The YEAR BOOK of
Dermatology
1982

Edited by
BRUCE H. THIERS, M.D.

and
RICHARD L. DOBSON, M.D.

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Journals Represented

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MYCOSIS FUNGOIDES AND THE SÉZARY SYNDROME

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Introduction

Mycosis fungoides (MF) and the Sézary syndrome (SS) are closely related lymphomas that clinically originate in the skin and eventually invade systemic lymphoid tissue—usually producing a progressive fatal systemic lymphoma. Because of the characterization of the atypical cells of MF and SS as T lymphocytes,[1] these diseases commonly are discussed as parts of a spectrum of cutaneous T cell lymphomas (CTCLs).[2] The low incidence of 1–2 new cases per million of population[3-4] is disproportionate to the interest of MF and SS to practicing dermatologists, experimental and theoretical immunologists, geneticists, epidemiologists, chemotherapists, and immunotherapists. During training, most dermatologists observe patients with prolonged and protracted cutaneous courses of MF or with rapidly progressive systemic disease and are frustrated by attempts of therapy, even in early disease. In practice and at regional and national clinical meetings, they observe the similarity of early and plaque-stage MF to other common papulosquamous or chronic eczematous diseases and become aware that many cases have been treated as various benign cutaneous diseases for protracted periods before accurate diagnosis was made. This conditions the practicing dermatologist to think of MF when he is confronted with a persistent and somewhat unusual papulosquamous eruption that does not respond to usual anti-inflammatory therapy. The interesting biology of the CTCL has induced immunologists and oncologists to use these diseases as models for better understanding of the induction and progression of lymphomas and of alterations in the normal regulation of immune responsiveness. The interest of geneticists and epidemiologists has been captured by the environmental factors that appear to influence the induction of the CTCL and by the chromosomal abnormalities and nuclear and enzymatic changes that verify cellular atypia. Specialists in immunotherapy and chemotherapy have designed therapeutic approaches tailored to the immunologic abnormalities described in these patients and to the characteristics of the atypical cells described in the blood and tissue of patients with CTCL.

The purpose of this review is to summarize the information that makes MF and SS important and interesting to the practitioner and to present the results of the burst of investigative activity that has so expanded our understanding of the CTCL. We begin by discussing the historical "discovery" of MF and the SS and describe the interesting clinical and histologic presentations of the different components of the spectrum of CTCL and the major controversies that have developed in understanding the clinical and histopathologic presentations of MF and the SS. We then will discuss the major modern controversy: What are the nature and pathogenesis of the CTCLs? We present in detail the background and evidence supporting the two major hypotheses for the pathogenesis of the CTCL: (1) that they represent monomorphous, monoclonal malignant proliferations of T helper lymphocytes with a predilection for the skin or (2) that they are initiated as reactive or inflammatory processes induced by antigenic or viral stimulation of an abnormal cutaneous immunologic network producing a polymorphous abnormal infiltrate. We present a model for the CTCL that we feel is most consistent with existing experimental information and that addresses both hypotheses fairly. Finally, we discuss the implications of this model in recent investigations of the therapy of MF and the SS, and what direction therapy might take in the future.

History

Armed only with the tools of clinical observation and histology, 19th century European dermatologists described MF and initiated the controversies concerning its nature, evolution, and pathogenesis. The astute French dermatologist Baron Alibert described the first case of MF[5] in 1806 and amplified the concept in a monograph in 1835, after nearly 30 years of clinical observation.[6] The concept of erythematous, plaque, and tumor stages of MF was described in 10 patients by Bazin[7] in 1870, and description of variants such as the tumeur d'emblee form of Vidal and Brocq (1885)[8] and the erythrodermic form of Besnier and Hallopeau (1892)[9] increased confusion as to the criteria for inclusion in this new disease category. Gillot, a colleague of Bazin, was intrigued by the relationship of MF to malignant reticuloses,[10] but the opinion of such noted dermatologists as Duhring,[11] Auspitz[12] and Koebner[13] favored an infectious etiology for MF. In 1938, Sézary and Bouvrian described the syndrome of edematous erythroderma with palmar-plantar keratoderma, nail dystrophy, adenopathy, and leukocytosis with large bizarre mononuclear cells that subsequently have been named Sézary cells.[14] The appreciation of the relation of MF and the SS has been based until recently solely on clinical and histologic criteria. The description by Lutzner et al. of the mycosis cell in the cutaneous infiltrates of MF[15] and the subsequent characterization of the mycosis cell and Sézary cell as T cells[16–17] have established the relationship of MF and the SS and have led to the increasing use of

the term "cutaneous T cell lymphoma" (CTCL)[1] to refer to a spectrum of disease with classic MF at one end and its leukemic and erythrodermic variant, SS, at the other. The identification of similar restricted T cell populations in the blood, skin, and lymph node infiltrates of MF and SS by Broder and others[18, 19] have further extended evidence for the biologic relationship of these diseases.

Clinical and Pathologic Characteristics

Several distinct forms of MF have emerged from consideration of a combination of clinical and histologic criteria[20–21] and by careful observation of unusual patients and unusual presentations.

Classic Alibert-Bazin Mycosis Fungoides

This form of MF is characteristically pruritic and evolves through three clinical stages.

The first stage of premycotic erythroderma consists of well-demarcated, erythematous, scaly patches that may suggest eczema, parapsoriasis, poikiloderma, or various papulosquamous dermatoses. The lesions may have serpiginous borders and persist for many years. Histologically, the lesions of "premycotic" MF may be nonspecific, with a mixed lymphohistiocytic infiltrate of the papillary dermis. Multiple biopsy specimens may be necessary to show epidermotropism of lymphoid cells.

In the second stage, large indurated and scaly plaques with gyrate or circinate borders predominate. Histology shows an increase in the lymphohistocytic infiltrate—frequently band-like in the epidermis—with a mixture of neutrophils and eosinophils and plasma cells. In distinction, other lymphomas with cutaneous involvement seem to spare the papillary dermis, leaving a clear zone between epidermis and dermal infiltrate. Exocytosis of mononuclear cells into the epidermis is characteristic especially of plaque-stage MF, forming so-called Pautrier's microabscesses. Atypical hyperchromatic cells ("mycosis cells") often are found in the mixed infiltrate in the papillary dermis. Attempts to quantify the degree of mononuclear infiltrate and atypia of the cells and use this to distinguish MF from benign mononuclear infiltrates in eczematous dermatitis have been unsuccessful,[22] and no biochemical or immunologic marker for MF currently exists. Even identification of the convoluted atypical Lutzner cells in the cutaneous infiltrates is not pathognomonic, because their presence in benign cutaneous inflammatory diseases is well established. Despite these shortcomings, the combination of a polymorphous band-like dermal infiltrate with cellular atypia, epidermal exocytosis with the formation of Pautrier's microabscesses, and persistent erythematous and plaque scaly lesions can be sufficient to make the diagnosis of MF in most cases of plaque-stage MF.

In the tumor stage of MF tumors arise from existing plaques or

normal skin, commonly affecting the face and flexures. The infiltrate of these lesions tend to be more monomorphous and less epidermotropic than that seen in plaque-stage MF.[23]

Cutaneous Variants

Tumeurs d'emblee

In most MF patients, sequential but irregular progression through the three classic stages occurs. In the tumeurs d'emblee form of Vidal and Brocq, patients present with multiple nodules and tumors without erythematous or plaque lesions. Degos,[24] Samman,[25] Souteyrand and Thivolet[21] and others feel that this form of MF may represent other nonepidermotropic cutaneous lymphomas and not a form of MF.

Woringer-Kolopp Disease

The epidermotropic or pagetoid reticulosis described by Woringer and Kolopp in 1939 is characterized by single or multiple circinate lesions that histologically demonstrate epidermal acanthosis with clear spaces containing groups of mononuclear cells with irregular hyperchromatic nuclei.[26–27] The dermal infiltrate is quite sparse compared to most cases of MF. The exact designation of this reticulosis is unclear.

Erythroderma of Hallopeau-Besnier

This form of MF shows diffuse and intense cutaneous erythema, adenopathy, and intense pruritus.[9] Many feel that this is simply a form of SS.[21]

Unusual Cutaneous Presentations

Granulomatous,[28] bullous,[29] papillomatous,[30] pustular,[31] and acneiform[32] variants of MF have been described and may delay the correct diagnosis in unusual presentations.

Sézary Syndrome

The classic Sézary syndrome consists of pruritic erythroderma, palmoplantar keratoderma, nail dystrophy, lymphadenopathy, and leukocytosis with circulating atypical Sézary cells.[14] The erythroderma may present de novo or develop in the setting of preexisting MF.

Biopsy specimens of the erythrodermic skin in SS show a diffuse band-like mononuclear infiltrate with many atypical mycosis cells. Pautrier's abscesses commonly are found. Peripheral blood leukocyte counts of as high as 100,000/sg mm[1, 21] can be found with 10%–70% atypical Sézary cells identified microscopically. Light microscopic ex-

amination of May-Grunwald-Giemsa–stained preparations of peripheral blood Sézary cells often enables distinction between large cell (12–18 μ in diameter, densely furrowed nucleus with a large nuclear to cytoplasmic ratio) and small cell (8–12 μ in diameter, mildly furrowed nucleus) variants.[1, 33] These Sézary cells are acid phosphatase, glucuronidase,[34] and PAS positive,[1] but monocyte esterase and peroxidase negative.[1] On transmission electron microscopy they possess hyperconvoluted cerebriform nuclear contours. However, cells with similar morphological characteristics also are seen in benign skin diseases[35] and can be produced by mitogen stimulation of normal peripheral blood mononuclear cells.[36]

Systemic involvement is far more common with erythrodermic forms of MF, and, in general, lymphadenopathy occurs in 60% of patients with all forms of MF.[37] Rappaport considers the histologic changes found in lymph nodes with MF involvement characteristic[38] and distinguishes them from adenopathy associated with other lymphomas. Hepatosplenomegaly can occur in advanced disease, as can bone marrow involvement. Involvement of nonreticuloendothelial structures such as the CNS, eyes, external auditory canal, gastrointestinal tract, heart, and bones[1, 21, 39] also has been described. The distinction between MF involvement in lymph nodes and reactive or "dermopathic adenopathy" is a matter of considerable debate, and, indeed, the determination of MF-related nodal abnormality is being redefined by use of more accurate methods of definition.[40–42] Use of modern techniques for evaluation of DNA content, chromosome alteration, and ultrastructural morphology of cells in the lymph nodes suggests a rate of lymph node involvement as high as 81% in patients with CTCL.[43] More accurate identification of atypical mononuclear cells may allow a better understanding of the extent of extracutaneous disease, even early in MF.

"Premycosis Fungoides"

The term "parapsoriasis" originally was applied to a variety of scaly dermatoses believed to be precursors to MF.[44] Parapsoriasis en plaque (PEP) is characterized by persistent indurated scaly plaques, of which some may develop MF (so-called malignant form) and some do not (benign form). This latter group has been referred to as benign parapsoriasis en plaque, xanthoerythroderma perstans, chronic superficial dermatitis, discrete parapsoriasis en plaque, and digitate dermatosis. The incidence of MF in the entire group of PEP is probably quite low, but the presence of parapsoriasis en plaque as precursor lesions in patients with proved MF is documented.[44]

Poikiloderma atrophicans vasculare (PAV) is a syndrome that occurs in a variety of clinical settings. It is characterized by atrophy, mottled hyperpigmentation and hypopigmentation, and telangiectasia and shows a bandlike dermal infiltrate histologically. It is an important sign in developing MF, or dermatomyositis, but confusion with