Sultan Qaboos University Med J, August 2015, Vol. 15, Iss. 3, pp. e317–321, Epub. 24 Aug 15. doi: 10.18295/squmj.2015.15.03.003.
Submitted 2 Jun 15
Revision Req. 28 Jun 15; Revision Recd. 12 Jul 15
Accepted 14 Jul 15

MEDICAL HISTORY

A Historical Tale of Two Lymphomas
Part II: Non-Hodgkin lymphoma

*Ritu Lakhtakia[1] and Ikram Burney[2]

قصة تاريخية عن نوعين من أورام الغدد الليمفاوية
الجزء الثاني: أورام الغدد اللمفاوية نوع هودجكين

ريتو لكتاكيا و إكرام بيرني

In 1865, Thomas Hodgkin was immortalised by his peer, Samuel Wilks, in the annals of medical literature through the eponymous use of the term 'Hodgkin's disease'.[1,2] Consequently, it must have seemed logical for the medical community of the time to name the other, more heterogeneous group of neoplastic lymph node enlargements as non-Hodgkin lymphoma (NHL). A century and a half later, NHL has emerged from those shadows and is now recognised as the leading haematological malignancy worldwide.[3] The second of this two-part medical history article provides a succinct narrative of what transpired in these 150 years to pique scientific curiosity and establish NHL in the centre stage. It follows the trail of classifications, aetiology and epidemiology, prognostic factors and, finally, the elusive holy grail of treatment which marked this period of medical history.

The Mother of All Classifications: *Confusion and logic*

It would not be an understatement to assert that the classifications of NHL are the outright frontrunners in terms of their complexity when compared with other tumour classifications. This is a reflection of the transition of pathological diagnosis from an 'eyes-only' morphological basis in the 19th century, to the more sophisticated tools of immunology and genetics that exist today.

In 1864 and 1865, Virchow and Cohnheim had recognised the diseased enlargement of lymph nodes as lymphosarcoma and pseudoleukaemia, respectively, although the term 'malignant lymphoma' was first used by Bilroth in 1871.[4] It appears that the diseases thus identified had resulted from a mix of neoplastic, infective and miscellaneous causes of lymph node enlargement. Between the end of the 19th century and the middle of the 20th century, little headway was made in identifying NHL, with the sporadic additions of reticulum cell sarcoma by Oberling in 1928 and giant follicular lymphoma by Brill and Symmers in 1925.[4,5] The first organised classification appeared through the efforts of Rappaport in 1956, with a modified version being published in an Armed Forces Institute of Pathology fascicle in 1966.[6] The categorisation of NHLs into nodular, diffuse and histiocytic, each with subtypes, was based on architectural organisation and the cell size of the neoplastic lymphoid infiltrate.[6] In subsequent years, the histiocytic category of NHLs was lost, as true histiocytic lymphomas were found to be exceedingly rare once immunomarker-based identification became possible.

The 1960s saw an ever increasing evolution in the science of immunology and associated tools. Scientists on both sides of the Atlantic Ocean drew on these resources to breathe new life into the concepts of lymphoid differentiation, trying to relate neoplastic cells to their normal counterparts in lymphoid tissue.[7–10] In the USA in 1974, Lukes and Collins' classifications combined the presumed cell of origin (B, T or histiocytic), site of origin (follicular) and state of transformation as evidenced by combinations of cell size (small/large) and nuclear shape (round/cleaved).[7,8] In Europe, the Kiel classification by Lennert and Luke (proposed in 1974 and extensively modified in 1988) introduced the concept of tumour grading, suffixing low grade tumour cells with "-cytic" and higher grades with "-blastic" (e.g. centrocytic, centroblastic and immunoblastic).[9] The Kiel classification continued to be updated with accumulating data, adding extranodal and T cell lymphomas. Yet another schema, the British National Lymphoma Investigation (BNLI) classification, was propounded in 1974 by Bennett *et al.*[10]

[1]*Department of Pathology, College of Medicine & Health Sciences, Sultan Qaboos University;* [2]*Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman*
**Corresponding Author e-mail: ritu@squ.edu.om*

To assuage the increasing frustration among clinicians, lost in a maze of classifications with questionable clinical relevance, a working formula for clinical usage was created by a group of experts appointed by the National Cancer Institute in the USA in 1978.[11] Six experts and six non-experts reviewed a thousand NHL cases with adequate clinical follow-up. They drew on previous classifications and separated low- and high-grade groups (respectively showing small and large cells) by an intermediate grade. However, this new grade was contentious because of the inclusion of 'mixed-bag' entities. Moreover, the universal application of the classification came into question as NHL subtypes varied in frequency in different parts of the world and the cases studied represented only those seen in the USA.[11] However, this remained a working formula until it was succeeded by later classifications. The 1970s and 1980s saw a trifurcated practice of NHL classification in the Western world: the working formulation favoured in the USA, the BNLI in the UK and the Kiel classification in Europe.[9–11]

Founded in 1990 by Stein and Isaacson, the International Lymphoma Study Group tried to unify transatlantic opinions in its Revised European-American Lymphoma (REAL) classification of 1994.[12] This schema tapped newly emerging data and combined clinical features, morphology and immunophenotyping and genetic information. Notably, the group was comprised of 19 histopathologists from around the world in an inclusive approach so as to encompass diversity in disease and scientific opinion.[12] The group emphasised the acronym of the classification, REAL, by endorsing the recognition of true clinicobiological entities.[12]

The World Health Organization classifications of haematopoeitic and lymphoid tissue tumours of 2001 and 2008 emerged from this foundation, grouping established and provisional categories of NHL under a broad umbrella based on cell lineage and differentiation (precursor/mature and B/T/natural killer/histiocytic/dendritic cell types).[13] Subtypes of Hodgkin lymphoma were also listed. In these now well-established and revised classifications, a close intertwining of clinicopathological features and definitive cytogenetics brought order and improved understanding. Notable examples of specific diagnostic entities determined by their genotype include follicular lymphoma (t[14:18]), Burkitt lymphoma (t[8:14]) and anaplastic large cell lymphoma (t[2:5]).[13] The emerging era of targeted therapy demands standardised reporting on potential targets in tumour cells, like cluster of differentiation twenty (CD20) and anaplastic lymphoma kinase (ALK); the diagnostic pathologist now has the onerous responsibility of being both a predictor and prognosticator.

Aetiology of Non-Hodgkin Lymphoma: *Immune dysregulation*

When lymphoma came to be recognised as a clinical entity, it was difficult to separate its neoplastic origin and intent from other causes of lymphadenopathy, especially infection. The distinction became easier once diagnostic patterns could be established via microscopy. In the last century, rapid advances in microbiological, immunological and molecular techniques have brought epidemiological evidence of risk and aetiology to light. Stimulation of the lymphoid cells or integration of the infectious agent with cellular DNA may provide the opportunity for uncontrolled proliferation—associations of hepatitis C and human immunodeficiency virus with multiple NHL-subtypes; Epstein Barr virus with Burkitt lymphoma; and *Helicobacter pylori* with gastric mucosa-associated lymphoid tissue lymphomas are established examples.[14–16] Altered regulation of immunological processes (autoimmune diseases) or their suppression (post-transplantation) provide the *milieu* for neoplastic lymphoid clones to grow without the usual checks.[17,18] Large-scale case-control studies from multiple continents under the International Lymphoma Epidemiology Consortium will provide additional data for future historians.[19]

Prognostic Factors: *Towards precision medicine*

Consistent with the history of the evolution of NHL classifications, a plethora of literature has emerged attempting to describe prognostic factors for the more common forms of NHL. The complexity of NHL does not end with descriptions of new subsets at major scientific meetings, but continues to evolve with new clinical and molecular features of each major subtype. These features help to describe prognostic groups or prognostic features within selected NHL subtypes.

Three major prognostic systems deserve special mention. The first was a predictive model for aggressive NHL developed in 1993 and known as the International Prognostic Index.[20] The index used clinical features including age, clinical stage, serum lactate dehydrogenase level, number of extranodal sites and performance status to stratify patients into low-, low-intermediate-, high-intermediate- and high-risk categories.[20]

The second major system describes two major types of B cell lymphomas at the molecular level. Alizadeh *et al*. used DNA microarrays to systematically characterise gene expression in B cell lymphomas.[21]

They described two forms of molecularly distinct diffuse large B cell lymphoma (DLBCL); one type expressed genes characteristic of germinal centre B cells and the other expressed genes induced during the *in vitro* activation of peripheral blood B cells (activated B-like DLBCL). The former had a better outcome compared to the latter.[21]

The third major attempt at disease prognostication came with the advent and widespread use of positron emission tomography (PET) scans in 2005.[22] Functional imaging with ^{18}F-fluorodeoxyglucose PET scans, and subsequently with combined PET/computed tomography, was found to increase the sensitivity and specificity of disease assessment and also predict outcomes.[22] Numerous studies have confirmed that mid-treatment PET scans are predictive of clinical outcomes, especially when the negative predictive value is very high.[23]

Treatment: *A tale of discovery, stalemate and invention*

At least 80 different forms of NHL have been described, the details of which are consequently beyond the scope of this article. Two entities representing the polar ends of the spectrum of biological behaviour—aggressive B cell NHL and indolent B cell NHL—are addressed below.

The treatment of NHL came into the limelight through serendipity. Towards the end of World War II, alkylating agents used in chemical warfare were observed to cause ulcers, infections and alopecia amongst the inmates of concentration camps. Subsequently, nitrogen mustard gas and its derivatives were used for the treatment of lymphoproliferative disorders as well as many other cancers in the 1950s.[24] Since the 1960s, alkylating agents used individually (chlorambucil) and in combination (cyclophosphamide, hydroxydaunomycin, vincristine and prednisolone [CHOP]) became the standard of care for the majority of patients with indolent and aggressive NHL, respectively, for the next 30 years.[25] Chlorambucil induced stable remission in a significant number of patients with symptomatic indolent NHL and CHOP not only induced remissions in the majority of patients with aggressive NHL, but also 'cured' a significant number. Further efforts to cure either indolent or aggressive forms of NHL met with disappointing results.[26]

Newer generations of alkylating agents or combinations with additional and different cytotoxic agents or dose-dense chemotherapy did not improve chances of a cure and were more toxic.[27,28] Chemotherapy combinations included m-BACOD (methotrexate with leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone); MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin); and ProMaCE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate and folinic acid). By the mid-1990s, a stalemate had been reached.

At the turn of the century, two significant strides were made. Research indicated that a second attempt at a cure was possible for a majority of patients with aggressive NHL: high-dose chemotherapy with autologous stem cell transplantation could cure 45% of patients, as compared to 12% of those who were treated with a second-line chemotherapy regimen.[29] Secondly, knowledge of the molecular structure and expression of cell surface antigens changed the face of treatment for almost all forms of NHL forever. A monoclonal antibody (rituximab) was engineered, targeting the CD20 antigen expressed on the surface of B lymphocytes (especially activated B cells) and a new paradigm of treatment emerged.[30] A combination of cytotoxic chemotherapy with the anti-CD20 antibody improved remission rates and cure rates.[31]

What has followed since this discovery has been nothing less than spectacular. The use of a monoclonal antibody as a single agent to induce remission and prolong remission and in combination to enhance the effect of salvage chemotherapy before high-dose treatment and autologous stem cell transplantation are options which have changed the outlook for patients with NHL.[32–34] More recently, radioimmunoconjugates, monoclonal antibodies against different antigens and molecule inhibitors, such as bruton tyrosine kinase inhibitors, have been added to the armamentarium of physicians treating NHL.[35] While the chances of a cure continue to improve with the advent of targeted therapy, parallel efforts are underway to reduce the short and long-term toxicity of these treatment options.

Lessons from the History of Non-Hodgkin Lymphoma

Pathological diagnostic challenges are often mirrored in taxonomic riddles that create a bewildering maze of classifications. For over a century and half, NHL classifications have been a prime example of the disconnect between the lexicon of the microscopist and the clinical relevance of the resultant diagnostic entity. The search for clarity is achieved most often through insight, pragmatism, the bridging of geographical divides and collaboration between

pathologists and physicians. Today, technology and advances in tumour biology may provide the missing links in our understanding, hopefully leading to diagnostic precision and tailored therapies.

For crude classifications and false generalisations are the curse of all organised human life. H. G. Wells.[36]

References

1. Wilks S. Cases with enlargement of the lymphatic glands and spleen (or Hodgkin's disease) with remarks. Guy's Hosp Rep 1865; 11:57–67.
2. Lakhtakia R, Burney I. A historical tale of two lymphomas: Part I: Hodgkin lymphoma. Sultan Qaboos Univ Med J 2015; 15:e202–6.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61:69–90. doi: 10.3322/caac.20107.
4. Norton AJ. Classification of non-Hodgkin's lymphomas. Ballieres Clin Haematol 1996; 9:641–52. doi: 10.1016/s0950-3536(96)80046-1.
5. van Besien K, Schouten H. Follicular lymphoma: A historical review. Leuk Lymphoma 2007; 48:232–43. doi: 10.10 80/10428190601059746.
6. Rappaport H. Tumors of the haematopoeitic system: Section 3 3, fascicle 8. In: Atlas of Tumor Pathology. Washington DC, USA: United States Armed Forces Institute of Pathology, 1966. P.442.
7. Lukes RJ, Collins RD. A functional approach to the classification of malignant lymphoma. Recent Results Cancer Res 1974; 46:18–30. doi: 10.1007/978-3-642-80829-6_4.
8. Lukes RJ, Collins RD. Immunologic characterization of human malignant lymphomas. Cancer 1974; 34:1488–503. doi: 10.1002/1097-0142(197410)34:8+<1488::AID-CNCR2820 340822>3.0.CO;2-C.
9. Stansfeld AG, Diebold J, Noel H, Kapanci Y, Rilke F, Kelényi G, et al. Updated Kiel classification for lymphomas. Lancet 1988; 1:292–3. doi: 10.1016/S0140-6736(88)90367-4.
10. Bennett MH, Farrer-Brown G, Henry K, Jaliffe AM, Gerard-Marchant R, Hamlin I, et al. Classification of non-Hodgkin's lymphomas. Lancet 1974; 405–6. doi: 10.1016/S0140-6736 (74)91786-3.
11. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage - The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 1982; 49:2112–35.doi:10.1002/1097-0142(19820515)49:10<2112::AID-CNCR2820491024>3.0.CO;2-2.
12. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 1994; 84:1361–92.
13. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., Eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: IARC Press, 2008.
14. Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: A model of antigen-driven lymphoproliferation. Blood 2006; 107:3034–44. doi: 10.1182/blood-2005-09-3679.
15. Dal Maso L, Franceschi S. Epidemiology of non-Hodgkin lymphomas and other haemolymphopoietic neoplasms in people with AIDS. Lancet Oncol 2003; 4:110–19. doi: 10.1016/S1470-2045(03)00983-5.
16. de Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol 2008; 6:451–8. doi: 10.1016/j.cgh.2008.02.011.
17. Ekström Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: A pooled analysis within the InterLymph Consortium. Blood 2008; 111:4029–38. doi: 10.1182/blood-2007-10-119974.
18. Clarke CA, Morton LM, Lynch C, Pfeiffer RM, Hail EC, Gibson TM, et al. Risk of lymphoma subtypes after solid organ transplantation in the United States. Br J Cancer 2013; 109:280–8. doi: 10.1038/bjc.2013.294.
19. Morton LM, Sampson JN, Cerhan JR, Turner JJ, Vajdic CM, Wang SS, et al. Rationale and design of the International Lymphoma Epidemiology Consortium (InterLymph) Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr 2014; 2014:1–14. doi: 10.1093/jncimonographs/lgu005.
20. A predictive model for aggressive non-Hodgkin's lymphoma: The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329:987–94. doi: 10.1056/NEJM199309303291402.
21. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000; 403:503–11. doi: 10.1038/35000501.
22. Haioun C, Itti E, Rahmouni A, Brice P, Rain JD, Belhadj K, et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: An early prognostic tool for predicting patient outcome. Blood 2005; 106:1376–81. doi: 10.1182/blood-2005-01-0272.
23. Cheson BD. Role of functional imaging in the management of lymphoma. J Clin Oncol 2011; 29:1844–54. doi: 10.1200/JCO.2010.32.5225.
24. DeVita Jr VT, Chu E. A history of cancer chemotherapy. Cancer Res 2008; 68:8643–53. doi: 10.1158/0008-5472.CAN-07-6611.
25. Devita VT Jr, Canellos GP, Chabner B, Schein P, Hubbard SP, Young RC. Advanced diffuse histiocytic lymphoma, a potentially curable disease. Lancet 1975; 305:248–50. doi: 10.1016/S0140-6736(75)91142-3.
26. Armitage JO. Treatment of non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1023–30. doi: 10.1056/NEJM199304083281409.
27. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1002–6. doi: 10.1056/NEJM199304083281404.
28. Pfreundschuh M, Trümper L, Kloess M, Schmits R, Feller AC, Rudolph C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: Results of the NHL-B1 trial of the DSHNHL. Blood 2004; 104:626–33. doi: 10.1182/blood-2003-06-2094.
29. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333:1540–5. doi: 10.1056/NEJM199512073332305.
30. Maloney DG, Grillo-López AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 1997; 90:2188–95.
31. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly M, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346:235–42. doi: 10.1056/NEJMoa011795.

32. Gribben JG. How I treat indolent lymphoma. Blood 2007; 109:4617–26. doi: 10.1182/blood-2006-10-041863.

33. Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. Lancet 2011; 377:42–51. doi: 10.1016/S0140-6736(10)62175-7.

34. Kewalramani T, Zelenetz AD, Nimer SD, Portlock C, Straus D, Noy A, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004; 103:3684–8. doi: 10.1182/blood-2003-11-3911.

35. Tees MT, Sokol L. Novel pharmacotherapies for B-cell lymphomas and leukemias. Am J Ther 2014; Epub ahead of print. doi: 10.1097/mjt.0000000000000164.

36. Wells HG. A Modern Utopia. London, UK: Penguin Modern Classics, 2005. P.205.