Clinics in Dermatology (2015) **33**, 563–571

ELSEVIER

Clinics in Dermatology

Systemic involvement in mycosis fungoides

Günter Burg, MD*

Department of Dermatology, University of Zurich, Switzerland

Abstract Mycosis fungoides (MF) represents almost 50% of all primary cutaneous lymphomas and more than 70% of cutaneous T-cell lymphomas (CTCL). Arising from preferentially skin-homing lymphocytes with genetic instability, MF evolves through stages (IA-IVB), producing inconspicuous inflammatory features in the beginning and finally resulting in a proliferation of cytomorphologic, phenotypic, and genotypic abnormal tumor cells. Over the past 200 years, there has been much confusion in the classification of lymphomas due to semantic disagreements (*MF, CTCL, parapsoriasis, lymphosarcoma, reticulum cell sarcoma,* and many other terms), lack of diagnostic standard criteria, and new molecular diagnostic methods. Studies on extracutaneous involvement in early stages (IA-IIA) are almost completely lacking. In advanced stages of MF (IIB-IVB), discovery of extracutaneous involvement is dependent on the methods used (physical examination, technology, molecular diagnostics, autopsy, and laparoscopy) and reveals a wide range of results. Due to the inflammation-simulating features in the beginning of the disease, early diagnosis is very difficult to assess. Extracutaneous involvement has previously been documented in more than 70% of autopsies. More recent studies give much lower figures. Like all lymphomas, MF is a systemic disease from the very beginning, with distinct homing preferences in tumor cells. Organs most commonly involved during the lengthy course of the disease are, in descending frequency, lymph node/peripheral blood, liver, spleen, lung, bone marrow, GI tract, pancreas, and kidney.

Historical perspective: Changing concepts in terminology, diagnostic procedures, and classifications

Over the past 200 years, there has been much confusion in the classification of lymphomas (Figure 1). Jean-Louis Alibert (1768–1837)[1] presented "a strange disorder of the skin with mushroom-like tumors," which he described in detail under the names of "Pianfungoides" (1814) and "Mycosis fungoides" (MF) (1832). Looking at the picture of Alibert's patient Lukas, today we probably would diagnose anaplastic large cell lymphoma, CD30+. The microscopic studies by Xavier Gillotand Louis Antoine Ranvier (1835–1922)[2] in Paris indicated for the first time that MF was caused by regeneration of lymphoid tissue in the skin, something he called *lymphadénie cutanée*. Pierre Antoine-Ernest Bazin (1807–1878) differentiated an erythematous stage (I), plaque stage (II), and tumor stage (III) in 10 patients with MF.[3] Jean Baptiste Emile Vidal (1825–1893) and Louis Brocq (1856–1928), in their *Etude sur le Mycosis Fongoïde*, used the term "Mycosis fungoides d'emblée."[4] Ernest Henri Besnier (1831–1909)[5] and Francois Henri Hallopeau (1842–1919)[6] described an erythrodermic variant of MF. Based on studies on the "reticuloendothelial system" (RHS, RES) by Ilja Iljitsch Metschnikow (1845–1916), later on referred to as "mononuclear phagocyte system" (MPS), in the beginning of

* Corresponding author.
E-mail address: g.burg@access.uzh.ch (G. Burg).

http://dx.doi.org/10.1016/j.clindermatol.2015.05.008
0738-081X/

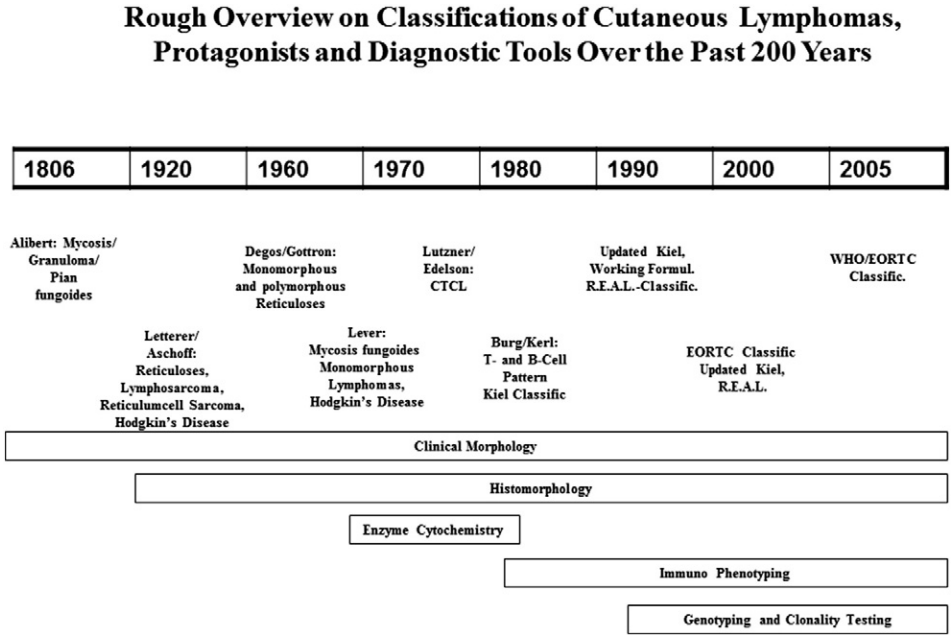

Fig. 1 Rough overview of classifications of cutaneous lymphomas, protagonists, and diagnostic tools over the past 200 years.

the 20th century most disorders, we today refer to as malignant lymphomas, have been designated as "reticulosis" or "reticulosarcoma" (7, 8). Today, we might refer to it as malignant lymphoma, designated *reticulosis* or *reticulosarcoma*.[7,8]

For many years, malignant lymphomas had been placed into three basic categories: Hodgkin disease, lymphosarcoma, and reticulum cell sarcoma. Dissemination often was interpreted as transformation into poorly differentiated types of lymphoproliferative disorders or Hodgkin disease. Every lymphoproliferative disorder with primary and exclusive manifestation on the skin usually was considered to be MF by hematopathologists. There was great confusion among pathologists over the use of these terms. Rappaport was the first to classify lymphomas by pattern (nodular or diffuse) and by cytologic subtypes.[9,10]

The complex field of lymphomas was elucidated by phenotyping tumor cells using immunocytology in diagnostic procedures, which led to the next stage of lymphoma classifications[11] (Kiel classification)[12] based on the ontogeny of lymphoid cells and the differentiation from stem cells to T cells and B cells and their subtypes. Cytogenetic studies for the demonstration of abnormal caryotypes also have been used for the detection of extracutaneous involvement in MF before phenotyping and genotyping were available.[13]

In addition to phenotyping, genotyping with confirmation of clonality by polymerase chain reaction (PCR) again generated new concepts for classifications: Working Formulation, revised European-American lymphoma (REAL) classification, and finally the World Health Organization (WHO) classification of tumors of the hematopoietic system.[14]

Variants and subtypes of MF and related cutaneous T-cell lymphomas have been reported, which increases the complexity of the field.[15–18] In dermatology the term *cutaneous T-cell lymphoma (CTCL)*,[19] used in the Anglo-American literature, has obscured the differences between MF, its variants, and non-MF CTCL.

The changing concepts in terminology and the availability of new diagnostic procedures over time partly explain the great differences in incidence reports on extracutaneous spread in MF. The high number of lymph node and visceral involvements reported in the early studies probably is due to imprecise identification of tumor cells and blurred definition of terms like *MF*. The impact of changing criteria also is reflected in delusive statistic evaluations. Within one decade (1975–1985) a significant shift in the incidence and the survival time of MF was reported.[20–22] These changes cannot be real but rather were due to changing diagnostic criteria for MF, which very often included patients suffering from atopic eczema or small plaque parapsoriasis, the latter of which can hardly be differentiated from early stage (IA and IB) MF by clinical or histologic criteria.[23–26] A major step in harmonizing the use of terms was the elaboration of the WHO classification for cutaneous lymphomas in accordance with the hematopathologic classification for nodal lymphomas.[17,27]

Staging classifications for MF (and other cutaneous T-cell lymphomas) also have changed over the past decades. Originally, Alibert[1] described only two stages of the disease: (1) tumors with a compact and hard consistency, and (2) tumors that undergo pustular ulceration and "start to lyse with a terrible smell." Classification into stages I-III (patch, plaque, tumor) was suggested by Alibert and Bazin[3] and was used until the middle of the 20th century. Considering the risk of extracutaneous involvement of lymph node and visceral organs in advanced stages of the disease, a new