson, 1987*) .

This Sezary Syndrome (S.S.) was not recognized in the american medical literature until Taswell and Winkelmann (1961) reported several similar cases from the Mayo-clinic.

Clendenning et al. *(1964)* was the first to suggest a more unified concept of a single disease as he noticed significant percentages of a typical mononuclear cells in patiets with plaque and tumour lesions of MF.

Demonstration that these clinical presentations represented neoplasms of lymphocytes came from studies using cytogenetic and cellular immunology. First Crossen et al. *(1971)* performed karyotype analysis to demonstrate that Sezary cells could occasionally proliferate in response to the lymphocyte mitogen, phytohemoagglutinin. In addition, the demonstration that the neoplastic cells of Mycosis fungoides *(Edelson et al. , 1974)* and Sezary syndrome *(Brouet et al., 1973)* exhibited membrane features characteristic of T-lymphocytes provided more definitive evidence that these disorders are malignancies of T cells.

The term "cutanous T cell lymphoma (CTCL)" was proposed by Lutzner et al *(1975)* to encompass malignent T-

ell proliferation involving the skin. This term was formally adopted in 1978 at the international meeting on cutaneous lymphoma sponsored by the National Cancer Institute *(Lamberg and Bunn, 1979)*. It should be noted therefore that "CTCL" constitutes a spectrum of deseases which includes not only MF and Sezary syndrome but other lynphoreticular neoplasms distinguished by apparent primary skin infiltration with neoplastic T cells *(Patterson & Edelson, 1987)*.

AETIOPATHOGENESIS OF MF

It is generally accepted that Mycosis Fungoides is defined as a malignant lymphoma, most commonly (and perhaps always) being an excess proliferation of helper T-lymphocytes *(Epstein, 1984)*. However, two controversial aspects of M.F. are found. First, avidence from epidemiologic and laboratory studies suggest a non-neoplastic etiology of the disorder. On the other hand, data indicating that M.F. may be a systemic disease from its inception, rather than a condition localized to the skin for many years before spreading internally, are also found *(Thiers and Charleston, 1982)*.

Non-Neoplastic Etioloy

Tan et al *(1974)* was the first to hypothesize that M.F. would begin as reactive granulomatus response to persistent unidentified antigen resulting in immunologic imbalance and neoplastic transformation.

(a) **Clinical Considerations:**

The clinical course and appearance of M.F. support the contention that the condition may begin as a reactive process. The disease usually begins by a chronic premycotic skin eruption which may be indistinguishable from chronic allergic contact or psoriasiform dermatitis. This premycotic stage may also involute spontaneously or may last many years before progressing to plaque and tumour stages *(Thiers and Charleston, 1982)* . In addition, unlike most other lymphomas, humoral and cellular immunity are intact until the terminal stage of the disease *(Norris & Le Feber, 1986).* In experimental allergic contact dermatitis, the infiltrate contains a mixture of helper T-cells and dendritic HLA-DR-positive cells with minimal suppressor T cell involvement which is also similar to what is observed in early M.F. *(Norris & Le Feber, 1986).* Furthermore the presence of intra-epidermal suppressor T-cells, seen in early M.F. is similar to what observed in contact dermatitis *(Tigelaar, 1983).*

(b) **Epidemiological Considerations :**

Epidemiologic studies also support the possibility of a non neoplastic origin of M.F.. Green et al.*(1979)* noted excessive M.F.mortality in regions where petroleum, rubber, primary and fabricated metals, machinary and printing industries were located. Also Cohen et al. *(1980)* in a case controlled study considering the importance of occupation in the pathogenesis of M.F., found that employment in the heavy industries was a significant risk factor.

(c) **Role of Langerhans Cells (LCs)**

Recent observations concerning the structural and functional characteristics of Langerhans cells lend further credence to the concept that M.F. originates as a reactive process.

Rowden and Lewis (1976) demonstrated that in early lesions of M.F., lymphocytes were found in close opposition with LCs and remenant of LCs were also found in pauterier microabscesses which characterize this disease.

In addition Mc-Millan et al *(1982)* also demonstrated that OKT6 positive denderitic cells (LCs) were found in skin secretions using monoclonal antibodies with almost central location within pauterier microabscesses. These findings led Thiers and Charleston (1982) to state that the apparent role of LCs in contact dermatitis suggested that an antigen recognition process might form the basis of this LC-T cell interaction. They also added that the similarity between reactive T-lymphocytes and mycosis cells supported the concept that destruction of LCs might act as a focus for development of the microabscesses.

In addition the finding of LCs throughout the epidermal and dermal infiltrate as well as finding cells in these infiltrate reacting positively with helper T-cells tempted McMillan et al *(1982)* to suggest some kind of immunologic interaction of these cells which eventually manifested as lymphoma.

Neoplastic Etiology

The view has been widely held that M.F. is a malignant process from its inception. Clinical, cytogenetic as well as

immunological observations were most consistent with monoclonality of the malignancy, initial involvement of localized areas of skin, subsequent progressive loss of epitheliotropism by neoplastic cells and parallel haematogenous spread to visceral and non-contiguous cutaneous sites *(Edelson, 1980).*

A- <u>Clinical Observations:</u>

The fact that the small number of mycosis cells in the begining is due to a pronounced inflammatory reaction of the tissue against lymphoma cells is supported by the observation that in other malignant diseases such as squamous cell carcinoma, malignant melanoma and Hodgkin's disease, an inflammatory host reaction is also often seen in the early stages but disappears as the malignancy of tumor cells increases *(Lever and Schaumburg Lever, 1983).*

Epstein (1984) stated that it was hard to mistake the disease for something other than an uncontrolled growth of cells, as in the late stage MF, tumours were filled with