Non-Hodgkin’s lymphoma: A review

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Abstract

Lymphomas constitute the third most common neoplasm in head and neck region arising from the lymphoreticular system. Malignant lymphomas are divided into Hodgkin’s disease and non-Hodgkin’s lymphoma (NHL). NHL comprises approximately 5% of head and neck malignancies and displays a wide range of appearances comparable with Hodgkin’s disease. Hodgkin’s and non-Hodgkin’s lymphomas are seen in the head and neck region, but extranodal disease, with or without lymph node involvement, is more common among NHL patients. Extranodal involvement includes the areas such as Waldeyer’s ring (i.e., the tonsils, pharynx, and base of the tongue), salivary glands, orbit, paranasal sinuses, and thyroid glands. There are several classification systems for categorizing NHL out of which WHO classification for lymphoid neoplasms is mostly followed. This review describes the pathogenesis of NHL and explains some of the important NHL (Marginal zone B-cell Lymphoma, follicular lymphoma, mantle cell lymphoma).

Keywords: Cell, lymphomas, Non Hodgkin’s lymphoma

Introduction

The malignant lymphomas constitute a group of neoplasms, of varying degrees of malignancy, derived from the basic cells of lymphoid tissue, the lymphocyte, and histiocytes in any of their developmental stages.

Lukes defined malignant lymphoma as “a neoplastic proliferative process of the lymphopoietic portion of the reticuloendothelial system, that involves cells of either the lymphocytic or histiocytic series in varying degrees of differentiation, that occurs in an essentially homogeneous population of a single cell type.” The character of histologic involvement is either diffuse (uniform) or nodular and the distribution of involvement may be regional or systemic (generalized); however, the process is basically multicentric in character.[¹]

NHL (Non-Hodgkin Lymphomas) are a heterogenous group of lymphoproliferative malignancies that are much less predictable than Hodgkin’s lymphomas and have a far greater predilection to disseminate to extranodal locations. Nearly 25% of NHL cases arise in extranodal locations and most of them are seen involving both nodal and extranodal sites.[²]

The most common NHL subtypes by far in developed countries are diffuse large B-cell lymphoma (about 30%) and follicular
lymphoma (about 20%). All other NHL subtypes have a frequency of less than 10%.[8] NHL is the sixth most common cause of cancer-related death in the USA after prostate, breast, lung, colorectal, and bladder cancer. Oropharyngeal lymphomas are the second most common malignant disease in the oral region after squamous cell carcinoma.[9]

On the basis of morphologic and laboratory data available, the International Lymphoma Study Group (ILSG) codified and published a “revised European-American lymphoid neoplasms (REAL)” classification. This classification proposed 34 biologically well-defined lymphoma entities and placed the emphasis on the underlying biologic aberrations of the specific lymphoma subtypes. Recently, this REAL Classification has been modestly revised to take an even more global stature as the World Health Organization (WHO) Classification.[8]

Proposed WHO Classification of Lymphoid Neoplasms

The International Lymphoma Study Group (I.L.S.G) developed a consensus list of lymphoid neoplasms, which was published in 1994 as the “Revised European-American Classification of Lymphoid Neoplasms” (R.E.A.L.). The classification was based on the principle that a classification is a list of “real” disease entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features. The relative importance of each of these features varies among diseases, and there cannot be any one “gold standard.”

In some tumors, morphology is paramount, and in others, it is immunophenotype, a specific genetic abnormality, or clinical features. An international study of 1300 patients, supported by the San Salvatore Foundation, was conducted to determine whether the R.E.A.L. Classification could be used by expert pathologists and had clinical relevance. Since 1995, the European Association of Pathologists (EAHP) and the Society for Hematopathology (SH) have been developing a new World Health Organization (WHO) Classification of hematologic malignancies, using an updated R.E.A.L. Classification for lymphomas and applying the principles of the REAL. The International Lymphoma Study showed that the R.E.A.L. Classification could be used by pathologists, with inter-observer reproducibility better than for other classifications (>85%). Immunophenotyping was helpful in some diagnoses, but not required for many others.[8] Based on experience with the REAL classification for several years and on input from the committees, several changes were proposed for the WHO version. These included some changes in nomenclature, splitting some categories that were believed to be heterogeneous, and adopting some “provisional” entities as “real.”[8]

B-cell neoplasms

1. Precursor B-cell neoplasm:

- Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia).

2. Mature (peripheral) B-cell neoplasms:

- B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma (follicle center-type)
- Hairy cell leukemia
- Plasma cell myeloma/plasmacytoma
- Extramedullary marginal zone B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma/Burkitt cell leukemia.

3. T and NK-Cell Neoplasms

- Precursor T-cell neoplasm
- Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
- Mature (peripheral) T-cell neoplasms**
- T-cell prolymphocytic leukemia
- T-cell granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell lymphoma/leukemia (HTLV11)
- Extramedullary NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides/Sezary syndrome
- Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
- Peripheral T-cell lymphoma, not otherwise characterized
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, T/null cell, primary systemic type.

4. Hodgkin’s lymphoma (Hodgkin’s disease)

1. Nodular lymphocyte predominance Hodgkin’s lymphoma
2. Classical Hodgkin’s lymphoma
   - Nodular sclerosis Hodgkin’s lymphoma (Grades 1 and 2)
   - Lymphocyte-rich classical Hodgkin’s lymphoma
   - Mixed cellularity Hodgkin’s lymphoma
   - Lymphocyte depletion Hodgkin’s lymphoma

Non-Hodgkin’s lymphomas on the basis of location[8]

1. Oral cavity, Waldeyer’s ring, and Pharynx
   - Small B-cell lymphoma
   - Marginal zone B-cell lymphoma
   - Mantle cell lymphoma
- Follicular lymphoma
- Extranodal plasmacytoma.

- Diffuse large B-cell lymphoma
- Extranodal NK/T-cell lymphoma, Nasal type (Secondary extension).

2. Nasal cavity and par nasal sinuses
- Small B-cell lymphoma
  - Lymphocytic lymphoma
  - Follicular lymphoma
  - Mantle cell lymphoma
  - Marginal zone B-cell lymphoma
  - Burkitt's lymphoma
  - NK/T cell lymphoma, Nasal type.

3. Larynx and trachea
- Small B-cell lymphoma
  - Marginal zone B-cell lymphoma
  - Extramedullary plasmacytoma.

- Diffuse large B-cell lymphoma.

**Etiology of non-Hodgkin’s lymphoma**

*Pathogenesis*

Central pathogenetic mechanisms include immunosuppression, especially in relation to T-cell function and loss of control of latent EBV infection, and chronic antigen stimulation.

B and T lymphocytes are important members of the immune system that above all serve to protect against infectious agents. In general, B-cells produce antibodies with antigen-binding capacity, whereas T-cells recognize antigen presented by other cells.

Immunosuppression in a variety of medical conditions increases the risk of NHL. The most well-established risk factors for malignant lymphomas are characterized by dysregulation or suppression of T-cell function (HIV/AIDS, organ transplantation) that allows for Epstein-Barr virus (EBV) driven B-cell proliferation and transformation.[9]

Chronic antigenic stimulation increases B-cell proliferation, which in turn increases the probability of a random genetic mistake, particularly related to immunoglobulin gene rearrangements. Factors that induce proliferation thereby potentially lead to more errors.

In cases in which a virus acts as the foreign stimulant, the virus itself may infect a normal cell and integrate viral DNA into the host genome, thereby transforming the cell into a malignant cell capable of self-replication. In either case, antigenic stimulation can also lead to a compensatory downregulation of the T-cell response, that is, an immunosuppressive state.

Lymphoma tumor cells are a malignant form of these precursor lymphocytes arrested at a specific stage of differentiation. Chromosomal translocations, usually balanced reciprocal recombinations, are the genetic hallmark of lymphoid malignancies; their presence has been confirmed in up to 90% of NHL cases. At a molecular level, these translocations with or without additional chromosomal deletions and mutations may precipitate oncogene activation or tumor suppressor gene inactivation.[10]

**Risk factors for NHL**

1. Immunosuppression
2. Ultraviolet radiations
3. Viruses and other pathogens (EBV, HTLV, HHV8, Hepatitis C, SV40, and *Helicobacter pylori*)
4. Autoimmune and chronic inflammatory disorders (Rheumatoid arthritis, Sjogren syndrome, and SLE)
5. Occupational exposure (pesticides like phenoxy acids, organophosphates, and organochlorines).

**Clinical Presentation**

**Nodal lymphoma**

Cervical lymphadenopathy is the most frequent head and neck presentation in NHL characterized by multiple painless nodes. These lesions are not as hard as metastatic nodules and are not fixed to either skin or the deep planes.

NHL spreads more commonly to non-contiguous nodes. Mediastinal involvement is rare, whereas abdominal involvement is more common.

**Extranodal lymphoma**

Sites for extranodal non-Hodgkin’s lymphoma include:

1. Waldeyer’s ring (Nasopharynx, palatine tonsils, base of the tongue, and oropharyngeal wall)
2. Oral cavity (Palate, gingiva, maxilla, and tongue)
3. Salivary glands
4. Thyroid
5. Larynx
6. Nasal cavity
7. Paranasal sinuses
8. Skin.

Half of the extranodal lymphomas of head and neck region are located in Waldeyer’s ring. Of all Waldeyer’s ring-NHL, the tonsils are the most frequent site. Patients with palatine tonsil involvement complain of dysphagia, sore throat, and asymptomatic enlargement of one of the tonsil. Symptoms of rhinopharyngeal lymphoma include enlarged neck node, increased nasal obstruction, and hearing loss. The base of the tongue is a very rare location for lymphomas. Lymph node involvement is usually the first sign leading to diagnosis.

Oral lymphomas occur more frequently in patients with HIV infections. Symptoms include swelling, pain, and ulcers. These may be seen as a tumor or ulcerated lesion anywhere in the
mouth but commonly involves gingiva, palate, and tongue. The lesions show rapid growth and can affect the underlying jaw bones producing lytic bone destruction.

Lymphomas of salivary glands account for 2%–5% of salivary gland neoplasms. They mainly involve the parotid gland and are associated with Sjögren’s syndrome. Lymphomas involving salivary glands include marginal zone B-cell lymphoma of MALT type (in parotid parenchyma), follicular lymphomas (involving intraparotid lymph nodes), and diffuse large B-cell lymphomas.¹⁰

**Histologic Features**

The non-Hodgkin’s lymphoma presents a histologic pattern which is described as either nodular or diffuse. In the nodular pattern, the neoplastic cells tend to aggregate in such a way that large clusters of cells are seen. The diffuse pattern is characterized by a monotonous distribution of cells with no evidence of nodularity or germinal center formation, with a complete effacement of lymph node architecture.¹¹

**Ann Arbor staging system**

The Ann Arbor staging system originally applies to Hodgkin’s lymphoma developed in 1971 but has been used for staging NHL. Unlike Hodgkin’s lymphoma in which spread of disease occurs through the involvement of contiguous sites, disease involvement in NHL is more random, limiting the utility of the Ann Arbor system [Table 1].¹¹

The Ann Arbor staging system was inconsistent in predicting outcome; later, the International NHL Prognostic Factors Project studied 12 variables and identified five pretreatment characteristics that remained independently significant in their analysis that include age, stage (III or IV), number of extranodal sites of disease, performance status, and serum lactate dehydrogenase level.

**International prognostic index for non-Hodgkin’s lymphoma**

- Parameters

| Stage | Defining status |
|-------|----------------|
| Stage I | Restricted to single lymph node region (I) or a single extranodal site (I-E). |
| Stage II | Two or more areas of nodal involvement on the same side of the diaphragm (II) or one or more lymph node regions with an extranodal site (II-E). |
| Stage III | Lymphatic involvement on both sides of the diaphragm (III), possibly with an extranodal site (III-E), the spleen* (III-S), or both (III-SE). |
| Stage IV | Liver, marrow, or other extensive extranodal disease. |
| Substage | |
| Substage E | Localized, extranodal disease. |
| Substage A | Absence of systemic signs. |
| Substage B | Presence of unexplained weight loss (10% in 6 months), and/or unexplained fever, and/or night sweat. |

*The spleen is considered nodal

These four groups had predicted 5-year survival rates of 73%, 51%, 43%, and 26%, respectively. This system was found to be significantly more accurate than the Ann Arbor classification in predicting long-term survival.

- The performance status of the International Prognostic Index was classified as:
  - 0 (the patient had no symptoms)
  - 1 (the patient had symptoms, but was ambulatory)
  - 2 (the patient was bedridden less than half the day)
  - 3 (the patient was bedridden half the day or longer)
  - 4 (the patient was chronically bedridden and required assistance with the activities of daily living).

**Marginal zone B-cell lymphoma**

MALT lymphomas constitute a group of low-grade extranodal B-cell neoplasms that share similar clinical, pathologic, immunologic, and molecular features and arise in areas of preexisting prolonged lymphoid proliferation in mucosal sites. Such lesions were earlier known as “pseudolymphoma.”¹² Many patients have a history of autoimmune disease such as Sjögren’s syndrome or Hashimoto’s disease or of Helicobacter gastritis.¹³

In the more recent World Health Organization (WHO) classification system, Marginal zone lymphomas comprise three subtypes:

- Nodal–Involving the lymph nodes
- Extranodal (MALT type)–Involving GI tract, ocular adnexa, salivary gland, thyroid, lung, thymus, and breast
- Splenic

**Histology**

This tumor is characterized by an infiltrate of “centrocyte-like” cells (small- to medium-sized lymphocytes with abundant cytoplasm and irregularly shaped nuclei), but scattered transformed blasts (large cells), plasma cells, and monocytoid B-cells are present.

- Nonmalignant reactive follicles are observed frequently.
- Presence of lymphoepithelial lesions (i.e. marginal zone B-cells infiltrate the epithelium) with invasion and partial
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**Immunophenotype**

- Tumor cells express surface immunoglobulin IgM, IgG and IgA lack IgD
- B-cell associated antigens (CD 19, 20, 22, 79a) are expressed
- Tumor is usually negative for CD5 and CD10 antigens that characterize small lymphocytic lymphoma, mantle cell lymphoma, and follicular lymphoma
- Expression of CD23, CD43, and CD11c is variable.

**Follicular Lymphoma**

Follicular lymphoma is defined as the tumor composed of follicle center cells, usually a mixture of centrocytes (cleaved follicle center cells) and centroblasts (large noncleaved follicle center cells). The pattern is at least partially follicular but diffuse areas may be present. Centrocytes typically predominate; centroblasts are in minority.

**Genetic abnormalities**

A translocation t (14;18), involving rearrangement of the bcl-2 gene, is mainly involved resulting in expression of this anti-apoptosis gene which is switched off at the translational level in normal germinal center cells; expression of bcl-2 protein permits accumulation of long-lived centrocytes.

When the resting B-cells that carry the bcl-2 translocation undergoes blast formation in response to antigen, failure to switch off the bcl-2 gene may contribute to the development of lymphoma.[13]

**Morphology**

The cells of follicular lymphomas are identical to those of the normal germinal center:

- Centrocytes (size less than twice the size of small lymphocytes, nuclei appear irregular and cleaved, single or multiple nucleoli may be present, and cytoplasm is scanty and pale)
- Centroblasts (size is 3-4 times the size of small lymphocytes, the nuclei are round or oval but may be irregular, indented or even have a cleft, have 1-3 basophilic nucleoli opposed to the nuclear membrane, and narrow rim of cytoplasm is present).[13]

**Grading**

Follicular lymphomas were initially divided into predominantly small, mixed small and large, and large cell categories. However, the terminology is not optimal because it ignores the fact that all the three categories are in fact mixed containing both centroblast and centrocytes.

For this reason, the International Lymphoma Study Group suggested the terms Follicular lymphoma grade I, II, and III, respectively, according to the number of centroblasts per high-power field (hpf). The grade of Follicular Lymphoma is based on counting the absolute number of centroblasts at 40 × magnification in 10 neoplastic follicles per hpf.[13]

**WHO classification system**

- Grade I (0–5 centroblasts/hpf)
- Grade II (6–15 centroblasts/hpf)
- Grade III (>15 centroblasts/hpf)

Various other methods for the grading are [Tables 2-5]

- Mann and Berard cell counting method
- Rappaport method
- Lukes–Collins method
- Jaffe’s modification of the Berard method

The WHO classification suggests further subdivision of Follicular Lymphoma grade 3 into 3a and 3b, based on the presence or absence of small cleaved cells (centrocytes), respectively:

- In Follicular Lymphoma 3a, the neoplastic follicles have more than 15 centroblasts per high-power field in a background of centrocytes
- In Follicular Lymphoma 3b, the neoplastic follicles are composed of sheets of centroblasts without admixed centrocytes
- In the Working Formulation, follicular lymphoma composed of small centroblasts (small noncleaved cells) had a more aggressive course. Nathwani *et al.* also found that follicular
lymphomas with more than 10 small noncleaved cells per hpf had a significantly worse overall survival.\[10]\)

**Pattern**

In addition to the cellular component, the proportions of follicular and diffuse areas vary from case to case. In the Kiel classification, the tumor is classified based on cell type (centroblastic/centrocytic) and further subdivided according to the pattern (follicular, follicular and diffuse, or diffuse). The presence of any diffuse component results in worse outcome, suggesting histologic progression to diffuse large B-cell lymphoma. The cases with purely follicular large cell lymphoma had a better prognosis than those with a diffuse component.\[14,17]\)

The pattern is considered to be follicular (>75% follicular), follicular and diffuse (25% to 75% follicular), or locally follicular (<25% follicular).

**Immunophenotype**

The tumor cells of follicle center lymphoma are usually surface immunoglobulin positive; about 50% to 60% express IgM, about 40% IgG and rarely IgA. Tumor cells express pan-B-cell associated antigens about 60% are CD10+ and are CD5-, CD23-/+, CD43-, and CD11c-. Lack of CD5 and CD43 distinguishes it from mantle cell lymphoma and presence of CD10 distinguishes it from marginal zone B-cell lymphoma.

**Mantle cell lymphoma**

In the early 1980s, Weisenburger et al. and Palutke et al.\[18]\ described a distinctive type of follicular lymphoma that was characterized by the proliferation of atypical small lymphoid cells in wide mantles around benign germinal centers. Weisenburger et al. coined the term mantle zone lymphoma for this entity and suggested that it represented the follicular counterpart of diffuse intermediate lymphocytic lymphoma.\[19]\)

**Clinical features**

Mantle cell lymphoma is characterized by a male predominance and median age of presentation above 60 years; 90% of patients present with advanced-stage (III–IV) disease.

- Many mantle cell lymphoma patients exhibit fever, night sweat, weight loss, and symptoms related to extranodal disease
- Most common sites of disease are the lymph nodes, spleen, Waldeyer’s ring, bone marrow, and blood
- Extranodal mantle cell lymphoma may be found in the gastrointestinal tract, most commonly in the form of colonic lymphomatous polyposis, and may also involve the lungs, soft tissue, central nervous system (CNS), and genitourinary tract
- A Peripheral blood lymphocytosis of >4,000/µL occurs in 20% to 40% of the cases, but absolute counts >20,000/µL are uncommon.

**Pathologic features**

The non-Hodgkin’s lymphoma of mantle cell type usually consists of atypical small lymphoid cells and has either a nodular or diffuse pattern of growth, or a combination of the two patterns.

Nodularity is present, at least focally, in approximately 30% of cases of mantle cell lymphoma at the time of initial diagnosis. In nodular mantle cell lymphoma, some or many of the nodules may consist of follicles with reactive germinal centers surrounded by broad and expansive mantles of small lymphoid cells, the so-called mantle zone.

Later in the course of disease, invasion and obliteration of the reactive germinal centers and interfollicular areas by neoplastic cells result in a diffuse pattern of growth. Residual vague nodularity may be seen in such cases.\[17]\)

Cytologically, mantle cell lymphoma usually consists of a monotonous population of atypical small to medium-sized lymphoid cells with irregular and indented nuclei, moderately coarse chromatin, inconspicuous nucleoli, and scant cytoplasm (typical “intermediate” cytology). Small round lymphocytes, some of which are T-cells, are admixed in variable numbers, and neoplastic cells with cleaved nuclei are often present as well.\[18]\)

**Morphologic Variants**

**Anaplastic large cell centrocytic lymphoma**

In about 20% of cases of mantle cell lymphoma, the neoplastic cells are larger than usual and have more finely dispersed nuclear chromatin and small nucleoli. Such cases have been referred to as large cell (“anaplastic centrocytic”) or blastic variants of mantle cell lymphoma.

**Centroblastoid variant**

Sometimes, a mixture of atypical small cells and larger blastic cells is present, imparting a more pleomorphic cytologic picture. In other cases, the blastic cells are quite monotonous, ranging from medium to large in size, with very fine chromatin and multiple small nucleoli (“centrocytoid centroblastoid” cytology).\[19]\)

**Lymphoblastoid**

A small proportion of cases have larger nuclei with more dispersed chromatin and a high proliferation fraction. Because some of these resemble lymphoblastic lymphoma, the blastic variant has been applied. The terms lymphoblastoid and blastoid are preferable to emphasize the cytologic resemblance to lymphoblasts rather than to large transformed blasts (centroblast or immunoblasts).\[19]\)

**Immunologic features**

Mantle cell lymphoma cells express CD5, CD19, CD22, CD20, CD24, CD43, CD79a, and bcl-2. Mantle cell lymphoma cells typically do not express CD10, CD23, or bcl-6.
The expression pattern allows the differentiation of mantle cell lymphoma from other types of NHL, such as B-cell chronic leukemia/small lymphocytic leukemia (CD23+) and follicular lymphoma (CD5-, CD10+).\(^{[18,20]}\)

**Implications for clinical practice**

The primary care physician is the first contact of a patient for the consultation of illness. Early diagnosis and a multi-disciplinary approach are key components of managing the various types of NHL. Increased awareness and research in this field have facilitated identification of risk factors and causation pathways. Certain drugs have shown increased effectiveness in the treatment of NHL. NHL requires different therapeutic approaches according to tumor burden. Better rates of remission and survival have been obtained since the introduction of newer drugs in combination with chemotherapy and in maintenance therapy. Rituximab-based chemoimmunotherapy has resulted in a marked improvement in patients with diffuse large B-cell lymphomas. More recently, the development of biological knowledge and the use of targeted drugs offer new therapeutic perspectives with chemo-free treatment strategies.\(^{[21,22]}\)

**Conclusion**

As described above, the REAL/WHO classification systems entitled us with well-defined morphologic, immunologic, and genotypic lymphoma entities. Most of these entities have clear-cut clinical definitions. Thus, by correlating the histopathological features of these entities one can come across the malignant nature and prognosis of different forms of lymphomas.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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