Classification of Malignant Lymphoma in Domestic Animals: History and Conceptual Evolution

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SUMMARY

Malignant lymphomas (ML) are an heterogeneous group of neoplasms with variable morphology, diverse clinical presentations and variable prognosis and treatment. For these reasons, numerous attempts have been made both in human and veterinary oncology, in order to establish rational classifications of these tumors. There were based upon the contemporary knowledges of normal blood cell and precursor morphology. Developments have occured in parallel with the progress in our knowledge as cytological methods of identification improved. Because of the numerous similarities between animal and human ML most of the proposed animal ML classifications were adapted from the human schemes. Nevertheless, due to major differences between human and animal lymphomas excepted for some categories of tumours the clinical value of these classifications remains to be accuratly demonstrated. The revised European American lymphoma classification (REAL) which is now accepted worldwide by clinicians and pathologists, provides for extensive subdivision of the ML based on both morphology and immunophenotype and on cytogenesis for some subtypes. The neoplasms are classified as distinct entities in regard to histogenic derivation and biological behaviour. The sophistication for tumor management in veterinary medicine and the growing availability of more immunological markers in animal hematology, prompted us to propose the REAL classification for animal oncology. The proof, however of relevance of this ML classification will depend on large clinico-pathological studies involving both clinicians and pathologists.

INTRODUCTION

Malignant lymphomas (ML) or Lymphomas are malignant proliferation of lymphocytes and lymphoid cells. They are responsible of solid tumours and/or acute or chronic leukemias. The terms of leukemia (1845) and lymphosarcoma (1863) were initially employed by Rudolf Virchow[42]. Theodore Billroth was the first to use the term "malignant lymphoma" (1871)[4]. In 1832, Sir Thomas Hodgkin described a syndrome characterized by the development of adenopathies: the Hodgkin's disease[15].

At the end of the 19 th century and at the begining of the 20 th century several attempts were made to identify the cellular origin of these tumours. All the tumours were considered to originate from the so-called reticulo-endothelial system described by Ashoff in 1924[2]. That is the reason why further terms were proposed such as: Reticulosarcome (Oberling, 1928)[25], Retothelsarkom (Roulet, 1930)[30], Reticulosis and Reticulosarcoma (Robb-Smith, 1938)[29] and Histiocytic lymphoma (Rappaport, 1966)[28]. The concept at that time was that a single undifferentiated mesenchymal cell could give rise to both all blood and connective tissue cells.

Lymphoid neoplasms are an heterogeneous group of tumours, with various morphologies, diverse clinical expressions and variable prognosis and treatment. For these reasons, numerous attempts have been made, both in human and veterinary oncology, in order to establish rational classifications of these tumours.

HISTORY OF THE CLASSIFICATION OF MALIGNANT LYMPHOMA IN MAN AND ANIMALS

Ideally a tumour classification should reflect the different morphologic categories and have clinical implications predicting the behaviour of the various subtypes and their response to standardized therapy. In addition, pertinent classification should corre-

spond, as far as possible, with the known or supposed mechanisms of the tumour pathogenesis and the origins of the neoplastic cells.

During the last decades, major developments have occured in parallel with the advances in our knowledge of normal blood cell lineages and in cytological methods of identification. Hence, the evolution of the ML classifications must be considered both methodologically and conceptually.

Because of the numerous similarities which exist between animal ML and human non-Hodgkin's lymphomas (NHL), most of the proposed animal ML classifications were adapted from the human ones[31].

1. The Gall and Mallory's classification (Table I)

The first serious attempt to classify ML in man was made by Gall and Mallory (1942)[11]. This classification was applied to the dog by Bloom et al. (1945)[5].

2. The Rappaport's classification (Table II)

In 1966, Henry Rappaport proposed a classification based not only on cell morphology, but also on the growth pattern of the neoplastic tissue[28]. This classification introduced the idea that architecture of the neoplastic tissue is indicative of the clinical prognosis of the tumour. It distinguished, for each cytological type, the nodular or follicular form and the diffuse form. Based on contemporary views of the hematopoietic cell lineages, this classification includes, as did Gall and Mallory's, a "histiocytic" type which is not retained in our modern concepts. Rappaport's classification was much in use in veterinary pathology up until recently[13,40,43]. In particular the first World Health Organization classification of animals tumours of lymphoid tissues was based on its principles[17]. Because most of the animal ML were classified as diffuse tumours with histiocytic cell morphology, Rappaport's classification had no prognostic value in veterinary medicine. In addition a link between nodularity and clinical stage of disease progression has never been reported in animals[37].

At the end of the sixties, new investigations on the immune system and lymphoid cell physiology led to new conceptual orientations. Essentially, two different systems were developed: the so-called "American concept" by Robert Luckes[21] and the "European Concept" by Karl Lennert[18]. For the first time it was attempted to distinguish between lymphomas derived from the B- and T-lymphocyte series.

Table I
Gall and Mallory classification

- Stem cell lymphoma
- Clasmatocytic *(monocytic)* lymphoma
- Lymphoblastic lymphoma
- Lymphocytic lymphoma
- Hodgkin's lymphoma
- Hodgkin's sarcoma
- Follicular lymphoma

Table II
Rappaport classification

Lymphocytic, well differentiated	Follicular (nodular)/diffuse
Lymphocytic, poorly differentiated	Follicular (nodular)/diffuse
Mixed Cell (lymphocytic-histiocytic)	Follicular (nodular)/diffuse
Histiocytic (Reticulum cell sarcoma)	Follicular (nodular)/diffuse
Undifferentiated	mostly diffuse

Table III
Kiel classification

Low-grade malignancy

ML lymphocytic:
- B-CLL*
- T-CLL*
- Mycosis fungoides and Sezary syndrome

ML lymphoplasmacytic / lymphoplasmacytoid (LP immunocytoma)

ML plasmacytic (plasmacytoma**)

ML centrocytic

ML centroblastic / centrocytic: (1)
- follicular
- follicular and diffuse
- diffuse

High-grade malignancy

ML centroblastic:
- pure (monomorphic)
- mixt (polymorphic)

ML lymphoblastic:
- B-lymphoblastic
- Burkitt type and others
- T-lymphoblastic, convoluted-cell type and others
- Unclassified

ML immunoblastic:
- with plasmablastic / plasmacytic differentiation (B)
- without plasmablastic / plasmacytic differentiation (B or T)

* CLL: Chronic lymphocytic leukemia
** Only extramedullary plasmacytoma
(1) with or without sclerosis

3. The Kiel classification (Table III)

The classification of Lennert and co-workers, supported by the European Lymphoma Club, was published in 1974 and it was called the Kiel classification[12]. It is based upon two concepts:

- 1st: ML cells are neoplastic equivalents of the various cytological forms of normal lymphoid cells.
- 2nd: tumour cells are - permanently or not - blocked ("frozen") at one of the various stages of the normal lymphoid cell evolution.

Two cell series, namely, the T- and the B-lymphocyte series, develop from a still poorly defined stem cell of the bone marrow. The "naive or virgin" T- and B- cells are called T1- and B1- lymphocytes, respectively. When these lymphocytes encounter antigenic stimulation for the first time, they transform into blast cells. T1-lymphocytes develop into large basophilic cells or T-immunoblasts. These immunoblasts either fulfill their function and die or they become T2- lymphocytes. The latter are sensitized and react more intensively and quickly when stimulated a second time by the same antigen. They represent the memory cells of the T-cell series.

When B1-lymphocytes encounter antigenic stimulation for the first time, they also transform into immunoblasts (B-immunoblasts) which at this time could not be morphologically distinguished from T-immunoblasts. B-immunoblasts give rise to plasma cells (which develop via plasmablasts and proplasmacytes). A further response to the first antigenic stimulation sets off the development of germinal centers with centrofollicular cells, namely centroblasts and centrocytes. In germinal centers, centroblasts give rise to centrocytes and these ultimately to B2-lymphocytes which are the memory cells of the B-cell system. Thus, germinal centers are first a site of B-lymphocytes multiplication and also produce the precursors of the plasma-cell series.

The Lennert's scheme is certainly an oversimplification and contains many flaws (where should be included the Killer cells, for example?). Nonetheless, it may help us to understand not only the main types of malignant lymphomas, but also the numerous possible borderline cases. The tumours that arise from both main cell types of the germinal centers (centroblasts and centrocytes) would mimic the follicular architecture.

From the prognostic point of view, the Kiel classification distinguishes two main groups of tumours: lymphomas of low-grade and those of high-grade malignancy. The terms used for the low-grade ML end with the suffix "-cytic" (or "cytoid") and those for the high-grade with "blastic". Generally, the cells of the low-grade tumours are small, with only occasional large blast forms intermingled among them. In contrast the high-grade malignant types consist of a pure population of larger "blastic" cells. The basic division into low- and high-grade malignancies correspond well with the results of kinetic studies and it does not take into account the histological growth pattern.

The original Kiel classification was extremely useful for describing the different cell types. In spite of the non-use of immunohistochemical techniques unavailable at this time and by mean of cell phenotype alone, the Kiel classification ascribed most NHL to the B- and, to a lesser extent, T- lymphocyte series. Lennert aknowledged that this ascription was easier for ML of the B-cell series than for those of the T-cell series since, at that time, the relationship between morphology and function for B-cell forms was better understood than it was for T-cells. He admitted that the morphology, cytochemistry and immunohistochemistry of the T-cells had to be studied further in order to find the counterparts of the various subtypes of neoplastic T-cells. The Kiel classification was (is) widely used, mainly in Europe, in veterinary oncology.

4. The Lukes and Collins classification (Table IV)

During the same period Lukes and Collins described what they called "the follicular centre cell (FCC) concept"[22]. In the normal human follicular centre, they characterized two types of cells they considered as B-cells:

- 1st: the cleaved nucleated cell with scanty cytoplasm,
- 2nd: the non-cleaved nucleated cell with prominent pyroninophilic cytoplasm.

There is a wide variation both in the size of the cells and in the degree of nuclear cleavage.

Table IV
Lukes and Collins classification

I - U Cell (undefined cell) type.

II - T cell types:
- 1 - Mycosis fungoides and Sezary syndrome.
- 2 - Convoluted lymphocyte.
- 3 - Immunoblastic sarcoma of T cell.

III - B cell types:
- 1 - Small lymphocytes (CLL)
- 2 - Plasmacytoid lymphocyte
- 3 - Follicular centre cell (FCC) types:
  (follicular, diffuse, follicular and diffuse, and sclerotic)
  - a - small cleaved
  - b - large cleaved
  - c - small non-cleaved
  - d - large non-cleaved

IV - Histiocytic type.

V - Unclassifiable.

They proposed that the follicular center is the site of B-cell transformation: the small B-lymphocyte under the influence of antigen undergoes nuclear cleaving. Gradually, the cleaved cell enlarges, acquires a narrow rim of pyroninophilic cytoplasm and the nuclear cleavage disappears as the nucleus becomes round or oval. Nucleoli appear and enlarge. The non-cleaved cell continues in its enlargement.

The small T-cell probably undergoes a parallel transformation in the interfollicular tissue, but without nuclear cleavage.

The Lukes and Collins' classification is essentially a "functional" classification, no subdivision was made according to the grade of malignancy.

In spite of different conceptual approaches both Lukes - Collins and Kiel classifications were based primarily on cytology and showed very close concordance[19].

They have been successfully applied to animal ML, mainly in bovine[27,40] and canine[1,13,26,35,40] species. This is not surprising in view of strong functional and morphologic similarities between canine[35], bovine[9,10], and human normal lymph nodes. Using both classifications almost all categories of human NHL could be recognized in animals. In both systems, large cell diffuse type is the most frequently observed in bovine and canine and its subtypes are the counterpart of the centroblastic, centroblastic-centrocytic and immunoblastic categories of the Kiel classification[1,26,27,35,40] or the large non-cleaved cells and immunoblastic ones of the Lukes-Collins classification[1,13,35,40]. According to these classifications most of the bovine ML both the enzootic and sporatic forms[27], and most of the canine ML[1,13,26,35] were B-cell derived. Bovine[27] and canine[1,13,26] lymphoblastic lymphomas are present in small numbers. Some of them could be considered to be T-cell derived although the immunophenotype cannot be predicted by morphological criteria alone. In both species most of the ML are considered high-grade malignant[1,13,26,27,35]. Nevertheless, in the dog, most of the studies failed to demonstrate clinical relevance of the two classifications[1,13,26].

5. The Working Formulation (Table V)

At the beginning of the seventies, several other classifications of human NHL were proposed concurrently mainly by Dorfman[8], the British National Lymphoma Investigation group[3], the WHO[23] and the Japanese group of ML study[32]. In an attempt to harmonize all these proposals, an international multi-institutional study was carried out under the auspices of the National Cancer Institute in 1980; it was called "the non-Hodgkin's lymphoma pathologic classification project". A total of 1250 NHL cases were classified by experienced pathologists, using the six major classifications including the Kiel and the Lukes and Collins ones. No difference in reproducibility and clinical relevance among these classifications was found. This clinicopathologic collaborative study resulted in the "Working Formulation (WF) of the non-Hodgkin's Lymphomas for Clinical Usage"[24]. The WF was not proposed as an additional classification but as a compromise between the terminologies used by the previous classifications in order to facilitate clinical comparison of therapeutic trials. It introduced a subdividision into low-grade, intermediate-grade and high-grade NHL. A major weakness of the WF is that it did not separate lymphomas according to their B- or T-cell origin. It does not attempt to relate ML to the immune system and it is not based on a functional concept.

Table V
A working formulation of non-hodgkin's lymphomas

Low-grade malignancy
ML small lymphocytic
consistent with CLL
plasmacytoid
ML Follicular
predominantly small cleaved cell
ML follicular
mixed, small cleaved and large cell
Intermediate-grade malignancy
ML follicular
predominantly large cell
ML diffuse
small cleaved cell
ML diffuse
mixed, small and large cell
ML diffuse
large cell:
cleaved cell
non- cleaved cell
High-grade malignancy
ML large cell, immunoblastic
plasmacytoid
ML lymphoblastic
convoluted cell
non convoluted cell
ML small non-cleaved cell
(Burkitt's)
Miscellaneous
Composite
Mycosis fungoides
Histiocytic
Extramedullary plasmacytoma
Unclassifiable
Other

The WF was easily adapted to canine ML[1,7,13,37]. In general, at least in the dog, the WF and the Kiel classification give consistant results regarding the main cytologic subtype prevalences. Most canine ML are of intermediate grade malignancy and consist mostly of large cell lymphomas[37]. As for the former Kiel and Lukes and Collins classifications unsufficiency was still the lack of correlation of the prognostic significance of the histopathological grade of malignancy. However in a recent study it was established that high-grade malignancy according to the WF was an unfavorable prognostic factor for survival in dogs[36].

The WF was also applied to bovine[40] and feline[38] lymphomas.

THE MODERN CLASSIFICATIONS OF NHL

1. The updated Kiel classification (Tableau VI)

Although the original classification of Kiel - as that of Lukes and Collins - distinguished between lymphomas derived from the B- and T- lymphocyte series, it was primarily based on the morphology of the cells and very little on functional or immunophenotype data. If various B-lymphocyte derived ML subtypes could be identified by morphological analogy with the normal lymphoid cells from which they are considered to originate, the so-called T-lymphocyte derived ML group was poorly documented. Progressively as more and more monoclonal antibodies specific to various lymphoid cells and precursors became available, new immunological criteria were introduced, using immuno-histochemical labelling. This led eventually to the publication of an updated Kiel classification in 1988[33] and 1990[20].

Table VI
Updated Kiel classification (1990)

B-cell lymphomas	***T-cell lymphomas***
Low-grade malignant lymphomas	
Lymphocytic Chronic lymphocytic leukemia Prolymphocytic leukemia Hairy-cell leukemia	Lymphocytic Chronic lymphocytic leukemia Prolymphocytic leukemia
Lymphoplasmacytic/-cytoid (LP-immunocytoma)	Small cell, cerebriform Mycosis fungoides, Sézary's syndrome
Plasmacytic	Lymphoepitheloid (Lennert's lymphoma)
Centroblastic follicular ± diffuse diffuse	Angioimmunoblastic (AILD, LgX)
Centrocytic	T-zone lymphoma
	Pleomorphic, small cell
High-grade malignant lymphomas	
Centroblastic	Pleomorphic, medium and large cell
Immunoblastic	Immunoblastic
Large anaplastic (Ki-1 +)	Large anaplastic (Ki-1 +)
Burkitt's lymphoma	
Lymphoblastic	Lymphoblastic
Rare types	*Rare types*

The updated Kiel classification is still based upon morphological criteria of tumour cells (size, chromatin aspect, nucleoli, width and staining of the cytoplasm...) and it further distinguishes between high-grade and low-grade ML. However, immunological criteria are introduced, allowing the phenotypic identification of new subtypes, especially in the T-cell derived group.

In addition to the definition of new subtypes, the most recent Kiel classification was extended to extranodal NHL.

The updated Kiel classification was applied to animal ML while specific markers of animal lymphoid cells became available, mainly in dog[35,36,37] and cat[6].

In the dog, Teske confirmed the results obtained by using the original Kiel classification[35]. In addition, he uncovered an unexpectedly high frequency of T-cell lymphomas which could not be identified by morphological criteria. Some lymphomas with B-cell morphology had, in fact, a T-cell immunophenotype. Some discrepancies could be explained by the existence of the so called T-cell- rich B-cell lymphoma which is now recognized in animals[34]. Regarding the prognostic significance of the cytological types, multifactorial analysis showed that T-cell phenotype is the most important independant prognostic factor associated with poor prognosis[36].

2. The REAL classification (Table VII)

In 1994, the International Lymphoma Study Group (ILSG) published a Revised European American Lymphoma (REAL) classification. The REAL system combines tumour cell morphology, immunophenotype, genetic features and clinical manifestations. The neoplasms are classified as distinct entities in logical lists in regard to histogenic derivation and biological behaviour though not with low- and high-grade separation as the Kiel and WF systems did. The inclusion of clinical criteria is one of the most novel aspects of the ILSG approach. The REAL also stresses the distinction between histologic grade and clinical aggressiveness; the histologic grade should be applied within individual entities and not across the entire spectrum of lymphoid neoplasms. Finally

the REAL system distinguishes between B-cell and T-cell-derived neoplasms that may have the same or similar histological architecture and cytomorphology; in this respect it presents an advantage over the Kiel and WF classifications.

The sophistication for tumour management in veterinary medicine and the availibility of more immunological markers in animal cytology led during the last years to the identification of numerous new ML and leukemia entities in animals with impressive analogies to their human counterparts. This is the reason why we have adopted the REAL system for the new edition of the Histological Classification of Hematopoietic and Lymphoid Tumours of Domestic Animals which will published soon by the Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the WHO Collaborating Center for Comparative Oncology[39]. Not only tumours of lymphoid system but also benign lymphoid proliferations, malignant and benign myeloid (including histiocytic) proliferations and miscellaneous tumours as mast cell tumours, thymoma and Hodgkin's-like tumours are included in this classification.

3. The new WHO Classification

Finally a new WHO classification of human neoplastic diseases of the hematopoietic and lymphoid tissues has been finalized[16]; it is based on the works of both the European Association for Hematopathology (EAHP) and the American Society of Hematopathology (SH). This classification incorporates both NHL and Hodgkin's disease and all the haematopoietic tissue derived neoplasms, including mast cell and histiocytic tumours. It is based on the same principles of disease definition as the REAL scheme. However since the publication of the REAL in 1994, significant new data have been generated for some categories of lymphoma and leukemia, which are incorporated in the WHO classification.

Table VII
The Revised European American Lymphoma (REAL) classification

B-cell Lymphoma
Precursor B-cell lymphoma
Precursor B- lymphoblastic leukemia/lymphoma
Peripheral B-cell lymphomas
1. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
2. Lymphoplasmacytoid lymphoma/Immunocytoma
3. Mantle cell lymphoma
4. Follicle center lymphoma
5. Marginal zone B-cell lymphoma Extranodal (MALT type +/- monocytoid B cells) Nodal (+/- monocytoid B cells) Splenic (+/- villous lymphocytes)
6. Hairy cell leukemia
7. Plasmacytoma/plasma cell myeloma
8. Diffuse large B-cell lymphoma
9. Burkitt's like

CONCLUSION

In veterinary oncology, all of these ML classifications were applied as they were developed and their application served to demonstrate a surprising level of variations in subtypes of animal lymphoid tumours. Many of them could be considered as close or identical to their human counterparts. It is generally admitted that major differences between human and animal lymphomas include a higher proportion of high-grade lymphomas in animals and a lower proportion of follicular types. Also, Hodgkin's-like tumours are rarely or not definitely identified in animals.

Nevertheless, except for some categories of tumours, the clinical value of these classifications

Table VII bis
The Revised European American Lymphoma (REAL) classification

T-cell and Putative NK-cell Lymphoma
Precursor T-cell lymphoma
Precursor T- lymphoblastic lymphoma/leukemia
Peripheral T-cell lymphomas
1. T-cell chronic lymphocytic leukemia/prolymphocytic leukemia
2. Large granular lymphoproliferative (LGL) disorder T-cell type NK-cell type
3. Mycosis fungoides/Sezary's syndrome (and others cutaneous T-cell lymphomas).
4. Peripheral (extranodal) T-cell lymphomas, unspecified (medium, mixed, large)
5. Adult T-cell lymphoma/leukemia (ATL/L)
6. Angioimmunoblastic T-cell lymphoma
7. Angiotropic/ angioinvasive lymphomas
8. Intestinal T-cell lymphoma (ITCL; +/- enteropathy associated)
9. Anaplastic large cell lymphoma, CD30+, T- and null-cell types
Miscellaneous
Mast-cell tumors
Hodgkin's-like lymphoma
Malignant thymoma

generally remains to be accuratly demonstrated. As a consequence, there is need for serious and large clinico-pathological studies involving both clinicians and pathologists in veterinary oncology programmes. We believe that REAL system which is now accepted worldwide by clinicians and pathologists, will offer a good tool for setting up such collaborative works.

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