

# The History of Lymphoma Classifications with Special Consideration of Cutaneous Lymphomas

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## Abstract

For the modern evidence based medicine classification systems are necessary to guarantee a unifying approach for therapy and for prognosis of diseases. The comparability of clinical studies depends of the usage of adequate classification systems. But because all classifications are artificial, they only mirror the technical possibilities of its area.

This review discusses the history of lymphoma classifications systems with a special focus on the topic of primary cutaneous lymphomas and the retikuloendothelial system. Furthermore special problems in terminology are discussed.

**Keywords:** Cutaneous lymphoma; Mycosis fungoides; Classification; Reticulosis

## Introduction

### Basics and background

The skin organ can be affected primarily or secondarily by a variety of neoplastic clonal B- or T-cell non-Hodgkin's lymphomas which exhibit heterogeneous clinical pictures in terms of clinical manifestations, histopathology, immunohistochemistry, cytogenetics and patterns of gene expression [1,2]. These are neoplasms of the immune system with a special tropism for skin and skin appendages [3].

If a lymphoproliferative skin disease occurs and if after completing the standard staging procedure no further extracutaneous manifestations are detectable, then a primary cutaneous lymphoma is present (PCL) [1,4]. Exclusion of a secondary skin involvement in a primary, mostly nodally located non-Hodgkin's lymphoma is prognostically and therapeutically crucial [5]. More than 30 different types of non-Hodgkin's lymphoma can affect the skin primarily or secondarily [6]. The existence of Hodgkin's disease initially displaying exclusively in the skin organ is uncertain, but would play a secondary role [7].

Depending on the inclusion criteria of the mesopharynx and/or palatine tonsil, the skin is the second or third most commonly affected extranodal organ respectively, with increasing annual incidence. 0.3-1.0 per 100,000 people are affected, depending on the author and place / region / country of the surveys [8].

The clinical course ranges from a very good prognosis, usually without treatment such as lymphomatoid papulosis, to fatal CD4 + / CD56 + hematodermic neoplasia despite intensive treatment [9].

Considering the many and various forms of differentiation and function of lymphoid cells, the complexity of the neoplastic is also partly due to an arrested stage of development and understanding of the abnormally proliferating lymphoid cells [10]. This complexity of non-Hodgkin's lymphoma is reflected in more than 50 different classifications, in contrast to only two classifications for Hodgkin's disease [11,12].

Primary cutaneous lymphomas usually have a distinctly different

clinical behavior and prognosis than histologically, cytomorphologically and immunohistochemically identical secondary cutaneous and nodal lymphomas [13]. However, for years the B-cell lymphomas in particular were divided into a classification system for nodal lymphomas which was partly not reproducible, resulting in serious consequences for treatment, which failed to meet the prognosis [13,14].

Despite the normally favorable prognosis it has to be noted that PCL, due to the movement of lymphoid cells, are usually systemic diseases with no curative therapy [15,16].

## General information on classifications

Medical classifications define and describe specific and characteristic features of disease entities and arrange them in an order [10]. The classifications thus represent a central component of medical pathology and are the conceptual and clinical basis for the 1. diagnosis, 2. therapy and 3. prognosis of diseases [10]. Particularly for diseases with low case numbers, a common classification is inevitable in order to arrive at adequate comparisons regarding incidence, prevalence, prognosis and therapeutic response [17].

Classifications are a reflection of methodological possibilities [18]. Since these possibilities are subject to continuous change, there is also persistent alteration in the classification models [18]. Formulating a classification based on the latest scientific findings and showing its clinical relevance is problematic with regard to practical clinical aspects [18].

The function of classifications is to arrange the existing knowledge of a subject at any one time into understandable and reproducible

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categories [18]. This can be achieved either epistemologically or according to practical clinical aspects [19]. Generally, a good tumor classification requires scientific accuracy, simplicity and clinical relevance. These requirements are not easy to fulfill, as shown by numerous classifications of lymphoma in recent years [19].

Based on a well-proven norm, malignant neoplasms are sorted first by their morphology, then according to functional criteria, and lastly according to clinical significance. This also applies to malignant lymphoma [20].

### Principles of attempts at classification

This section aims to give a systematic portrayal of the main criteria of the common nodal and two primary cutaneous Lymphoma classifications.

The heterogeneity of the classification approaches is presented. The classification is coded in alphabetical order as follows, for the individual classification criteria (see points 1 to 12 below) indicated in brackets in each example.

- a. Rappaport classification und updated Rappaport [21]
- b. Former German classification according to Lennert [22]
- c. Lukes and Collins [23]
- d. Kiel and updated Kiel [24]
- e. Dorfman [25]
- f. BNLI [26]
- g. Working Formulation [26]
- h. REAL [27]
- i. WHO [28]
- j. EORTC [29]
- k. WHO-EORTC [1]
- l. Isaacson [30]
- m. WHO 2008 [31]

### Historical

Eponyms appear in almost all classifications: Sezary (a), and Wroinger Kolopp (j), Ketron and Goodman (j), Brill-Symmers (b.), Burkitt (c.), Lennert (c.), Bennet (d), Waldenstrom (m.).

### Clinical

The clinical picture appears in the naming of some disease classifications and is therefore important:

Progress: aggressive behavior (i), lethal (h)

Prognosis: relative prognostic factors: low, intermediate or high (g).

Expressions: subcutaneous panniculitis-like lymphoma (j), hydroa vacciniform-like (middle), effusion (middle), mononucleosis-like (m.).

Comparisons: mycosis fungoides (d).

Local preference: leg type (j), nasal (i), mediastinal thymic (i), multilocular or unilocular (l), intestinal, hepatosplenic (i), bone (m.) CNS (m.)

Age at diagnosis: pediatric (m.)

Presence of a post-transplant status (m.)

Temporal relation to post-transplant status: early lesion (m.)

### Histological

Histology and cytomorphology were and still are the gold standard in diagnosis of lymphoma [24].

Patterns: nodular versus diffuse growth technique (a).

Predominant conformation: pagetoid, granulomatous (j).

Local preference: folliculotropic (j), intravascular (j), angioimmunoblastic (i), epidermotropic (l).

Non-neoplastic cellular or noncellular accompanying reaction: T-cell-rich BCL with diffuse sclerosis (g), connective tissue proportion (d) and T-cell rich / histiocyte rich diffuse large B-cell lymphoma (i).

Composition: composite (1), mixed cellular lymphohistiocytic (g).

Imitation behavior: follicle center (j), marginal zones (j), MALT (m.) (j).

### Immunohistochemical

Thanks to immunohistochemistry, morphologically indistinguishable cells can be distinguished by their functional form:

T-cell (c.), B-cell (c.), NK-cell (h), null-cell (d), CD4 + (j), CD8 + (j), CD56 + (k), CD30 (k) Ki1 (d), ALK + (m.)

### Tinctorial qualities

The tinctorial qualities are irrelevant for the nomenclature of all classifications listed in this paper except the Dorfman classification. Here the ability to transform is verified by means of the dye pyronin: Pyroninophil (e.)

### Cytomorphological

Cell maturation: cytic, blastic (d.), poorly or well differentiated (a.), anaplastic (d.).

Nucleus shape: Cleav. (c.) conv. (c.) hyperchrom. (c.), cerebriform (c.) nucleus size: medium to large (c.).

Differentiation and maturity: peripheral or central (h.).

Cell size: small-cell, large-cell (g.), villous versus non-villous (i.), indicating <6.5 microns or <8 microns (d.), monomorphic or polymorphic (l.), small-medium (m.)

Imitative behavior: Follicle center cell (j.), centroblastic (d.), centrocytic (d.).

### Etiological

The goal of any classification, also with PCL, should be based on a statement of etiology [31]. In neurology, this is partly realized in the classification of hereditary ataxia of the cerebellum by specifying the pathological nucleotide sequences [10].

This etiological classification feature in the form of a viral HTLV lymphoma genesis gave its name explicitly in the REAL classification. However, it was not taken up in the following classifications established by the WHO in 2001.

Etiology: HTLV-proof positive or negative (j.). This viral causal aspect could also be subsumed under the classification criterion "infectious".

WHO classification of 2008 (m) HHV 8, EBV

### Molecular

The molecular-based naming of the classifications is constructed on proof of the  $\gamma/\delta$ -configuration of the T-cell receptor. This  $\gamma/\delta$  terminology appeared in 1994 in the REAL classification and at that

time was the preferred practise of clinical study in molecular biology [10].

However, this proof can now be established by means of the  $\beta$ F1 monoclonal antibody.

Molecular: gamma / delta (k.), HTLV virus negative or positive (j.)

### Location

Nodal versus extranodal (h.).

### Lymphoma / leukemia

With or without washout lymphoid cells (b.).

### Provisory or definitely

Immunocytopoma (j.); Maltom (j.).

### Unclassifiable lymphomas: (g.).

From the mid-1930s until the late 1970s four different lymphoid neoplasms were distinguished: 1) lymphosarcoma, 2) reticulosarcoma, 3) giant follicular lymphoblastoma (Brill-Symmers' Disease) 4) Hodgkin's disease [22]. These concepts were not based on a uniformly accepted definition [21].

In 1964, the term non-Hodgkin's lymphoma was used for the first time [22]. Other sources report the first citation as being not until 1974 [18].

The discovery of the functional division of the immune system into B- and T-cells – along with the corresponding peripheral zones by Cooper [32] in 1964 and the morphologically reversible physiological adaptability of small lymphoid cells due to phytohemagglutinin of the green bean in large lymphoid cells by Nowell [33] in 1960 – revolutionized lymphoma research [20].

The concept of reticulosis that shaped the classification of lymphoid neoplasms for over 50 years is chronologically outlined below.

### Reticuloendothelial system and reticulum cells

In 1924, Letterer [34] introduced the term "reticulosis" since the term lymphoma – referring to any swelling of a lymph node – did not seem to be sufficiently specific [22]. However, in North America the term lymphoma was largely retained [35].

At the beginning of the 20<sup>th</sup> century and based on Ehrlich's concept of vital staining, Metchnikoff observed phagocytosis through cells which he called macrophages. Metchnikoff's scientific concept was based furthermore on investigations of Aschoff [36] who introduced the functional and not primarily morphological concept of the reticuloendothelial system (RES) in 1924.

In 1930, Maximow [37] tried to provide a morphological foundation for this originally functional concept based particularly on the Marchand's [38] hypotheses from 1898.

The RES was morphologically defined as an accumulation of pluripotent mesenchymal reticular cells which were believed to be located in the vascular adventitia of the entire vascular tree. According to this definition, reticular cells had the potential of differentiation of embryonic mesenchyme and could under certain conditions differentiate in hematopoietic, lymphopoietic, reticuloendothelial and fibroblastic cells [39-44].

Siegmund [45] described the RES as "active mesenchyme" with the

ability of lympho- and myelopoiesis. Extramedullary erythropoiesis by these cells would be possible as well, but rare. The RES could produce all blood cells and certain connective tissue cells [39,40].

The reticular cell was defined as a reticulin-fiber-producing support cell close to pluripotent embryonic mesenchymal cells [39].

In 1932, Pullinger [46] highlighted that there would be neoplasms of the reticular cells from their numerous offspring.

The term reticulosarcoma was introduced by Oberling [47] in 1928. In the German-speaking world it was designated by Rössle as Retothelsarkom [48].

The meaning of the term RES was specified differently in the literature. Thus Harrison [49] believed reticular cells to form channels in the form of endothelial cells. Fresen [40], however, mentioned the assumed involvement of the vascular endothelial cell layer as part of the RES [40]. Also, the term "reticular" itself has been explained using the observed tinctorially verifiable reticulin fiber formation, but also using the loose mesh-like arrangement of the cellular elements [50,51].

The RES concept was superseded partly by the reticuloendothelial system (RHS) of Fresen or the rethelien system [40].

Table 1 shows the common classification of reticuloses of the skin in the German-speaking world during the mid-1950s.

Until the late 1970s, there was no precise morphological description of the reticulum [44]. One of the most concrete definitions states that the reticulum is an "advential pluripotent reticulin-producing sustentacular cell" [44].

As opposed to Naegeli's [52] hematological dualism, the theory of a third independent leukocyte system, proposed by Schilling [53] with the reticulum cell concept, represented trialism in hematology from a genetic standpoint as well [53].

For decades, it was the common opinion that monocytes derived from reticulum cells. The RES would thus form blood monocytes and was believed to be independent of the myeloid and lymphoid system [43,54-56].

### New Interpretation of the RES

Due to radioactive isotopic methods in the late 1960s, it was found that the designated reticulum cells are not stem cells [56]. Rather than from the RES, monocytes derived from the bone marrow, which is not a third hematopoietic system, but closely related to the myeloid system [56].

Thus, the RES was replaced by the mononuclear phagocyte system, which is not independent, but closely related to the myeloid system [55,56]. A third blood-cell-forming system, as previously assumed for the RES, does not exist [55-58].

### New Interpretation of the reticulum

Steigleder [59] showed that the postulated reticulum cells of the skin are primarily fibroblasts, histiocytes and lymphocytes.

Proliferation	Benign	Malignant
Disseminated	Reticulosis Lymphadenosis	Reticulo-Sarcomatosis Lymphosarcomatosis
Localized	Reticuloma Lymphocytoma	Reticulosarcoma = Retothelsarkoma Lymphosarcoma

**Table 1:** Classification of the "reticuloendothelial system of the skin" in 1953 [40] and 1959 [41].

The reticulum cells demonstrated by Müller-Hermelink [60] in 1976 using electron microscopy and immunohistochemistry were described as interdigitating, fibroblastic, dendritic and histiocytic, having no common morphological structure with the originally designated reticulum cell [56,57,60]. However, the postulated origin of the initial cell of the CD4 + / CD56 + hematodermic neoplasm might be of interest, namely a plasmacytoid dendritic cell [1].

In some classifications neoplasia from large reticulum cells were referred to as histiocytic lymphoma, but actually mainly represent - according to the present knowledge - neoplasia of large transformed lymphoid cells, neoplasia of monocytes, or actual histiocytic proliferations [56].

The continental European usage of the term reticulosis of the skin impressed with the clinical picture of a uniform type of efflorescence, usually of multiple nodes of different sizes with a smooth surface. However, they proved to be low malignant B-cell lymphomas [56]. Likewise, the reticulosarcoma impressing clinically by a singular tumor proved to be a B-immunoblastic lymphoma and only in rare cases as neoplasia of histiocytes [56,58].

The monocytic leukemia/ reticulosarcomatosis cutis Gottron, described by Eva Gottron [61] in 1951 as a disease with paroxysmally occurring nodes proved to be - according to some authors - a skin manifestation of a myelomonocytic leukemia, while others stressed the high proportion of immunoblastic B-cell lymphomas in this disease [18].

This clinical picture shows clearly the difficulty of retrospective analysis of "reticulosis" diagnoses.

In 1978, Braun-Falco [35] suggested replacing the term reticulosis with the term "malignant lymphoma". Table 2 summarizes these results.

### Methodological milestones

Each tumor classification is based on the characterization of the proliferating neoplastic cells and on the discovery of functional and cytomorphologic similarities with a physiologically postulated sister cell [11].

In the past, lymphoreticular classifications were influenced by concepts based on ideas of the reticuloendothelial or lymphoid system prevailing at the time [56].

The following six points illustrate the methodological developments.

#### Technical

Advancements in the field of light microscopy, electron microscopy, the "camera lucida" [23], enabled us to improve the assessment of cell morphology [62]. The reproducibility of cytomorphologic results was further improved by computer-supported morphometry [63].

In 1967, Lennert [62] succeeded in identifying the endoplasmic reticulum in reticular cells using electron microscopy.

Furthermore, by using microtomes, semithin sections could be produced which represented, in addition to optical apparatus innovations, the precondition for better assessment of the slices [64].

#### Tinctorial

As early as the late 19th century, lymphatic cells could be distinguished from myeloid cell lines using Ehrlich's staining methods [12]. Azure-II-eosin stainings of Maximov and the industrially produced Giemsa staining represented further progress in the re-evaluation of cytomorphology [64]

#### Enzyme cytochemistry

Cytochemical representation of different nonspecific and specific esterases and acid phosphatases made the distinction between lymphoid cells of monocytes and histiocytes possible [64].

#### Cytological diagnosis of function

A so-called mitogenic stimulation with phytohemagglutinin resulted in a reversible transformation of small lymphoid cells into large blastic cells. As a result of the transformation tests, T-cell lymphocytes could be distinguished from B-cell lymphocytes [33].

#### Immunocytology

In a cell suspension produced from lymphoid cells by incubation with polyvalent anti-human Ig or by quantitative immunoglobulin detection, a B-cell lineage was demonstrated [65].

Through incubation with anti-human T-cell globulin, the lymphoid T cells reacted with a spontaneous rosette formation when adding sheep blood erythrocytes [56].

Kohler and Milstein [66] facilitated the production of monoclonal antibodies, which have been further optimized by the development of common paraffin antibodies. The obligatory and routine use of fresh preparations or cryostat gradually became less necessary.

The development of detection systems in the form of immunoperoxidase "bridge" technology in immunohistochemistry and newer methods for epitope demasking made retrospective assessment of paraffin preparations possible [67].

#### Molecular biological methods

Use of Southern-blot-hybridization and the polymerase chain reaction (PCR), placed proof of monoclonality of lymphoid infiltrates on a new methodological basis [68]. The DNA of neoplastic cells can now be selectively obtained by laser-assisted microdissection [68].

Structural chromosome aberrations, such as gene duplication or gene amplification, are often initially causally represented in a neoplastic process and are - since the REAL classification - an equal classification feature for defining entities [69]. By PCR, fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH) these changes can be specifically detected at the chromosomal level [69].

Neoplastic cells have been characterized by pathological changes to the pattern of their gene expression [69]. Evidence of this change can

<b>Former definition:</b>	<b>Autonomous atypical irreversible system-like proliferation reticulo-histiocytic cells of the reticuloendothelial system (RES)</b>
<b>Contemporary sense:</b>	<ol style="list-style-type: none"> <li>1. Neoplasms of the lymphoid tissue (usually B-cell)</li> <li>2. Myeloproliferative diseases</li> <li>3. Malignancies of the monocyte-histiocyte-macrophage system or the Merkel cell</li> </ol>

**Table 2:** Reticuloses of the skin according to [35].

be provided at the genomic, transcriptional or proteomic level [70,71]. Due to the Human Genome Project, the semiconductor industry and bioinformatics, the characteristic expression profiles of transformed and non-transformed lymphoid cells can now be collected [70,71].

## Classification of cutaneous lymphomas

### Mycosis fungoides

In 1806, Alibert [72] described the “Pian fongoide”, considering it a contagious European form of *frambesia tropica* and going on to name it *mycosis fungoides* (MF) in 1832. He adopted a text by Bontius [73].

According to other sources, Besnier et al. first used the term *Pian fungoides* in 1812 [74].

The designation was based on the similarity of the tumors of the MF with the fruiting body of certain mushroom species, such as *Bovista* [75]. The fact that both the fungi and the MF tumors share the characteristic feature of bursting on the “apex” reinforces the admissibility of this comparison [75,76].

Alibert [72] also distinguished at times a *mycosis syphiloides* and *mycosis framboesoides* from *mycosis fungoides*, assigning them all to the venereal diseases – a fact that was critically noticed by Hebra and Kaposi ten years later [77].

It was only later that a clear distinction between *frambesia tropica* and *mycosis fungoides* was made. Thus, a reference to the first description of *mycosis fungoides* is not possible [74]. In the following decades, *mycosis fungoides* was often compared to or equated with *molluscum of Bateman*, a disease that is now known as *neurofibromatosis* [74].

The initially flaky rash of *mycosis fungoides* has already been mentioned by Alibert. However, it was his student Bazin [78] who described the three phases of *mycosis fungoides* in 1870. Other sources mention the year as 1876 [75]. Bazin’s student Guerard spoke of “indigenous leprosy” [74].

In 1885, Vidal and Brocq [79] described the form *mycosis fungoides d’emblée* as a cognisant opposition to what is now well-known as a classic MF appearance. However, it proved to be not *mycosis fungoides*, but probably a primary cutaneous aggressive epidermotropic CD8<sup>+</sup>-T-cell lymphoma or cutaneous  $\gamma/\delta$  T-cell lymphoma [1].

Ranvier and Cornill [80] in 1868 and Gillot [81] in 1869 mentioned – albeit a misconception – the relation of the MF to the lymphatic system. In 1892 Hallapeau and Besnier [82] described the erythrodermic form [65]. Other authors, however, consider Leredde [83] to be the original describer [75].

In 1874, Port [84] emphasized the sarcomatous neoplastic nature of *mycosis fungoides*, which Auspitz [85] however diametrically opposed to a chronic inflammatory granulomatous aspect.

There were two opinions about the assessment of malignancy of *mycosis fungoides*:

1. “Inflammatory granulomatous theory” by Koebner [86] (“sponge-like skin”), Paltauf and von Zumbusch because of polymorphic inflammatory cell infiltrate and
2. The primary neoplastic model by Fraser and Montgomery, also preferred by Kaposi.

Auspitz [85] acknowledged the histological chronic inflammatory

granulomatous aspect so much that he suggested a renaming as *granuloma fungoides*. This terminology can be found until the late 1970s in the classification of Keining and Braun-Falco [87] and corresponds with PCL to the patient population of the dermatological clinic.

This abovementioned fundamental problem mirrors the still unclear issue of whether lymphoproliferative diseases of the skin are primarily a neoplastic “ab initio” or an initially inflammatory process [75]. The dermatopathologist encounters this difficulty in the differential diagnosis of “initial” *mycosis fungoides* or inflammatory dermatosis. In 1909, Paltauf emphasized the systemic nature of the MF [63]. Thanks to PCR T-cell receptor studies, Muche et al. [88], while detecting circulating neoplastic lymphoid cells also in the initial stages of *mycosis fungoides*, placed the systemic nature of the early MF on a molecular basis.

At this point, however, it has to be stressed that many benign dermatoses, such as the *Lichen ruber et planus* also partially exhibit monoclonal circulating T lymphocytes [88].

The Sézary syndrome was first described by Zumbusch [89] and in 1939 by Baccareda [90] as “reticulohistiocytosis cutanea benigna cum melanodermia”. It was Lutzner and Jordan [91] who succeeded with the electron microscopic cytologic description. However, the syndrome was named by Taswell and Winkelmann [92]. In 1964, Clendening et al. [93] described the Sézary syndrome to be a leukemic form of *mycosis fungoides*. In 1971, Crossen [94] not only laid the foundation for a non-lymphoid and reticuloendothelial origin of the Sézary or Lutzner cell, but also emphasized the neoplastic nature of the cells, demonstrating abnormal chromosome conditions such as in malignant cells. In 1975, the Sézary cell was characterized as belonging to the T-cell systema, and in 1978 the lymphoid cells were described as TH<sub>2</sub> helpers with corresponding cytokine profile [12].

As to the subtypes of *mycosis fungoides*, the following should be noted. The “Granulomatous slack skin syndrome” was clinically described by Bazex [95] in 1968 and eponymously coined by Ackerman [96] in 1978. Pagetoid reticulosis was described by Ketron and Goodman [97] in 1931 and in 1939 by Woringner and Kolopp [98]. However, it was named by Braun-Falco et al. [99]. The Ketron-Goodman type is defined by the WHO-EORTC classification not as pagetoid reticulosis, but as a primary cutaneous aggressive epidermotropic CD8 + T-cell lymphoma [1].

In 1984, Vakilzadeh and Brocker [100] described the syringotrope *mycosis fungoides* as “syringolymphoid hyperplasia with alopecia” [100].

### Classification Problems

The problem of classification, as well as the temporarily divergent view of malignancy, is illustrated below using a primary cutaneous T- and B-cell lymphoma.

#### Example of T-cell lymphoma: Lymphomatoid papulosis

As an example, lymphomatoid papulosis may serve well: first description and naming do not coincide. Dupont [101] described the disease in 1965. It was named, however, by Mcaulay [102] in 1968. Before 1965, lymphomatoid papulosis was known as “regressive atypical histiocytosis,” “atypical paradoxical reticulopathy” cutaneous Hodgkin’s disease, *mycosis fungoides* or as T-cell pseudolymphoma [75]. In 1975, based on morphological and immunological studies, Lutzner et al. [103] mentioned the relation of LyP to the CTCL.

In 1982, histologic subtyping in A, B or C was performed in a doctoral thesis by Willemze [104]. These subtypes are included in the WHO-EORTC classification, although they exhibit –without prognostic significance – different monoclonality of the T-cell receptor depending on the type and are often represented simultaneously within one lesion [1]. Lymphomatoid papulosis is not exclusively considered as an entity, but as part of a spectrum of CD30+ lymphoproliferative diseases [105,106]. The superordinate immunohistochemical classification appears problematic because the lymphomatoid papulosis type B must “by definition” be CD30 negative [1]. Furthermore, infectious or benign dermatoses with CD30-positive cells are called “simulators” [107].

### **Example of B-cell lymphoma: Primary cutaneous marginal zone B-cell lymphoma**

Marginal zone lymphomas were first described by Isaacson in 1984 [108]. They were designated as saltoma, immunozytome, lymphoplasmazytoide lymphoma, marginal zone lymphoma, plasmacytoma of the skin or maltome of the skin [109,110]. The distinction between immunozytomes and marginal zone lymphomas as separate entities seemed justified due to different clinical aspects (age difference, localization), histology (in the form of Dutcher or Russel bodies) and proportion of non-neoplastic cells as accompanying infiltrate [111,112]. In the WHO-EORTC classification, all of the terms mentioned above subsumed under the clinical picture, “primary cutaneous marginal zone B-cell lymphoma (PCMZL)” [1]. Many of the skin lesions formerly known as B-pseudo lymphoma retrospectively turned out to be primary cutaneous marginal zone B-cell lymphomas [109,113].

### **Systematic classification of cutaneous lymphomas and reticuloses**

#### **Classifications before the mid-1970s**

For many decades, mycosis fungoides, Sézary syndrome, lymphomatoid papulosis and pagetoid reticulosis were the only cutaneous lymphomas that were clearly defined as entities [114,115]. Notifications of skin lymphomas which did not correspond to those mentioned above were casuistic rarities. They were referred to as malignant reticulosis or reticulum cell sarcoma, terms that were only used for forms of expression of a systemic process with an unfavorable prognosis [116].

Until the mid-1970s, cutaneous lymphomas/reticuloses were classified in visceral versus cutaneous forms, according to the nature of the skin lesion, according to the course of the disease, according to a known or unknown etiology, or histologically according to the predominance of a monomorphic or granulomatous infiltrate component [35].

#### **Application of nodal classifications for cutaneous lymphomas**

By abandoning the concept of reticulosis in favor of the lymphoma designation and by introducing and adapting nodal classifications [50] to the skin organ of Lever and Schaumburg-Lever [117] in 1974, the cutaneous lymphoma classification was placed on a new basis [11]. By immunohistochemistry, reticuloses were considered malignant lymphomas of T- or B-cell type being locked in their particular stage of differentiation, [118].

The Kiel classification was applied to the malignant lymphoma of the skin in the form of a “periodic table” [118] or simply according to a high or low degree of malignancy [118]. Furthermore, the Working Formulation was applied to skin lymphomas [119].

Further investigations led to the discovery of other B-and T-cell lymphomas differing in their clinical appearance, behavior, prognosis and histology, and subject to an inconsistent nomenclature:

1. the use of nodal classifications or
2. striking histological appearances (vascular-stressed, subcutaneous fat) or
3. immunophenotypic appearance of neoplastic cells [117].

Because of the clinical and terminological heterogeneity, reproducibility was low, which in turn led to the use of histological nodal classifications.

Modern contemporary therapeutic approaches need an adequate classification [1]. However, there was no generally accepted classification for cutaneous lymphomas.

Instead, the Rappaport classification, Kiel classification and WF were used for the systematic classification of cutaneous lymphomas, originating however in the lymph node pathology [119]. In summary, it can be stated that until the mid-1980s it was beyond dispute that malignant lymphomas not constituting mycosis fungoides/ Sézary syndrome, lymphomatoid papulosis or pagetoid reticulosis, were inevitably manifestations of systemic lymphomas [115,120].

#### **Independent classification for cutaneous lymphomas**

However, as early as a hundred years ago there was already anecdotal evidence of reticuloses, originating primarily in the skin with a long disease course, as represented by Buschke and Hirschfeld in 1911 [121].

At this point the Italian dermatologists Mariani [122], Flarer [123], Fieschi [124] and the French Sézary [125] and Cazal [126] are to be mentioned as pioneers in the recognition of primary cutaneous lymphomas.

Observations of indolent lymphomas confined for a long time to the skin organ were interpreted as casuistic rarities [127,128].

In a retrospective study by Evans et al. [129], patients who died five years after initial manifestation of the lymphoma were categorized as diseased with malignant lymphoma, while the surviving patients were classified with “lymphoid hyperplasia”.

The classifications previously developed for nodal lymphoma could never fully take into account the particularities of organ-specific lymphomas with corresponding “homing” receptors. Thus, it was understandable that in dermatology many classifications were drawn up differing from nodal ones, which in turn led to a lack of understanding and recognition from the pathologists and hematopathologists [129]. As a further organ-specific classification of lymphoid neoplasms, the lymphoma of the gastrointestinal tract may be mentioned [130,131].

The concepts of classifying cutaneous lymphoma were based on anatomical structures of the lymph node, which are not represented in the skin [114,115]. Clinical pictures of the skin, such as lymphomatoid papulosis, mycosis fungoides, pagetoid reticulosis and folliculotropic mycosis fungoides, have no nodal equivalent [116]. In addition, as early as 1980 Lennert [132] mentioned the significant differences in terms of B-and T-cell proportion in nodal and cutaneous NHL [131]. Histologically, it is almost impossible to distinguish a lymphomatoid papulosis of Willemze type B from a mycosis fungoides in the plaque stage without providing clinical data [116].

Only occasionally have lymphomas of the skin been included in nodal NHL classifications: e.g. MF in the Kiel classification [18,20].

In 1975, all cutaneous lymphomas in the North American region (including mycosis fungoides, Sézary syndrome, pagetoid reticulosis) were summarized under the category “cutaneous T-cell lymphoma” (CTCL) [133]. A further subdivision was drawn up by Edelson [134] in 1980, observing the presence of an epidermotropic or non-epidermotropic infiltrate component [134]. The establishment of primary cutaneous B-cell lymphomas (PCBCL) succeeded in the early 90s [135].

It must be explicitly emphasized that no distinction was made between primary and secondary lymphomas occurring in the skin. The diametrical opposition of visceral and cutaneous form mentioned above was not supposed to express a fundamental difference in the nature of the disease, but only meant to demonstrate the chronicity and clinical aspects, as well as to provide a better prognosis in the individual case [136].

In the cytomorphologic Kiel classification, the germinal center lymphoma and anaplastic large cell lymphoma CD30 + were shown to be highly malignant. This observation was, however, contrary to the clinical observation attesting an excellent prognosis to diseases of the skin organ [115].

Furthermore, differences between histologically identical nodal and cutaneous lymphomas were discovered according to oncogenic expression, the presence of adhesion molecules, chromosomal translocations and occurrence of viral sequences proving the inadequacy of the exclusive consideration of the histology [115]. However, this was already known to dermatologists, since – as mentioned above – a mycosis fungoides can only be differentiated from a lymphomatoid papulosis type B or a small and medium cell pleomorphic T-cell lymphoma considering clinical information [136]. Furthermore, there is no nodal correspondence for numerous cutaneous lymphoid neoplastic clinical pictures, as for example for LyP, folliculotropic MF and pagetoid reticulosis [137]. Thus clinically definite entities and not histologic subtypes have been characterized [138].

In 1991, Kerl [138] classified CTCL according to the updated Kiel classification and precursor T and peripheral T-cells. The final concept was introduced three years later by the REAL classification.

In 1993, Pimpinelli et al. [139] classified CTCL in 1. MF, 2. CD 30+ CTCL of non-MF-type and 3. CD 30-CTCL of non-MF-type. PCBCL were viewed as a homogeneous group, without prognostic subtype [138].

Burg’s [140] classification from 1994 included and arranged all cutaneous lymphomas known at that time that could affect the skin

primarily and secondarily. The division was performed using the updated Kiel classification and Working Formulation [141].

A co operation between the dermatology clinics in Munich and Graz in the form of the “German-Austrian Cutaneous Lymphoma Study Group” began in 1973 [141]. In 1980, von Burg and Kerl [135] established the “EORTC cutaneous lymphoma task force” which, in 1982, now including more centers, acquired the project group status [140], whose main objectives were summarized by the Breur Committee in 1984 [141]. The classification by Willemze [114] in 1994, as a result of the Breur commission of the CTCL, represented the basis for the subsequent EORTC classification which corresponded approximately to the classification of Russell-Jones in 1996 [141]. It was based on the patient collective of all Dutch university hospitals and the university hospital of Ghent. The EORTC classification, published in 1997, was the first classification of exclusively primary cutaneous lymphomas subdividing reproducible disease entities according to clinical prognostic criteria. Pathologies that differed histologically, but not clinically with any certainty were assigned the adjective “provisional” [29].

Like any organ-specific classification, it was subject to criticism for its inability to communicate cross-disciplinarily [75]. A uniform communication is essential, however, especially for primary cutaneous lymphomas, as not only dermatologists and pathologists, but also hematology oncologists are involved in diagnosis, therapy and treatment [75].

The REAL classification, published in 1994 by the “International Lymphoma Study Group” (ILSG) [27] and based on the fundamental principles of the updated Kiel classification, contained numerous primary, but also secondary cutaneous lymphoma entities, and no histological subtypes. Thus, as already mentioned, it was the first joint classification of NHL, created by 24 experts from North America and Europe [27].

In 2001, the REAL classification was superseded by the WHO classification, which also contained defined clinical pictures not yet known to the EORTC classification in 1997 [30].

The main benefit of the EORTC classification for the hematopathologists was the awareness of the clinical features of primary cutaneous lymphomas with similar histo- and cytomorphology [141-143].

Table 3 [138,144-158] illustrates the significant systematic classifications of reticuloses of the skin and cutaneous lymphomas.

### WHO-EORTC classification

Being subject-specific, the EORTC classification consisted

Year	Authors/Main Proponents	Year	Authors/Main Proponents
1949	De Graciansky and Paraf [143]	1976	Burg and Braun-Falco [153]
1956	Lindner and Meyer [144]	1976	Pinkus and Mehregan [154]
1957	Degos et al. [145], Winkelmann and altman [147]	1978	Lever and Schaumburg [117]
1958, 1957	Gans and Steigleder [148]	1979	Kerl et al. [155]
1960	Gottron [149]	1991	Kerl et al. [155], Pimpinelli et al. [139]
1962	Gertler [150]	1994	Willemze et al. [115], Isaacson [30]
1964	Cazal [151]	1994	Burg et al. [139], Slater [158]
1966,1967	Musger [152]	1996	Knobler et al. [141]
1969, 1961	Keining and Braun-Falco [87]	1997	EORTC [29]
1975	Lutzner [103]	2005	WHO-EORTC [1]

**Table 3:** Overview of systematic attempts at classification of lymphomas and reticuloses of the skin.

exclusively of lymphomas initially emerging in the skin organ. According to the WHO classification, primary cutaneous lymphomas are partially classified in the general classification context by denomination as special entities [1]. However, as mentioned above, even within the same academic institution different classifications were used [1]. Thus, as with nodal classifications, studies and therapy results could not be compared.

The differences between the two classifications were not only linguistic, but also represented fundamentally different conceptions. The WHO classification assigned the sum of diffuse large B-cell lymphomas of the skin organ to the category of DLBCL, frequently implicating the therapeutic measure of chemotherapy [159]. Lymphomas comprising follicular structures were classified as follicular lymphomas of the type "follicle center", usually not requiring chemotherapeutic treatment [1,159].

In contrast, according to the EORTC classification PCFCL consists of germinal center cells with diffuse, diffuse and follicular, or only follicular structure, normally not requiring chemotherapeutic intervention [29].

By means of two consensus conferences, in Lyon in September 2003 and in Zurich in January 2004, the first common classification for primary cutaneous lymphomas was adopted: the WHO-EORTC classification [1].

According to Burg et al. [160], the current WHO-EORTC classification represents only a working basis for a further increase in knowledge through prospective gene expression pattern analyses, epigenetic and proteomic analyses also influencing the classification of PCL [160-162].

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