Chapter

B-Cell Lymphomas

Subramanian Kalaivani Selvi, B.H. Srinivas and Sadhanandham Shrinuvasan

Abstract

B-cell lymphomas arise from different stages of differentiation of B-cells and constitute a broad spectrum, extending from small- to large-cell types, and from low to high grades of clinical behavior. It has undergone several terminologies and classifications. Because of the diverse terminology that is used in the multiple classifications of lymphomas, there have been attempts to develop uniform pathologic descriptions with clinical usefulness. The current WHO classification uses morphologic, immunophenotypic, genotypic, and clinical features to classify the lymphoid neoplasms into five broad categories as precursor B-cell neoplasms, peripheral B-cell neoplasms, precursor T-cell neoplasms, peripheral T-cell neoplasms and Hodgkin lymphoma. Hodgkin lymphoma though originates from B-cell has distinctive pathologic features and is treated as a separate entity. This chapter discusses about the etiology and pathogenesis, clinical features, recent WHO classification of B-cell lymphoma (2016), the highlights of modifications brought in, the morphology, immunophenotype, staging, treatment and prognosis of various B-cell lymphomas.

Keywords: B-cell lymphomas, recent WHO classification, pathogenesis, morphology, immunophenotype, treatment, prognosis

1. Introduction

B-cell lymphomas are malignant neoplasms that arise from different stages of differentiation of B-cells and constitute a broad spectrum, extending from small- to large-cell types, and from low to high grades of clinical behavior. It constitutes the major type of non-Hodgkin's lymphoma (NHL) [1–3].

The recognition of lymphoma evolved from Thomas Hodgkin's 1832 paper entitled "On Some Morbid Appearances of the Absorbent Glands and Spleen" [4], followed by various nomenclatures and classifications that classified lymphomas into Hodgkins and non-Hodgkin's lymphomas [5–11]. In 1974, Lennert et al. [12] and Lukes and Collins [13] classified NHL on the basis of the cell of origin as B cell lymphomas and T cell lymphomas which was later confirmed at the molecular level with the identification of specific Ig gene and T-cell receptor (TCR) gene rearrangements [14–17]. In 1982, a Working Formulation (WF) classified NHL according to histologic grade as low, intermediate, and high [18]. In 1994, a Revised European American Lymphoma (REAL) Classification was proposed which diagnosed lymphomas by identifying clinical features, morphology, immunophenotype, and genetic data [19]. The World Health Organization (WHO) then adopted the diagnostic principles of the REAL Classification, and is used as the schema for the diagnosis of all hematopoietic neoplasms [20, 21].

The 2001 and 2008 World Health Organization classification of hematopoietic and lymphoid tumors established guidelines for the diagnosis of malignant lymphomas; however, subsequently, there have been major advances with significant clinical and biologic implications which necessitated further revisions [22, 23]. Hence further revision was done in 2016 which reflects a consensus among hematopathologists, geneticists, and clinicians regarding both updates to current entities as well as the addition of a limited number of new provisional entities leading to more targeted therapeutic strategies. The current WHO classification uses morphologic, immunophenotypic, genotypic, and clinical features to classify the lymphoid neoplasms into five broad categories as precursor B-cell neoplasms, peripheral B-cell neoplasms, precursor T-cell neoplasms, peripheral T-cell neoplasms and Hodgkin lymphoma. Hodgkin lymphoma though originates from B-cell has distinctive pathologic features and is treated as a separate entity. This chapter discusses about the etiology and pathogenesis, clinical features, recent WHO classification of B-cell lymphomas (2017), the highlights of modifications brought in, the morphology, immunophenotype, staging, treatment and prognosis of various B-cell lymphomas [24–26].

2. B-cell lymphomas: origin and development

The differentiation of the B-cell lineage starts from stem cells the common lymphoid precursor to plasma cells that occurs successively in the fetal liver, bone marrow, and lymph nodes. The characteristic marker of B cells is the presence of immunoglobulins, which act as the cell surface antigen receptor. The genes that code for antibody are rearranged in the course of differentiation from stem cell to pre-B cell [20]. Understanding the stages of B-cell maturation has facilitated the recognition of the interrelationships between the various types of B-cell lymphomas and leukemia.

The WHO classification distinguishes two major categories within B-cell lymphomas: precursor and mature. The precursor B-cell lymphomas comprise those lymphoblastic lymphomas and leukemia that derive from progenitor cells that have not yet been activated by antigen and are still in an undifferentiated stage. All other lymphomas representing different stages of differentiation are included in the category of mature B-cell lymphomas. Naïve B-cell can give rise to mantle cell lymphoma, small lymphocytic lymphoma/ chronic lymphocytic lymphoma. Lymphomas originating in the cells of the germinal centres are follicular lymphomas, Burkitt lymphoma and diffuse large B cell lymphoma. Post germinal center cells can give rise to marginal zone lymphoma, small lymphocytic lymphoma/ chronic lymphocytic lymphoma, diffuse large B cell lymphoma, plasma cell myeloma, lymphoplasmacytic lymphoma [1, 20, 22–25].

B-cell lymphomas constitute a broad spectrum, extending from small- to large-cell types, and from low to high grades of clinical behavior. The term “grade” is defined by the size and shape of cells and nuclei; density of chromatin; the number of mitoses (proliferation index), which may indicate the aggressiveness of a tumor; and by its clinical behavior. However, aggressiveness and tumor grade cannot be used synonymously because their correlation is not consistent; some lymphomas of highly aggressive behavior, such as mantle cell lymphoma, may exhibit low histologic grades.

Hodgkin lymphoma (HL) encompasses another group of lymphoid neoplasms that are characterized by neoplastic Reed-Sternberg cells derived from the germinal center or post-germinal center B cells and differ from NHL in several respects. Hence it is treated as a separate category though it is derived from B-cells.

3. Etiology and pathogenesis

Chromosomal Translocations and Other Acquired Mutations are present in the majority of lymphomas. Many specific rearrangements are associated with particular neoplasms, suggesting a critical role in their genesis. The mutation can produce a "dominant negative" protein that interferes with a normal function (a loss of function) or inappropriate increase in some normal activity (a gain of function). Oncoproteins created by genomic aberrations often block normal maturation, turn on pro-growth signaling pathways that enhance the self-renewal of tumors cells, or protect cells from apoptotic cell death. Pro-growth signaling mutations produce a constitutively active tyrosine kinase; oncogenic tyrosine kinases activate RAS and its two downstream signaling arms, the phosphoinositide-3-kinase/AKT8 virus oncogene cellular homolog (PI3K/AKT) and mitogen-activated protein kinases (MAPK) pathways and thereby drive cell growth. Oncogenic mutations most frequently occur in germinal center B cells during antibody diversification. B cells that enter germinal centres after antigen stimulation upregulate the expression of activation-induced cytosine deaminase (AID), a specialized DNA-modifying enzyme which is essential for immunoglobulin (Ig) gene modifications: (1) class switching, an intragenic recombination event in which the IgM heavy-chain constant gene segment is replaced with a different constant segment leading to a switch in the class (isotype) of antibody produced; and (2) somatic hypermutation, which creates point mutations within Ig genes that may increase antibody affinity for antigen. Certain protooncogenes, such as myelocytomatosis oncogene cellular homolog (MYC), are activated in germinal center B-cell lymphomas by translocations to the transcriptionally active Ig locus. Other proto-oncogenes, such as BCL6, a transcription factor that has an important role in many B cell malignancies, are frequently activated in germinal center B-cell lymphomas by point mutations that also seem to stem from "mistargeted" DNA breaks induced by AID. A different type of regulated genomic instability is unique to precursor B cells, which express a V(D)J recombinase that cuts DNA at specific sites within the Ig [1].

Other factors include immunosuppression; infectious agents like Epstein-Barr virus, Human T-cell lymphotropic virus type 1, *Helicobacter pylori*, Hepatitis C virus, Human herpesvirus 8 (Kaposi sarcoma), Human herpesvirus 6, Human T-cell lymphotropic virus type 2 are known to be associated with lymphomas [27–31]. Male gender, increasing age, family history of non-Hodgkin's lymphoma, prior cancer history, drug history, immunosuppressive agents like phenytoin, methotrexate; occupational history like exposure to herbicides, pesticides, wood dust, epoxy glue, solvents; jobs in farming, forestry, painting, carpentry, tanning, hair dye use, sunlight exposure, nutritional factors, blood transfusion are the other possible etiologic factors [1, 32–37].

4. Clinical features

The clinical presentation of the various lymphoid neoplasms is most often determined by the anatomic distribution of disease. Two-thirds of non-Hodgkin's Lymphomas present as enlarged nontender lymph nodes. The remaining one-third of NHLs present with symptoms related to the involvement of extranodal sites leading to mass effect, obstructive and compressive signs and symptoms. The lymphocytic leukemia most often come to attention because of signs and symptoms related to the suppression of normal hematopoiesis by tumor cells in the bone marrow. Plasma cell neoplasm, multiple myeloma, causes bony destruction of the skeleton and often presents with pain due to pathologic fractures. Other symptoms related to

lymphoid tumors are frequently caused by proteins secreted from the tumor cells or from immune cells that are responding to the tumor. Specific examples include the plasma cell tumors, in which much of the pathophysiology is related to the secretion of whole antibodies or Ig fragments; Significant cytopenias are rare, unless marrow involvement is extensive, or there are associated immune-mediated cytopenias, hypersplenism, or, rarely, hemophagocytosis. Hepatosplenomegaly is a common feature of advanced low-grade B-cell lymphoma. Bleeding manifestations are common in lymphoblastic lymphomas/leukemia with marrow involvement [1, 2].

5. Investigations

Complete history and physical examination; inquiry about B symptoms, human immunodeficiency virus risk, infections, autoimmune diseases, immunosuppressive therapy.

Complete blood cell count and peripheral smear examination including hemoglobin, total leukocyte count with differential and platelet count.

Biochemistry profile—lactate dehydrogenase; alkaline phosphatase, uric acid, creatinine, calcium, and albumin.

Imaging—computed tomography of chest, abdomen, pelvis, and neck, Selected radiologic procedures as clinically appropriate (e.g., gallium, positron emission tomography scan, magnetic resonance imaging, ultrasound, bone scan).

Bone marrow aspiration and biopsy—morphology, immunophenotyping, cytogenetics, molecular tests, and gene rearrangement studies.

Lumbar puncture with cytology in patients with CNS involvement.

Gastrointestinal endoscopy for patients with Waldeyer ring involvement or abdominal symptoms.

Cytologic assessment of third space fluids (pleura, peritoneum) in case of effusions.

Other blood evaluations: levels of ß 2-microglobulin and cytokines (interleukin-2 receptor, tumor necrosis factor).

6. 2016 WHO classification of B lymphoid neoplasms

The current WHO classification uses morphologic, immunophenotypic, genotypic, and clinical features to classify the lymphoid neoplasms into five broad categories as precursor B-cell neoplasms, peripheral B-cell neoplasms, precursor T-cell neoplasms, peripheral T-cell neoplasms and Hodgkin lymphoma. Hodgkin lymphoma though originates from B-cell has distinctive pathologic features and is treated as a separate entity (**Table 1**).

The WHO classification distinguishes two major categories within B-cell lymphomas:

a. Precursor B-cell neoplasms

b. Mature B-cell neoplasms

6.1 Precursor B-cell neoplasms

Acute lymphoblastic leukemia/lymphoma (ALLs) are neoplasms composed of immature B (pre-B) which are referred to as lymphoblasts. About 85% are B-ALLs, which typically manifest as childhood acute "leukemia." Many of the chromosomal aberrations seen in ALL dysregulate the expression and function of transcription factors required for normal B development. B-ALLs have loss-of-function mutations

in genes that are required for B-cell development, such as Paired Box 5 (PAX5), E2-alpha (E2A), and early B-cell factor (EBF), or a balanced t(12;21) involving the genes translocation-Ets-leukemia virus (ETV6) and Runt Related Transcription Factor 1 (RUNX1), two genes that are needed in very early hematopoietic precursors. All of these varied mutations disturb the differentiation of lymphoid precursors and promote maturation arrest, and in doing they induce increased self-renewal, a stem cell-like phenotype. Approximately 90% of ALLs have numerical or structural chromosomal changes. Most common is hyperploidy (>50 chromosomes), but hypoploidy and a variety of balanced chromosomal translocations are also seen [1, 25, 38].

Patients present with fatigue due to anemia; fever due to infections secondary to neutropenia; and bleeding due to thrombocytopenia. They can so present with mass effects caused by neoplastic infiltration, including bone pain, generalized lymphadenopathy, splenomegaly, hepatomegaly; testicular enlargement; headache, vomiting, and nerve palsies due to central nervous system involvement [1, 25].

6.1.1 Morphology and immunophenotype

In leukemic presentations, the marrow is hypercellular and packed with lymphoblasts, which replace the normal marrow elements, lymphoblasts have more condensed chromatin, less conspicuous nucleoli, and smaller amounts of cytoplasm that usually lacks granules. Histochemical stains show periodic acid-Schiff–positive cytoplasmic material. Immunostaining for terminal deoxynucleotidyl transferase (TdT), is positive in more than 95% of cases in addition to B-cell markers. B-ALLs are arrested at various stages of development. The lymphoblasts usually express the pan B-cell marker CD19/CD22/CD79a and the transcription factor PAX5. CD10 is expressed in common ALL and pre-B ALLs express in addition cytoplasmic IgM heavy chain (μ chain) and surface immunoglobulins in mature forms (**Figure 1**).

6.1.2 New provisional entities in recent WHO classification

- B-ALL with intrachromosomal amplification of chromosome 21 [24, 39, 40].

- B-ALL with translocations involving tyrosine kinases or cytokine receptors ("BCR-ABL1—like ALL").

6.1.3 Treatment and prognosis

Treatment includes chemotherapy, steroids, radiation therapy and marrow transplantation. About 95% of children obtain a complete remission, and 75–85% are cured

WHO classification of B lymphoid neoplasms
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);BCR-ABL1 B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);KMT2A rearranged B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1 B-lymphoblastic leukemia/lymphoma with hyperdiploidy B-lymphoblastic leukemia/lymphoma with hypodiploidy B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1 Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
Mature B-cell neoplasms

WHO classification of B lymphoid neoplasms
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenstro¨m macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
m heavy-chain disease
g heavy-chain disease
a heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
Large B-cell lymphoma with IRF4 rearrangement*
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV1 DLBCL, NOS*
EBV1 mucocutaneous ulcer*
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK1 large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV81 DLBCL, NOS*
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration*
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Changes from the 2008 classification.

Table 1.
WHO classification of B lymphoid neoplasms

with chemotherapy, whereas only 35–40% of adults are cured. Treatment of t(9;22)-positive ALLs with BCR-ABL kinase inhibitors in combination with conventional chemotherapy is highly effective and has greatly improved the outcome in children. The outlook for adults with ALL remains more guarded, in part because of differences

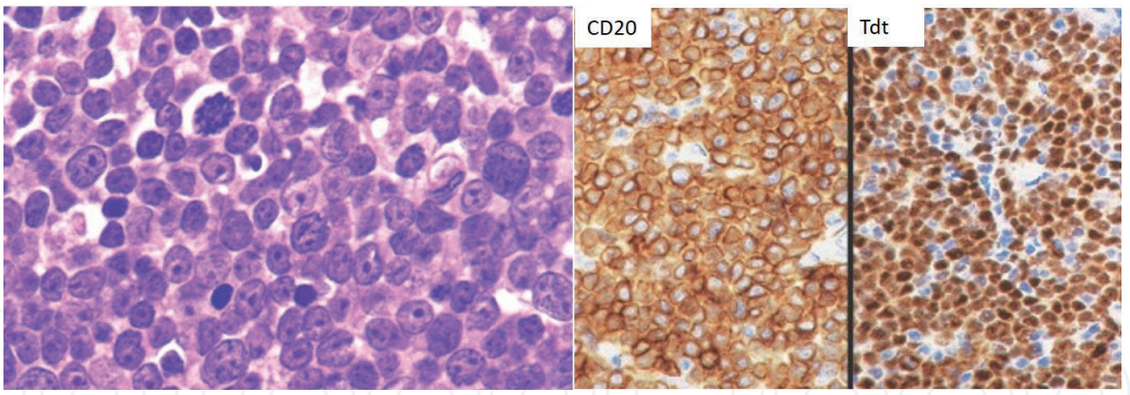

Figure 1.
B-lymphoblastic lymphoma showing CD20, Tdt positivity.

in the molecular pathogenesis of adult and childhood ALL, but also because older adults cannot tolerate the very intensive chemotherapy regimens that are curative in children. Factors associated with worse prognosis includes: (1) age younger than 2 years, (2) presentation in adolescence or adulthood; and (3) peripheral blood blast counts greater than 100,000. Factors associated with favorable prognosis include (1) age between 2 and 10 years, (2) a low white cell count, (3) hyperdiploidy, (4) trisomy of chromosomes 4, 7, and 10, and (5) the presence of a t(12;21) [1, 25, 38].

6.2 Chronic lymphocytic leukemia/small lymphocytic lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are used interchangeably by the degree of peripheral blood lymphocytosis. CLL is the most common leukemia of adults with absolute lymphocyte count >5000 per mm^3. The median age at diagnosis is 60 years. SLL constitutes only 4% of NHLs and has lymph node involvement The common genetic anomalies associated are deletions of 13q14.3, 11q, and 17p, and trisomy 12q [1, 25]. Patients are usually asymptomatic at diagnosis and can present with easy fatigability, weight loss, and anorexia. Generalized lymphadenopathy and hepatosplenomegaly are present in 50–60% of patients. The leukocyte count is high in most cases; leukopenia can be seen in individuals with SLL and marrow involvement.

6.2.1 Morphology and immunophenotype

Peripheral blood contains large numbers of small round lymphocytes with scant cytoplasm. Some of these cells are usually disrupted in the process of making smears, producing smudge cells. Prolymphocytes can also be circulating based on which it is classified as CLL or CLL/PLL or PLL (Prolymphocytic leukemia). The bone marrow is almost always involved by interstitial infiltrates or aggregates of tumor cells. Infiltrates are also virtually always seen in the splenic white and red pulp and the hepatic portal tracts. Lymph nodes are diffusely effaced by predominantly small lymphocytes with mild irregular nucleus, condensed chromatin, and scant cytoplasm along with proliferation centers, which contain aggregates of mitotically active larger activated lymphocytes. (**Figure 2**).CLL/SLL has a distinctive immunophenotype. The tumor cells express the pan B-cell markers CD19 and CD20, CD23, CD5, LEF1 (Lymphoid Enhancer Binding Factor 1), CD200. Negative for SOX11 (SRY (sex determining region) - Box 11), CD10.

6.2.2 Highlights in recent WHO classification

Cytopenias or disease-related symptoms are now insufficient to make a diagnosis of CLL with $<5 \times 10^9$/L PB CLL cells.

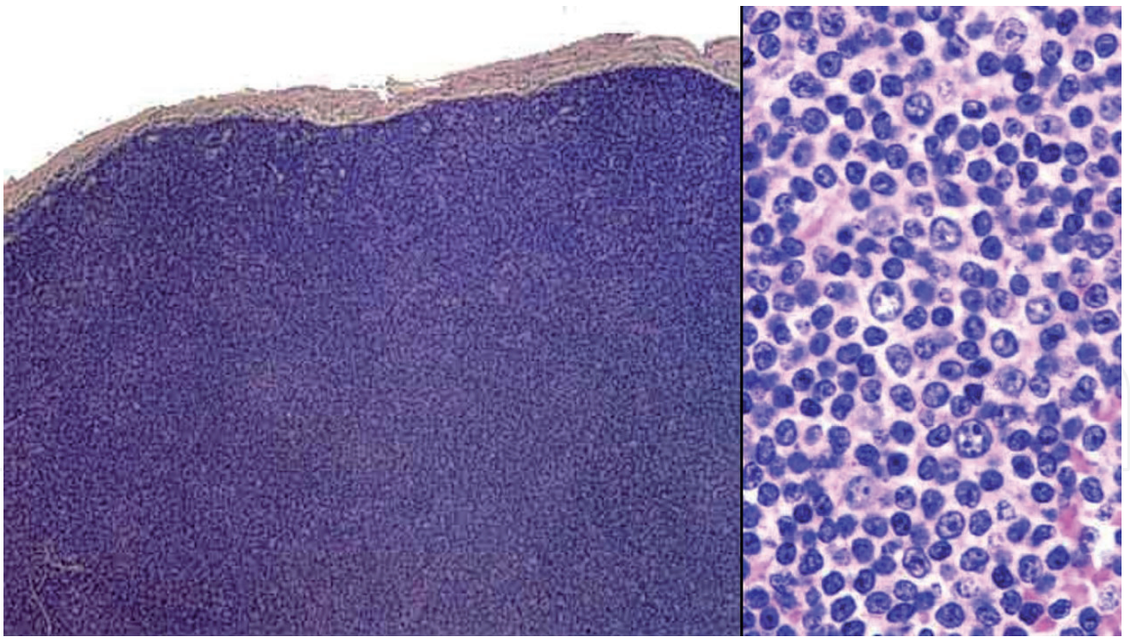

Figure 2.
Small lymphocytic lymphoma showing diffuse effacement by small lymphoid cells.

Large/confluent and/or highly proliferative proliferation centres are adverse prognostic indicators [24, 41–44].

Mutations of potential clinical relevance, such as TP53 (tumor protein 53), NOTCH1 (*Notch* homolog *1*), SF3B1 (Splicing Factor 3b Subunit 1), ATM (Ataxia telangiectasia mutated), and BIRC3 (Baculoviral IAP repeat-containing protein 3), have been recognized

6.2.3 Treatment and prognosis

The treatment, course and prognosis depend primarily on the clinical stage. Median survival is 4–6 years but can be more than 10 years in those with minimal tumor burdens. Factors associated with worse outcome include (1) deletions of 11q and 17p, (2) lack of somatic hypermutation, (3) expression of ZAP-70(z-chain-associated protein kinase), and (4) presence of NOTCH1 mutations. CLL also have the risk of transformation into diffuse large B -cell lymphoma [1, 25]. Symptomatic patients are generally treated with "gentle" chemotherapy and immunotherapy with antibodies against proteins found on the surface of CLL/SLL cells, particularly CD20. Hematopoietic stem cell transplantation is being offered to the relatively young. The most promising new therapy is Bruton's tyrosine kinase (BTK) inhibitors [1, 25].

6.3 Follicular lymphoma

Follicular lymphoma (FL) is the most common form of indolent NHL. It usually presents in middle age and afflicts males and females equally. Follicular lymphoma likely arises from germinal center B cells and is strongly associated with chromosomal translocations involving BCL2 (B-cell lymphoma 2). Its hallmark is a (14; 18) translocation that juxtaposes the IGH locus on chromosome 14 and the BCL2 locus on chromosome 18. The t (14; 18) is seen in up to 90% of follicular lymphomas and leads to overexpression of BCL2. Follicular lymphoma tends to present with painless, generalized lymphadenopathy. Involvement of extranodal sites, such as the gastrointestinal tract, central nervous system, or testis, is relatively uncommon [1, 25, 45, 46].

6.3.1 Morphology and immunophenotype

Follicular lymphoma usually shows effacement of nodal architecture by follicular nodules that occupy both cortex and the medulla with two cell types in varying proportions: (1) Centrocytes which are small cells with irregular or cleaved nucleus and scant cytoplasm (2) Centroblasts which are larger cells with open nuclear chromatin, several prominent nucleoli, and modest amounts of cytoplasm. Based on the number of these centroblasts FL is classified into Grade 1, 2, and 3a,b. Grade 1 follicular lymphomas have 0–5 centroblasts per HPF; 6–15 centroblasts per HPF as grade 2, and greater than 15 per HPF as grade 3 follicular lymphomas. Low-grade (grades 1 and 2) follicular lymphomas are composed of a relatively homogeneous population of small cleaved lymphocytes. Grade 3 follicular lymphomas, which by definition have an increased number of large noncleaved cells and have been provisionally subcategorized into 3a and 3b, with the former having a mix of cleaved and large noncleaved cells, and the latter having sheets or large clusters of large noncleaved cells Peripheral blood involvement is seen in about 10% of cases. Bone marrow involvement occurs in 85% of cases and characteristically takes the form of paratrabecular lymphoid aggregates. The neoplastic cells express CD19, CD20, CD10, surface Ig, and BCL6 (B-cell lymphoma 6). BCL2 is expressed in more than 90% of cases. CD5 and cyclin D1 are negative. Ki67 is low [25] (**Figure 3**).

6.3.2 Highlights in recent WHO classification

- Mutational landscape better understood but the clinical impact remains to be determined [24, 47–51].

In situ follicular neoplasia.

- New name for in situ follicular lymphoma reflects low risk of progression to lymphoma.

6.3.3 Pediatric-type FL

- A localized clonal proliferation with excellent prognosis; a conservative therapeutic approach may be sufficient.
- Occurs in children and young adults, rarely in older individuals.

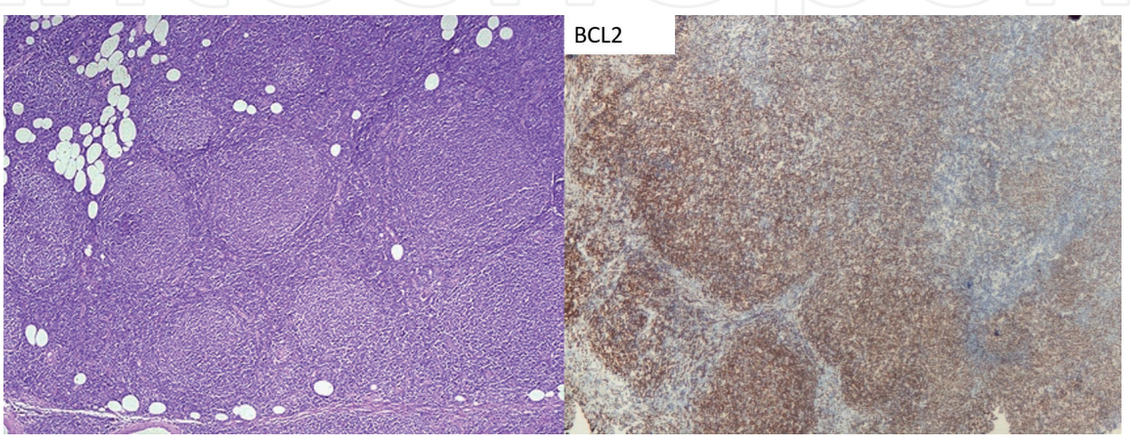

Figure 3.
Follicular lymphoma showing nodular pattern with neoplastic follicles occupying cortex and medulla and showing BCL2 positivity.

6.3.4 Duodenal-type FL

- Localized process with low risk for dissemination. Predominantly diffuse FL with 1p36 deletion.

- Accounts for some cases of diffuse FL lacks BCL2 rearrangement; presents as a localized mass, often inguinal.

6.3.5 Treatment and prognosis

Histological grade correlates with prognosis with grade 1–2 follicular lymphoma cases being indolent and usually not curable by aggressive therapy; and needs to palliate patients with low-dose chemotherapy or immunotherapy (e.g., anti-CD20 antibody). Median survival is 7–9 years. Histologic transformation occurs in 30–50% of follicular lymphomas, most commonly to diffuse large B-cell lymphoma [1, 25].

6.4 Mantle cell lymphoma

Mantle cell lymphoma (MCL) is an uncommon lymphoid neoplasm. It usually presents in the fifth to sixth decades of life and shows a male predominance. Virtually all mantle cell lymphomas have an (11; 14) translocation involving the IgH locus on chromosome 14 and the cyclin D1 locus on chromosome 11 that leads to overexpression of cyclin D1. The most common presentation is painless lymphadenopathy. Symptoms related to the involvement of the spleen (present in ~50% of cases) and extranodal sites are also common. In GIT present as lymphomatous polyposis of the lower gastrointestinal tract [1, 25, 52].

6.4.1 Morphology and immunophenotype

MCL consists of a homogeneous population of small lymphocytes with irregular to occasionally deeply clefted (cleaved) nuclear contours. In most cases the nuclear chromatin is condensed, nucleoli are inconspicuous, and the cytoplasm is scant. It usually has a diffuse growth pattern or surrounds reactive germinal centers in a mantle zone pattern. Extension of the lymphoma into the capsule and perinodal fat is common Occasionally, tumors composed of intermediate-sized cells with more open chromatin and a brisk mitotic rate are observed; immunophenotyping is necessary to distinguish these "blastoid" variants.

Mantle cell lymphomas express high levels of cyclin D1. Most tumors are also express CD19, CD20. It is usually CD5+, SOX11 +, FMC7+ (Flinders Medical Centre), BCL1+ and CD23−, CD10−, CD200−, LEF1−, which help to distinguish it from CLL/SLL. The IgH genes lack somatic hypermutation, supporting an origin from a naive B cell [25] (**Figure 4**).

6.4.2 Highlights in recent WHO classification

- Two MCL subtypes recognized with different clinicopathological manifestations and molecular pathogenetic pathways [24, 52–54]

    1. unmutated/minimally mutated immunoglobulin heavy chain gene (IGHV) and mostly SOX11 positive

    2. mutated IGHV and mostly SOX11 negative (indolent leukemic non-nodal MCL with PB), bone marrow (BM), (splenic involvement, may become

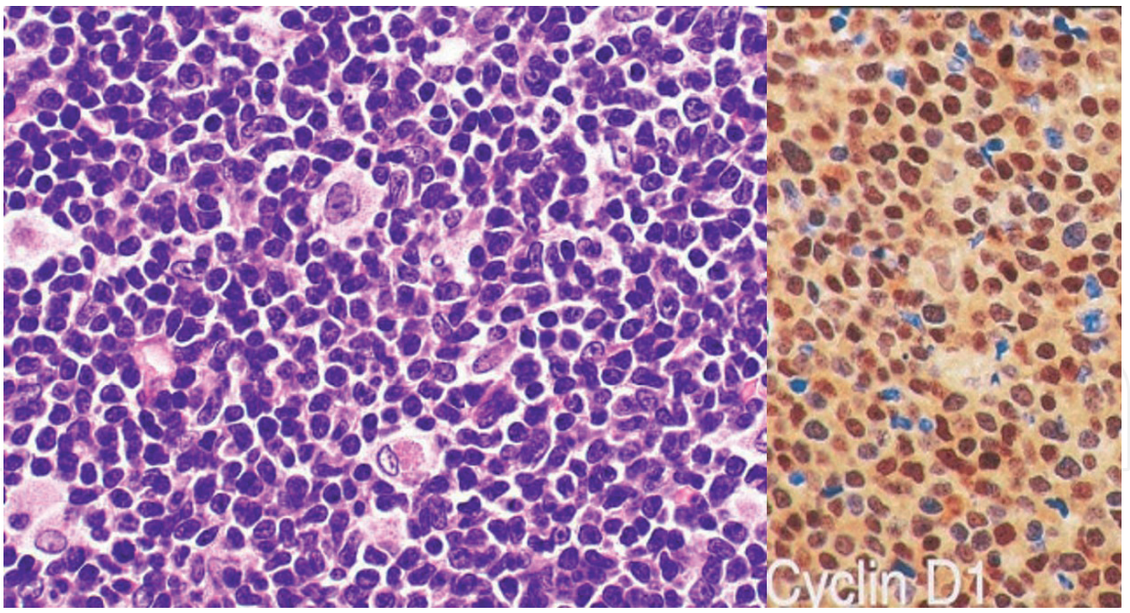

Figure 4.
Mantle cell lymphoma showing cyclin D1 positivity.

more aggressive).Mutations of potential clinical importance, such as TP53, NOTCH 1/2, recognized in a small proportion of cases.

- CCND2 (Cyclin D2) rearrangements in approximately half of cyclin D1 negative MCL.

  In situ mantle cell neoplasia—New name for in situ MCL, reflecting low clinical risk.

6.4.3 Treatment and prognosis

MCL is usually not curable with conventional chemotherapy, and most patients succumb to organ dysfunction caused by tumor infiltration. The prognosis is poor with median survival of only 3–4 years. The blastoid variant is associated with even shorter survivals. Hematopoietic stem cell transplantation and proteasome inhibitors are newer therapeutic approaches that show some promise [1, 25].

6.5 Marginal zone lymphomas

Marginal zone lymphoma (MZL) is a group of B-cell tumors that arise from lymph nodes, spleen, or extranodal tissues. In most cases, there is evidence of somatic hypermutation of memory B-cell origin. The disease begins as a polyclonal immune reaction. With time, however, tumors may acquire additional mutations that render their growth and survival antigen-independent, such as the (11; 18), (14; 18), or (1; 14) chromosomal translocations, which are relatively specific for extranodal marginal zone lymphomas [1, 25].

6.5.1 Nodal marginal zone B-cell lymphoma

Nodal marginal zone B-cell lymphomas are uncommon lymphomas in which the tumor cells resemble the cytology of those in splenic and extranodal marginal zone B-cell lymphomas of MALT, but there is no evidence for splenic or extranodal disease. Clinically, these lymphomas appear more extensive at presentation than

MALT lymphomas. They have a tendency to early relapse, and a small minority transform to large cell lymphoma.

6.5.2 Splenic marginal zone B-cell lymphoma

Splenic marginal zone B-cell lymphoma (SMZL) is a small B-cell lymphoma of the white pulp of the spleen that often involves the splenic hilar lymph nodes, bone marrow, and peripheral blood. Patients with splenic marginal zone B-cell lymphoma characteristically present with splenomegaly and many have B-symptoms (fever, weight loss, and night sweats). Peripheral blood shows circulating neoplastic lymphocytes that have a villous appearance. These cases were previously termed 'splenic lymphoma with villous lymphocytes'.

6.5.3 Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue

Extranodal marginal zone B-cell lymphomas arises in normal sites for mucosal immunity (MALT), such as intestinal Peyer patches, or in sites of inflammation triggered by autoimmune disorders, such as Hashimoto thyroiditis or Sjögren syndrome, or by infection (*Helicobacter pylori*-associated chronic gastritis. They may regress if the inciting agent (e.g., *Helicobacter pylori*) is eradicated suggesting that extranodal marginal zone lymphomas arise in chronically inflamed tissues that lie on a continuum between reactive lymphoid hyperplasia and full-blown lymphoma. Transformation to large cell lymphoma may occur. The t(11; 18) chromosomal abnormality is more specific and involves fusion of the API2 gene (an apoptosis inhibitor) on chromosome 11q21 and the MLT1 gene (a caspase-like protease) on chromosome 18q21. It is found in 40% of patients with MALT lymphomas. Two, less common, translocations are t(1; 14) (p22; q32) and t(14; 18) (q32; 21). These three translocations are not found in marginal zone B-cell lymphomas of spleen and lymph node.

6.5.4 Morphology and immunophenotype

These lymphomas are composed of small- to medium-sized lymphocytes that exhibit variable cytological features. In some cases, lymphocytes with irregular nuclear contours resembling follicular small cleaved cells or centrocytes may predominate. Other cases may be composed primarily of cells with abundant pale cytoplasm resembling monocytoid B cells. Cases with an abundance of small lymphocytes or plasma cells also may be seen. Regardless of the neoplastic cells' appearance, they produce a diffuse infiltrate that invades epithelial structures, producing lymphoepithelial lesions (**Figure 5**).

The lymphoid component expresses B-cell markers such as CD20, CD19 and CD43 and monotypic surface Ig (usually IgM without IgD). Negative for CD5, CD10, CYCLIN D1, and CD23.

6.5.5 Treatment and prognosis

Management of gastric MALToma with antibiotic therapy for *H. pylori* resulted in regression of lymphoma. Cases with the t(11;18)(q21;q21) appear to be resistant to *H. pylori* eradication therapy, Radiation therapy or single-agent chemotherapy is also effective in low-grade MALToma. MALT lymphomas have an indolent natural course and are slow to disseminate. Recurrences that can occur after many years. Median survival has been variable. SMZL tends to respond favorably to splenectomy alone in contrast to its poor response to chemotherapy [1, 25].

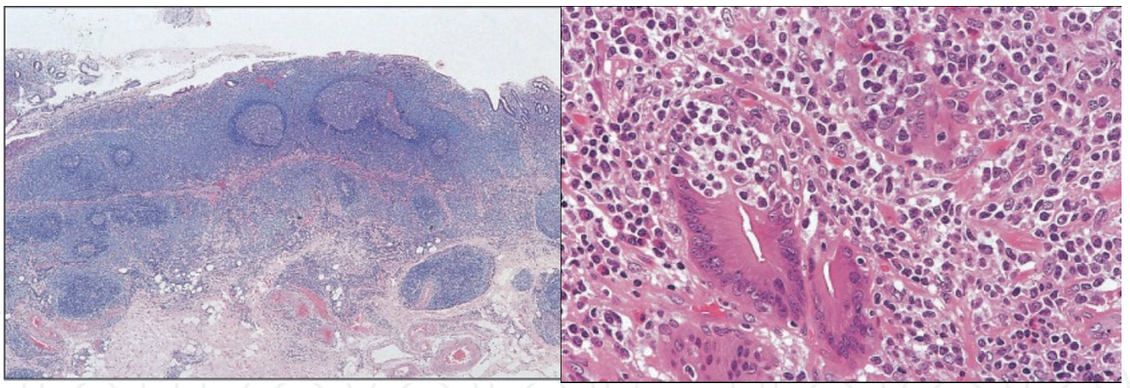

Figure 5.
Extranodal marginal zone lymphoma of stomach showing lymphoepithelial lesions.

6.6 Lymphoplasmacytic lymphoma

Lymphoplasmacytic lymphoma is a B-cell neoplasm of older adults that usually presents in the sixth or seventh decade of life and is characterized by tumor cells that undergo terminal differentiation to plasma cells. Most commonly, the plasma cell component secretes monoclonal IgM, often in amounts sufficient to cause a hyperviscosity syndrome known as Waldenström macroglobulinemia. Unlike multiple myeloma, complications stemming from the secretion of free light chains (e.g., renal failure and amyloidosis) are relatively rare and bone destruction does not occur. About 90% of Lymphoplasmacytic lymphoma are associated with acquired mutations in Myeloid differentiation factor 88 (MYD88) [55, 56]. The dominant presenting complaints are nonspecific and include weakness, fatigue, and weight loss. Approximately half the patients have lymphadenopathy, hepatomegaly, and splenomegaly. Anemia caused by marrow infiltration is common. About 10% of patients have autoimmune hemolysis caused by cold agglutinins. Cryoglobulinemia resulting from the precipitation of macroglobulins at low temperatures, which produces symptoms such as Raynaud phenomenon and cold urticaria [1, 25].

6.6.1 Morphology and immunophenotype

The neoplasm is composed of infiltration of lymphocytes, plasma cells, and plasmacytoid lymphocytes in varying proportions, often accompanied by mast cell hyperplasia. The lymphoid cells expresses CD20 and surface Ig, the plasma cells secretes the same Ig that is expressed on the surface of the lymphoid cells. This is usually IgM but can also be IgG or IgA (**Figure 6**).

6.6.2 Highlights in recent WHO classification

MYD88 L265P mutation in the vast majority of cases impacting diagnostic criteria even though finding is not specific for LPL [24, 55, 56].

IgM monoclonal gammopathy of undetermined significance (MGUS) is more closely related to LPL and other B-cell lymphomas than to myeloma.

6.6.3 Treatment and prognosis

LPL is an incurable progressive disease, however the tumor growth can be controlled with low doses of chemotherapy and immunotherapy with anti-CD20 antibody. Symptoms caused by the high IgM levels like hyperviscosity and hemolysis can be alleviated by plasmapheresis. The clinical course is typically indolent,

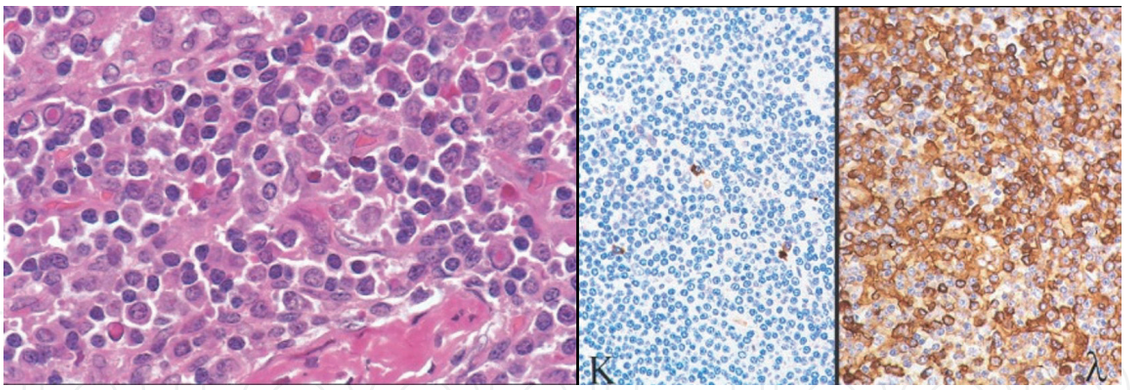

Figure 6.
Lymphoplasmacytic lymphoma showing lambda restriction.

with median survivals of 5–10 years. Transformation to large-cell lymphoma is uncommon [1, 25].

6.7 Burkitt lymphoma

Burkitt Lymphoma is a high-grade B-cell lymphoma composed of medium-sized, rapidly dividing lymphocytes. Less commonly, they have a leukemic phase. It is classified into (1) African (endemic) Burkitt lymphoma, (2) sporadic (nonendemic) Burkitt lymphoma, and (3) a subset of aggressive lymphomas occurring in individuals infected with HIV. Translocations of the MYC gene on chromosome 8 lead to increased MYC protein levels. The translocation partner for MYC is usually the IgH locus [t (8; 14)] but may also be the Ig κ [t (2; 8)] or λ [t (8; 22)] light chain loci. The translocated MYC allele often harbors additional point mutations. Endemic Burkitt lymphomas are seen to be latently infected with Epstein bar virus (EBV) (100%) and 20 to 40% in sporadic and immunodeficiency-associated Burkitt lymphomas. Both endemic and sporadic Burkitt lymphomas are found mainly in children or young adults. Most tumors involve extranodal sites. Endemic Burkitt lymphoma usually presents as mandibular mass and unusually involves abdominal viscera. In contrast, sporadic Burkitt lymphoma often involves the ileocecum and peritoneum [1, 25, 57–59].

6.7.1 Morphology and immunophenotype

Burkitt Lymphoma shows diffuse infiltrate of intermediate-sized lymphoid cells with round or oval nuclei, coarse chromatin, several nucleoli, and a moderate amount of cytoplasm with high mitotic index and numerous apoptotic, cells the nuclear remnants of which are phagocytosed by interspersed benign macrophages. These phagocytes have abundant clear cytoplasm, creating a characteristic "starry sky" pattern. These are tumors of mature B cells that express surface IgM, CD19, CD20, CD10, and BCL6, and negative for BCL2 and Tdt. Ki 67 approaches nearly 100% [1, 25] (**Figure 7**).

6.7.2 Highlights in recent WHO classification

- TCF3 (Transcription Factor 3) or ID3 (Inhibitor of DNA Binding 3), mutations in up to; 70% of cases [24, 57–61].

6.7.3 Burkitt-like lymphoma with 11q aberration

- A new provisional entity that closely resembles Burkitt lymphoma but lacks MYC rearrangement and has some other distinctive features.

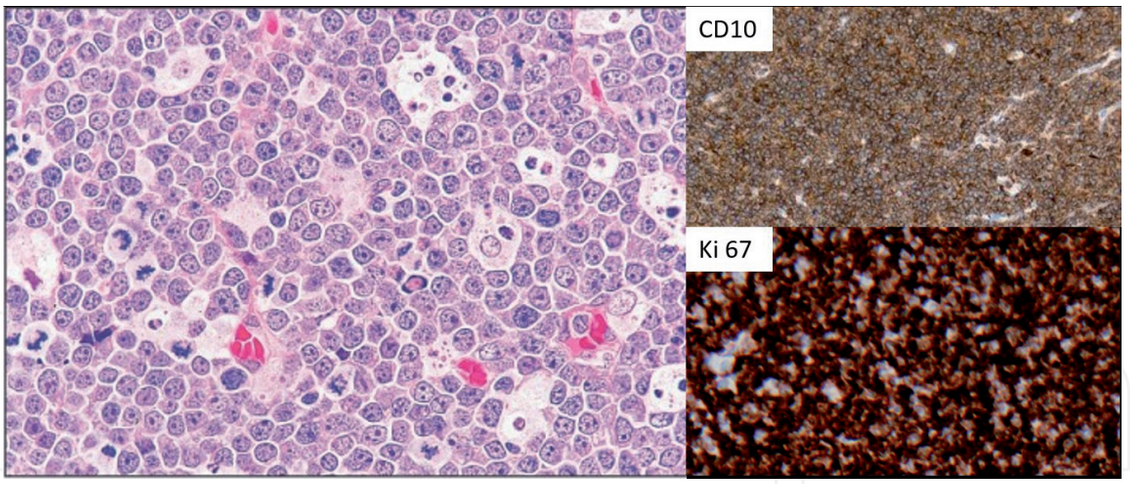

Figure 7.
Burkitt lymphoma showing starry sky pattern with CD10 positivity and high Ki67.

6.7.4 Treatment and prognosis

Burkitt lymphoma is very aggressive but responds well to intensive chemotherapy. Most children and young adults can be cured. The outcome is more guarded in older adults.

6.8 Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL. There is a slight male predominance. The median patient age is about 60 years, but can also occur in young adults and children.

DLBCL is molecularly heterogeneous. One frequent pathogenic event is dysregulation of BCL6. About 30% of DLBCLs contain various translocations that have in common a breakpoint in BCL6 at chromosome 3q27. Mutations are also seen in multiple other oncogenes including MYC and overexpression of the antiapoptotic protein BCL2. Tumors with BCL2 rearrangements usually lack BCL6 rearrangements. Co-expression of MYC with BCL2 and or BCL6 is now considered as double hit or triple hit lymphomas [1, 25, 63]. DLBCL typically presents as a rapidly enlarging mass at a nodal or extranodal site. Extranodal sites include the gastrointestinal tract, skin, bone, brain, and other tissues. Bone marrow involvement is relatively uncommon and usually occurs late in the course. Rarely, a leukemic picture emerges.

6.8.1 Morphology and immunophenotype

DLBCL usually shows a diffuse pattern of growth by a monotonous population of large cells that have a round or oval nucleus that appears vesicular due to margination of chromatin to the nuclear membrane, but large multilobated or cleaved nuclei are prominent in some cases. The cytoplasm is usually moderately abundant and may be pale or basophilic (**Figure 8**). More anaplastic tumors may even contain multinucleated cells with large inclusion-like nucleoli.

DLBCL express CD19 and CD20 and show variable expression of germinal center B-cell markers such as CD10 and BCL6 and for markers IRF4 (interferon regulatory factor4) and MUM1 (melanoma associated antigen (mutated) 1) which classifies DLBCL into germinal center type and non-germinal center type. Cases with CD10 expression by >30% of cells are regarded as GC type as well as cases that are CD10−, BCL6+, IRF4/MUM1−. All other cases are regarded as of non-GC type [25, 62].

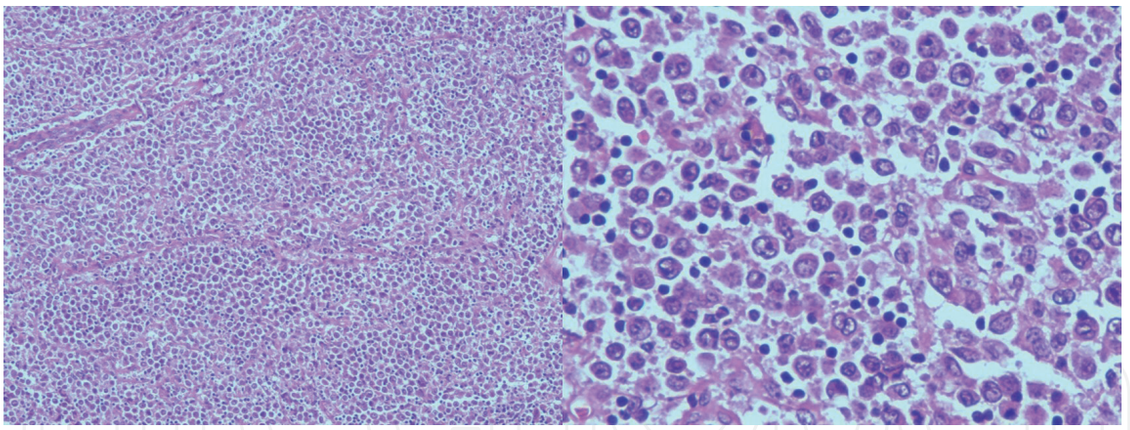

Figure 8
Diffused large cell lymphoma showing diffuse effacement by large cells.

6.8.2 Highlights in recent WHO classification

- The distinction of germinal center B-cell-like (GCB) vs. activated B-cell-like (ABC)/non-GC type required with the use of immunohistochemical algorithm may affect therapy [24, 62–65].

- Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma).

- Mutational landscape better understood but the clinical impact remains to be determined. EBV+ DLBCL, NOS.

- This term replaces EBV+ DLBCL of the elderly because it may occur in younger patients.

- Does not include EBV+ B-cell lymphomas that can be given a more specific diagnosis.

6.8.3 Treatment and prognosis

DLBCLs are aggressive tumors that are rapidly fatal without treatment. With intensive combination chemotherapy, 60–80% of patients achieve a complete remission, and 40–50% are cured. Adjuvant therapy with antiCD20 antibody improves both the initial response and the overall outcome. DLBCLs with MYC translocations have a worse prognosis than those without and may be better treated with chemotherapy regimens for Burkitt lymphoma [1, 25].

6.9 Hairy cell leukemia (HCL)

Hairy cell leukemia (HCL) is a rare but distinctive B-cell neoplasm constitutes about 2% of all leukemia. It is predominantly a disease of middle-aged white males, with a median age of 55 and a male-to-female ratio of 5:1. Hairy cell leukemia are associated in more than 90% of cases with activating point mutations in the serine/threonine kinase BRAF (B-Raf) [66]. Patients usually presents with massive splenomegaly. Hepatomegaly is less common and lymphadenopathy is rare. Pancytopenia is seen in more than half the cases [1, 25].

6.9.1 Morphology and immunophenotype

On routine peripheral blood smears, the cells have round, oblong, or reniform nuclei and moderate amounts of pale blue cytoplasm with thread-like or bleb-like extensions. On bone marrow aspiration the cells cannot be aspirated and gives "dry tap", Bone marrow biopsy shows diffuse interstitial infiltrate of tumor cells enmeshed in an extracellular matrix composed of reticulin fibrils giving fried egg appearance. Spleen appears beefy red on gross appearance. Microscopy shows heavily infiltrated splenic red pulp leading to obliteration of white pulp.

The classic immunophenotypic profile of HCL consists of bright monotypic surface immunoglobulin, bright coexpression of CD20, CD22 and CD11c, and expression of CD103, CD25, CD123, T-bet, Annexin A1 (ANXA1), DBA.44 (CD72), FMC-7 and cyclin D1 (usually weak) [1, 25].

6.9.2 Treatment and prognosis

Hairy cell leukemia follows an indolent course and is sensitive to "gentle" chemotherapeutic regimens, which produce longlasting remissions. BRAF inhibitors appear to produce excellent responses in tumors that have failed conventional chemotherapy. The overall prognosis is excellent [1, 25].

6.10 Plasma cell neoplasms and related disorders

These B-cell proliferations contain neoplastic plasma cells that virtually always secrete a monoclonal Ig or Ig fragment. These plasma cell neoplasms are also termed as plasma cell dyscrasias. Multiple myeloma is associated with frequent rearrangements involving the IgH locus and various proto-oncogenes. Included among the loci that are recurrently involved in translocations with the Ig heavy-chain gene on chromosome 14q32 are the cell cycle-regulatory genes cyclin D1 on chromosome 11q13 and cyclin D3 on chromosome 6p21. Deletions of chromosome 17p that involve the TP53 tumor suppressor locus also occur and are associated with a poor outcome. Late-stage, highly aggressive forms of the disease such as plasma cell leukemia are associated with the acquisition of rearrangements involving MYC. More recent deep sequencing of myeloma genomes has identified frequent mutations involving components of the nuclear factor κ B (NF-κB) pathway, which supports B-cell survival. Based on these studies, it is evident that myeloma is molecularly heterogeneous [1, 67].

The various spectrum of plasma cell dyscrasias are [68]:

Non-IgM monoclonal gammopathy of undetermined significance

Serum monoclonal protein (non-IgM type) <30 g/dl.
Clonal bone marrow plasma cells <10%.

The absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder.

IgM monoclonal gammopathy of undetermined significance

Serum IgM monoclonal protein <30 g/dl.
Bone marrow lymphoplasmacytic infiltration <10%.

No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the underlying lymphoproliferative disorder.

Light-chain monoclonal gammopathy of undetermined significance

Abnormal free light chain (FLC) ratio (<0.26 or >1.65).

Increased level of the appropriate involved light chain (increased κ FLC in patients with a ratio >1.65 and increased λ FLC in patients with a ratio).

No immunoglobulin heavy chain expression on immunofixation.

The absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder Clonal bone marrow plasma cells<10%.

Urinary monoclonal protein <500 mg/24 h.

Solitary plasmacytoma

Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells.

Normal bone marrow with no evidence of clonal plasma cells.

Normal skeletal survey and *magnetic resonance imaging* (MRI) or Computed tomography (CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder.

Solitary plasmacytoma with minimal marrow involvement

Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells.

Clonal bone marrow plasma cells <10%.

Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions that can be attributed to a lymphoplasma cell proliferative disorder.

Heavy-chain disease is a rare monoclonal gammopathy characterized by synthesis and secretion of free heavy-chain fragments and is seen associated with diseases including lymphoplasmacytic lymphoma and an unusual small bowel marginal zone lymphoma that occurs in malnourished populations (so-called Mediterranean lymphoma).

Smoldering multiple myeloma—both criteria must be met.

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%.

- Absence of myeloma defining events or amyloidosis.

Multiple myeloma is a plasma cell neoplasm commonly associated increased plasma cells in the marrow with accompanying features like lytic bone lesions, hypercalcemia, renal failure, and acquired immune abnormalities. It is commonly seen in older adults, with a peak age of incidence of 65–70 years.

Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smoldering multiple myeloma [68].

Definition of multiple myeloma

- Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

Myeloma defining events:

- Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
- Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance 177 μmol/L (>2 mg/dL)
- Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/l
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or positron emission tomography-computed tomography (PET-CT)

Anyone or more of the following biomarkers of malignancy

- Clonal bone marrow plasma cell percentage* ≥60%
- Involved: uninvolved serum free light chain ratio§ ≥100
- 1 focal lesion on MRI studies

6.10.1 Morphology and immunophenotype.

Multiple myeloma is characterized by infiltration of marrow by plasma cells in the interstitium, nodules or in diffuse sheets that completely replace normal elements (**Figure 9**). Plasma cells can be relatively normal-appearing plasma cells, plasmablasts or binucleated and multinucleated cells. Other cytologic

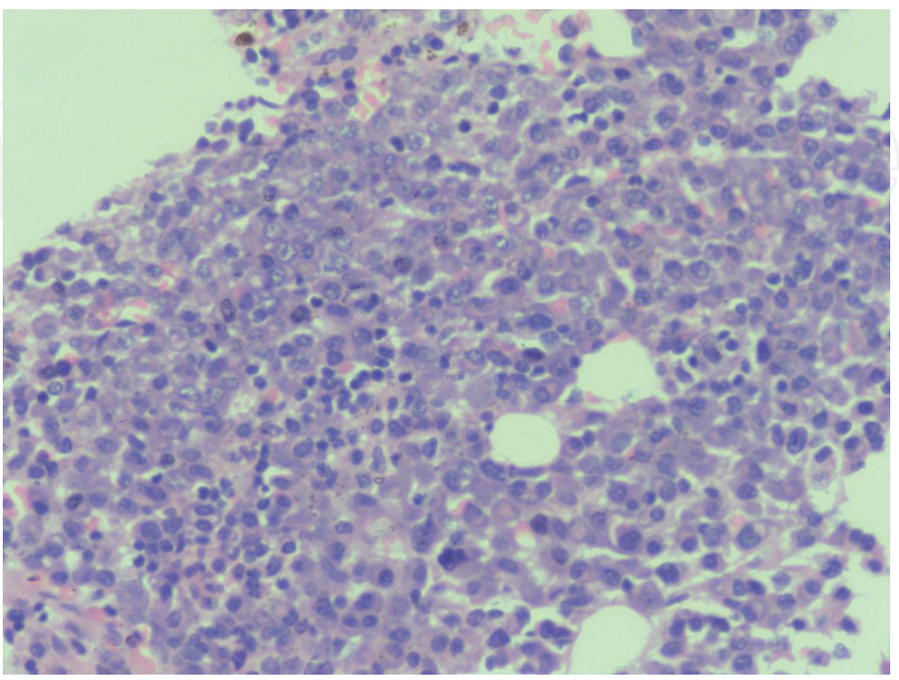

Figure 9.
Bone marrow biopsy showing sheets of plasma cells replacing normal hematopoietic elements.

variants include flame cells with fiery red cytoplasm, Mott cells with multiple grapelike cytoplasmic droplets, and cells containing a variety of other inclusions—Russell bodies (cytoplasmic) or Dutcher bodies (nuclear), including fibrils, crystalline rods, and globules. Peripheral blood smears shows rouleaux formation. Rarely, tumor cells enters the peripheral blood, giving rise to plasma cell leukemia. Plasma cell tumors are positive for CD 38, CD138, and often express CD56, a feature that can be helpful in identifying small populations of neoplastic cells.

6.10.2 Treatment and prognosis

The prognosis is variable but has improved in recent years with new therapeutic approaches. The median survival is 4–7 years. Translocations involving cyclin D1 are associated with a good outcome, whereas deletions of 13q, deletions of 17p, and the t(4;14) are associated with more aggressive course. Hematopoietic stem cell transplantation prolongs life but has not yet proven to be curative. Solitary osseous plasmacytoma almost inevitably progresses to multiple myeloma but can take 10–20 years or longer. In contrast, extraosseous plasmacytomas, particularly those involving the upper respiratory tract, are frequently cured by local resection. About 75% of patients of smoldering myeloma progress to multiple myeloma over a 15-year period. Approximately 1% of patients with MGUS develop asymptomatic plasma cell neoplasm, usually multiple myeloma, per year, a rate of conversion that remains roughly constant over time [1, 25, 68].

7. Staging, prognosis, and treatment

The Ann Arbor staging classification (**Table 2**) which was developed for HD in 1971, has been the standard scheme for NHL [69, 70]; however, it does not account for tumor burden and does not correlate well with prognosis. The Prognosis and

Stage I	Involvement in a single lymph node region or single extralymphatic site
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm; localized contiguous involvement of only one extralymphatic site and lymph node region (stage IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm; may include spleen
Stage IV	Disseminated involvement of one or more extralymphatic organs with or without lymph node involvement

Table 2.
The Ann Arbor staging classification.

International Prognostic Index	Adverse factors	Risk group	No. of factors
	Performance status = 2	Low	0, 1
	Lactate dehydrogenase > normal	Low-intermediate	2
	Extranodal sites = 2	High-intermediate	3
	Stage III and IV disease	High	4, 5
	Age >60 years		

Table 3.
International Prognostic Index.

treatment depends not only on the stage but also on a variety of clinical parameters that reflect tumor bulk and kinetics including the size of the mass, lactate dehydrogenase (LDH) level, number of extranodal sites, etc.

The international prognostic index (IPI) (**Table 3**) was developed to correlate clinical parameters with prognosis and appears to be more useful than the Ann Arbor staging system in predicting survival. Studies have indicated that the IPI correlates with prognosis for all histologies [71–73]. Additional biologic and genetic parameters, particularly genomic profiling, further subdivide prognostic groups in NHL.

Therapy follows the assessment of the patient, the pathology, and the stage of the disease. The ability of the patient to tolerate therapy is dependent on age, performance status, and, if present, immunodeficiency due to a prelymphomatous condition. Various treatment modalities include observation, radiotherapy for localized disease, chemotherapy, immunotherapy, and stem cell transplantations.

8. Conclusion

B-cells though plays a major role in humoral immunity can also lead to various pathologic diseases. B-cell lymphomas are malignant neoplasms that arise from various stages of differentiation of B-cells which are classified based on the cell of origin and behavior. Historically, there has been much controversy in the classification of lymphoid neoplasms, but consensus has been reached through the use of objective molecular diagnostic tools. The current WHO classification uses morphologic, immunophenotypic, genotypic, and clinical features to classify the lymphoid neoplasms into five broad categories as precursor B-cell neoplasms, peripheral B-cell neoplasms, precursor T-cell neoplasms, peripheral T-cell neoplasms and Hodgkin lymphoma. B-cell lymphomas include precursor B-cell neoplasms and peripheral B-cell neoplasms. Hodgkin lymphoma though originates from B-cell has distinctive pathologic features and is treated as a separate entity. B-cell lymphomas range in their clinical behavior from low grade to high grade and also have histological or clinical progression during a patient's clinical course. For these reasons, the WHO classification does not attempt to stratify lymphoid malignancies in terms of grade. Also both morphology and immunophenotype often change over time with the acquisition of additional genetic changes. Hence B-Cell lymphomas are expanding with emerging new entities due to its wide molecular/genetic landscape and are being revised frequently for better understanding and diagnosis which helps in managing with targeted therapies.

Conflict of interest

Authors declare no conflict of interest.

Author details

Subramanian Kalaivani Selvi[1*], B.H. Srinivas[2] and Sadhanandham Shrinuvasan[3]

1 Department of Pathology, Sri Manakula Vinayagar Medical College and Hospital, Puducherry, India

2 Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

3 Department of Radiology, Indira Gandhi Medical College and Research Institute, Puducherry, India

*Address all correspondence to: klvnselvi@yahoo.co.in

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