ORIGINAL RESEARCH PAPER

Pathology

HISTORY AND CLASSIFICATION OF MALIGNANT LYMPHOMAS - A REVIEW

KEY WORDS: Lymphoma, classification, history, REAL.

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ABSTRACT

Lymphomas are malignant neoplasms of lymphocyte group of cells. Due to their varied presentation, immunologic and genetic qualities, their classification has been the cause of study for decades now. Knowledge of various subtypes and their properties yielded way for better diagnosis and treatment modalities. This review is an attempt to understand the history and the development of the numerous classification systems of lymphomas - both Hodgkin and non-Hodgkin lymphoma.

INTRODUCTION

Lymphomas are malignant clonal neoplasms of lymphocytes and their precursor cells. (Goldblum et al., 2011) According to GLOBOCAN, non-Hodgkin lymphoma constituted 2.8% of all new cases and 2.6% of all cancer deaths whereas Hodgkin lymphoma constituted 0.4 and 0.2 % of the same respectively. (Globocan, 2011)

Since lymphomas are highly variable in clinical presentations, genetic subtype and sensitivity to drugs, the more we study about them, the more complex they seem.

Better understanding of immunologic and molecular processes will enable detection of subtypes having diverse etiologies, different prognosis, with variable targeted treatment options and outcomes.

"The more you know about the past, the better prepared you are for the future"
-Theodore Roosevelt

Hodgkin lymphoma (HL)

The term lymphoma came into existence when Hodgkin lymphoma was first discovered by Dr Thomas Hodgkin.

He was a medical school graduate who worked as the curator of Guy's Hospital Museum in London in 1825. Through his keen observations in the autopsy room and examination of specimens, he noticed a disease which predominantly affected the lymph nodes. He published his observations under the name "On some morbid appearances of the absorbent glands and spleen" in 1832. (Hodgkin, 1973)

Dr Hodgkin Thomas also combined Dr Carswell's case in his series due to the striking similarities between them. Dr Carswell is more than worthy of mention, as his water colour illustrations were the first ones to have ever been made of any lymphoma. These paintings were displayed whilst Dr Hodgkin presented his findings to the Medico Chirurgical society of London. (Dawson, 1999)

Dr Hodgkin wrote an extensive well compiled report describing the clinical history, course of the disease and findings at autopsy. He achieved numerous accolades in his name, but ironically his most famous contribution came to the fore just a year before his death in 1866.

In 1865, Sir Samuel Wilks brought it to light with a study of similar cases which he had collected between 1856 and 1877 and named it as Hodgkin's disease.

Characteristic giant cells were described in 1878 in Hodgkin's disease patients by Greenfield. (Aisenberg, 2000) In 1887, Pel and Ebstein described the cyclical fever.(Bonadonna, 2000) Carl Sternberg published his description of histology of these large cells in 1898. However, he was yet to distinguish tuberculosis from Hodgkin's lymphoma, since many of his cases suffered from both the diseases.

In 1902, a young female doctor by the name Dorothy Reed who worked at John Hopkins identified the pathognomonic cell, which was thus named after her. She also delineated this condition from tuberculosis. (Aisenberg, 2000)

In 1926, Herbert Fox from America traced back the tissue of Dr Hodgkin's cases and studied their histology. Two out of three of these turned out to be Hodgkin lymphoma and one turned out to be non-Hodgkin lymphoma [6].(Ashton-Key et al., 2016)

In 1947, the first histologic classification of Hodgkin lymphoma was proposed by Jackson and Parker. Lukes and Butler modified it and presented the Rye classification in 1966 and also added another entity – nodular sclerosis. (Aisenberg, 2000)

Non-Hodgkin lymphoma (NHL)

After Thomas' discovery of Hodgkin's disease, Virchow and Bennett (both 1845) independently described the first cases of leukaemia. In his book in 1864, Virchow described the term lymphosarcoma under aleukemic leukaemia.

At around the same time in 1865, Cohnheim used the term pseudoleukaemia.

In 1871, the term malignant lymphoma came into picture when used by Bilroth [7]. (Mann et al., 1979)

In 1925, Brill et al described the follicular or nodular variety, but not as a malignancy.

Later in 1927, both Brill and Symmers were convinced of its malignant potential [8]. (van Besien & Schouten, 2007)

In 1958, Denis Burkitt described a new type of lymphoma which was thus named after him (Burkitt's lymphoma). This type was prevalent in areas of high temperature and heavy rainfall and more so in African children [6]. (Ashton-Key et al., 2016)

In 1973, Lennert et al put forward that the follicle centre cell was the progenitor of a majority of adult NHL. This formed the basis of a classification which was put forward by Lukes and Collins in the USA (1974). Barcos and Lukes in 1975 and Lennert et al in 1978 discovered lymphoblastic lymphoma as a separate clinicopathologic entity.

Another subtype was added to the growing list in 1977 when ATLL (Adult T cell leukemia/lymphoma) was described in Japan. More recent discoveries were those of MALT (Mucosa associated lymphoid tissue) lymphoma [9](Isaacson & Wright, 1983) and Mantle cell lymphoma [10,11]. (Banks et al., 1992; Lakhtakia & Burney, 2015)

CLASSIFICATION OF LYMPHOMAS

Classification of this ever-growing list was becoming a Herculean task. Rappaport, in 1956 observed the cell types in NHL and proposed a classification system. He also focused on

the pattern - if nodular or diffuse, and identified follicular lymphoma.

In 1972, lymphomas were immunophenotyped into B and T types by cell surface clonal immunoglobulin (Ig) [12](Aisenberg & Bloch, 1972; Sader-Ghorra et al., 2014) and/or sheep cell receptor [13]. (Aisenberg & Bloch, 1972)Subsequently immunophenotyping was done with specific B and T monoclonal antibodies [14]. (Knowles, 1992)

Monoclonal antibodies helped in determining the true nature of many lymphoid proliferations, but the importance of morphology had not yet receded.

The trilemma!

In USA in 1974, Lukes and Collins proposed a classification system based on the cell of origin, site of origin, combinations of cell size and nuclear shape. They also stressed the need for a functional immunological classification system. (RJ Lukes & RD Collins, 1974) At the same time, in Europe, Lennert and Luke proposed the Kiel classification, which focused on cell types and used suffixes like 'cytic' and 'blastic'. While, in the United Kingdom, The BNLI (British National Lymphoma Institution) scheme was put forward by Bennett et al [16]. (Lakhtakia & Burney, 2015)

Yet another attempt was made in the United States of America by the National Cancer Institute when a group of experts reviewed around 1175 cases of NHL and introduced a Working Formulation for clinical usage. It divided NHL into ten types based on morphologic criteria only. An intermediate grade was introduced between the existing low and high grade in this working formulation [17]. ("National Cancer Institute Sponsored Study of Classifications of Non.hodgkin's Lymphomas. Summary and Description of a Working Formulation for Clinical Usage," 1982)

Therefore, this period saw the practice of three different classification systems - the Kiel in Europe, The BNLI in UK and the Working formulation in the USA [16]. (Lakhtakia & Burney, 2015)

The harmonisation of this transcontinental situation was attempted by the International Lymphoma Study group which was founded in 1990 by Stein and Isaacson.

And thus, in 1994, humanity came close to a solution to the conundrum that was lymphomas, when the International Lymphoma Study Group (which included Harris Jaffe, Chan and others) presented the Revised European-American Lymphoma (REAL) classification system. A group of 19 pathologists were part of this study and it was finalised in Berlin, Germany. In the article, there is mention of the futility of trying to classify lymphomas based on similarity to normal cell counterparts. Hence, the classification was kept very 'real' It categorised lymphomas based on the clinicomorpho logical features and also on immunologic and genetic types [18]. (Nancy et al., 2015)

World Health Organisation

From the REAL classification was born the WHO (World Health Organisation) classification. It was a collaboration between the European Association for Haematopathology and the Society for Haematopathology. Beginning in 1995, it had members of both societies as well as ten other disease related committees. Though its majority was based on the REAL classification, it factored in additional inputs from experts. And put forward an updated and broader consensus building - the first worldwide consensus on the classification [19]. (Jaffe ES et al., 2001)

So as to achieve clinical utility, a clinical advisory committee (CAC) was also established. Consequently, a meeting was held in 1997 amongst both the societies and the CAC and a few modifications were made to the classification system. It was also agreed upon to necessitate the periodical update to keep up with the progress of genetic analysis [19]. (Jaffe ES et al., 2001)

Thus, the WHO 3rd edition 'Classification of tumors of the Hematopoietic and Lymphoid tissues' was published in 2001. It was called the 3rd edition since it was published as part of the 3rd edition of the 'WHO classification of Tumors' series. (Vardiman et al., 2009)

In 2008, the 4th edition was published. This edition incorporated all the new data available from various studies done since 2001. It clarified few diagnostic criteria and added few new entities.

The most recent update was published in 2017 as the Revised 4th edition. Thanks to high throughput genetic technologies (like Next- Generation sequencing), since 2008, new mechanisms of tumorigenesis were found and have opened up new potential avenues of targeted therapies. This was considered as an update of the fourth edition and not as the 5th edition since it was not yet complete (release of many volumes are pending). [21] (Swerdlow et al., 2016)

Chronology of the development of classification systems of lymphomas

Year	Development
1832	Thomas Hodgkin published "On some morbid appearances of the absorbent glands and spleen" which was later termed Hodgkin disease. (HD)
1845	Virchow and Bennett (both independently) described first cases of leukemia
1856 - 1877	Samuel Wilks brought Hodgkin lymphoma into light again and named it so
1864	Virchow described the term lymphosarcoma under aleukemic leukemia
1865	Cohnheim used the term pseudoleukemia
1871	Bilroth used the term malignant lymphoma
1878	Greenfield described characteristic giant cells in HD
1902	Dorothy Reed identified the pathognomonic cell in HL which was named after her
1925	Brill et al described the follicular or nodular variety, but not as a malignancy
1926	Herbert Fox traced back and studied Dr Hodgkin's cases and classified one of them as NHL
1927	Brill and Symmers were convinced of malignant potential.
1947	First histologic classification given by Jackson and Peter
1958	Dennis Burkitt described a new type of lymphoma thus named after him
1966	Luke and Butler proposed the Rye classification system and added nodular sclerosis entity
1972	Lymphomas were divided into B and T cell subtypes by cell surface clonal receptor
1974	Lukes and Collin put forward a classification system at USA
1974	Lennert and Luke proposed the Kiel system at Europe, used terms 'cytic' and 'blastic'
1974	Bennett et al propounded the BNLI scheme in UK
1975	Barcos and Luke discovered lymphoblastic lymphoma as a separate entity
1977	ATLL was discovered in Japan
1978	Lennert et al discovered lymphoblastic lymphoma as a separate entity
1990	Stein and Isaacson found the International Lymphoma Study group
1994	International lymphoma study group (I.L.S.G) published Revised European-American Classification of Lymphoid Neoplasms (REAL classification)
2001	WHO classification of lymphomas 3rd edition
2008	WHO classification of lymphomas 4th edition
2017	Revised 4th edition of WHO

CONCLUSION

The lymphomas have come a long way, as has their classification. And studying of these classifications will lead to better and faster diagnosis, better prediction of the disease process and more treatment options - targeted therapy or otherwise.

For, is that not the primary objective of the medical fraternity!

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