CHAPTER

25 Hematolymphoid Malignancies

The present chapter covers hematolymphoid malignancies which are presented in three different sections. The first section reviews the subject of malignant lymphomas including: Hodgkin lymphoma (HL) and non-Hodgkin Lymphoma (NHL) subtypes. The second section is devoted to bone marrow pathology, myelodysplastic syndromes and leukemias. Finally, the last section covers splenic tumors.

In USA, hematolymphoid malignancies contribute about 10% of all cancers. The annual incidence (in hundred thousands) is 3 for Hodgkin lymphoma, 10 for non-Hodgkin lymphoma, 11 for leukemia and 4 for myeloma (SEER data, Ries et al., 2007). The increase of non-Hodgkin lymphoma in USA during the past 4 decades is probably due to better diagnosis or AIDS-related lymphomas (DeVita et al, 2011).

In Egypt, the epidemiology of hematolymphoid malignancies is outlined in chapter 2 based on data of NCI, Cairo (Ali-Eldein, 2012 and Mokhtar et al, 2007). To summarize, they contributed 26% of all malignancies ranking the 3rd among different cancers. Their relative frequencies were 46% for lymphomas and 54% for leukemia (a ratio of 1.2:1). This difference in frequency is age dependent, thus in adults lymphoma predominates (a ratio of 1.6:1), whereas, in children leukemias predominate with the same ratio. In lymphomas, NHL (77%) predominated over HL (23%), a ratio of (3:1). However, in adolescent patients this predominance is reversed due to the overlap of the early age peak of HL with this age group

HISTOLOGY AND ONTOGENY

Lymph Node Structure

A lymph node has a capsule, a cortex, a medulla and sinuses (subcapsular, cortical and medullary). The cortex contains two types of follicles, namely: primary follicles (immunologically inactive) composed of small lymphocytes without germinal centers. Secondary follicles (immunologically active) contain germinal centers with peripheral mantle and marginal zones of lymphocytes (Fig 25-1). Both types of follicles contain B-lymphocytes and follicular dendritic cells. The latter presents antigens to B-lymphocytes.

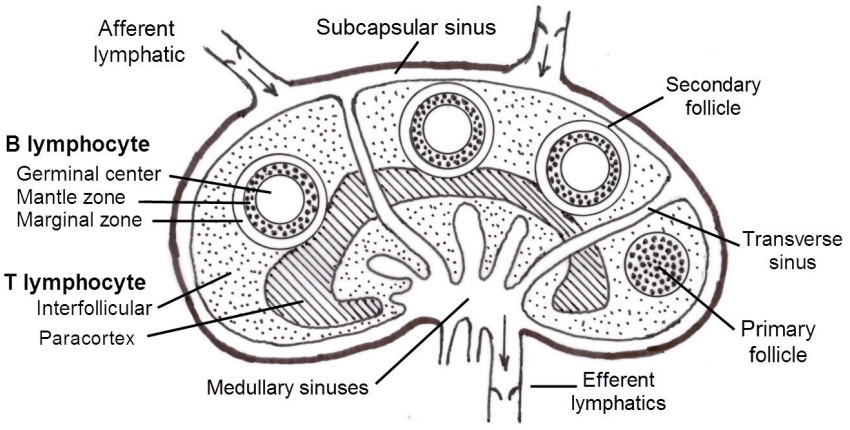

Fig 25-1 *Histology of lymph node. The cellular compartments are distributed among four distinct regions. The cortex is the B-cell zone located in lymphoid follicles. The interfollicular area and paracortex are rich in T-lymphocytes and interdigitating dendritic cells. Sinuses contain phagocytic histiocytes and medullary cords contain a mixed population of B-cells, T-cells, plasma cells and histiocytes.*

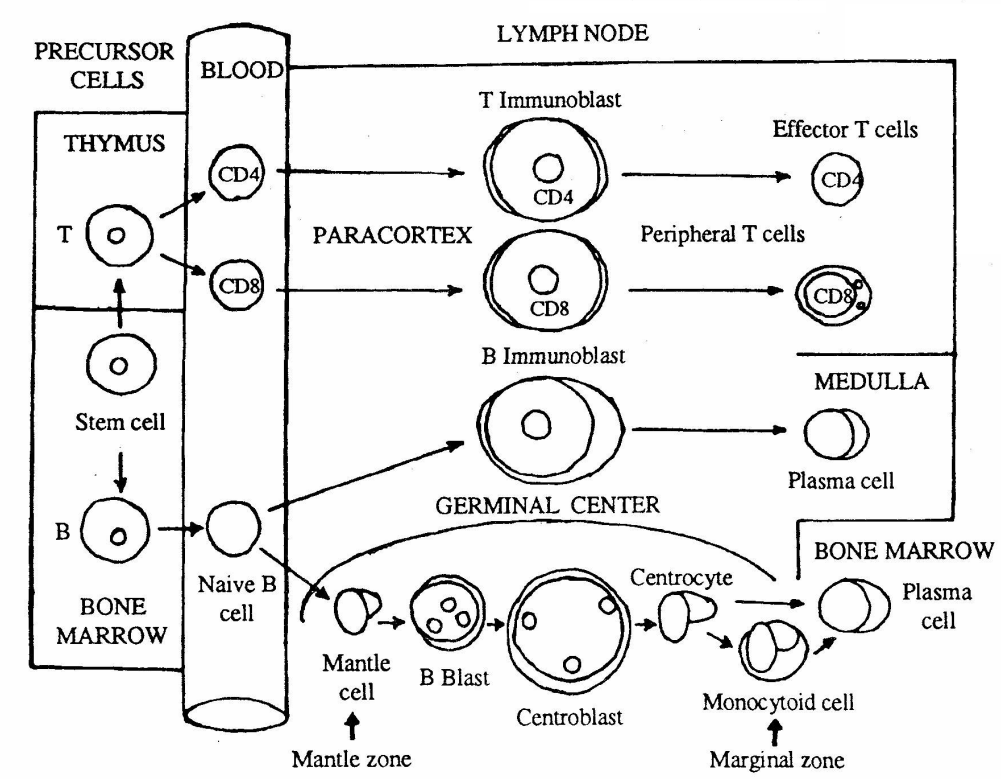

Fig 25-2 *Normal lymphocyte differentiation pathway. Both B-cell and T-cell lineages arise from a common stem cell in bone marrow. T-cells differentiate in thymus, but B-cells differentiate in peripheral lymphoid germinal centers.*

The paracortex is the area in between the follicles and deep to them. It contains mainly T-lymphocytes, immunoblasts and interdigitating dendritic cells which present antigens to T-cells. The sinuses contain phagocytic histiocytes which take up and process antigens and then present them to germinal centers (B-cells) and T-lymphocytes in paracortex. Plasma cells and effector T-cells generated by immune reactions accumulate in the medullary cords and exit via the medullary sinuses (Fig 25-1).

Lymphocyte Differentiation (Ontogeny)

The pathogenesis of lymphoid neoplasia can be understood in a rational way by first reviewing and comprehending the normal differentiation pathways of lymphocytes. Lymphoid tissues are divided into two major categories: (1) *central or primary* including the bone marrow and thymus, and (2) *peripheral or secondary* lymphoid tissues including the lymph nodes, spleen, and a collection of mucosa associated lymphoid tissue (MALT). Central lymphoid tissues are the sites of immature lymphoid cells (precursor cells) where antigen independent primary differentiation takes place, whereas, peripheral lymphoid tissues are the sites of more mature lymphocytes (peripheral lymphocytes) where antigen dependent secondary differentiation occurs. Lymphocytes normally migrate from peripheral sites into the blood and home again to the lymphoid system following a complex and highly ordered pathway of traffic. This homing phenomenon is also manifested in many lymphoid tumors.

Lymphocytes arise from a common stem cell in the bone marrow, which differentiates initially into pre-B and pre-T lymphocytes under the stimulating effect of hematopoietic growth factors (Fig. 25-2). A third line of lymphoid cells are called natural killer (NK) cells (or large granular lymphocytes) because they can kill certain targets without previous sensitization or major histocompatibility (MHC) restriction. T-cells migrate to the thymus where they undergo differentiation, as well as, apoptosis to eliminate autoreactive cells. So, in

addition to providing a pool of mature T-cells, the thymus plays a major role in selecting T-cells that do not react with self antigens. Naive T-cells leave the thymus, enter the circulation and reach the paracortex of lymph nodes. On encountering an antigen, naive T-cells become immunoblasts, which are large cells with prominent nucleoli. The T-immunoblastic reaction generates antigen-specific effector cells of either: CD4 (T-helper/inducer), or CD8 (T-cytotoxic/suppressor), as well as, T-cell memory (Fig. 25-2). T-immunoblasts and effector cells constitute the peripheral T-cell population and they participate in adaptive immune response (chapter 8).

The antigen-dependent B-cell differentiation occurs in germinal centers. On encountering an antigen, naive B cells become blast cells (small non-cleaved) and start to proliferate and produce IgM antibodies. Blasts then migrate to the center of germinal center and differentiate into immunoglobulin-negative centroblasts (large non-cleaved). Centroblasts mature to non-proliferating medium-sized cells with irregular nuclei, indistinct nucleoli and scanty cytoplasm, called centrocytes (small and large cleaved cells). Centrocytes may give rise to plasma cells or monocytoid lymphocytes which accumulate at the marginal zone of the germinal center.

Phenotypic Changes During Ontogeny

Lymphocytes acquire their specific gene structure and surface markers at different stages of development (Fig 25-3). An initial step for both B and T lymphocytes is to acquire their specific gene rearrangement at precursor cell stage. Also, a common feature of both B and T precursor cells is nuclear reactivity to TdT which is considered a marker of immaturity.

T-lymphocytes undergo differentiation in the thymus. They acquire their surface markers (CD4 and CD8) in three stages, namely: double negative, double positive and single positive (Fig 25-3).

In bone marrow, precursor B lymphocytes acquire PAX-5 (paired box family) which encodes BSAP (B-cell specific activator protein) a transcription factor required for early B-lymphocyte

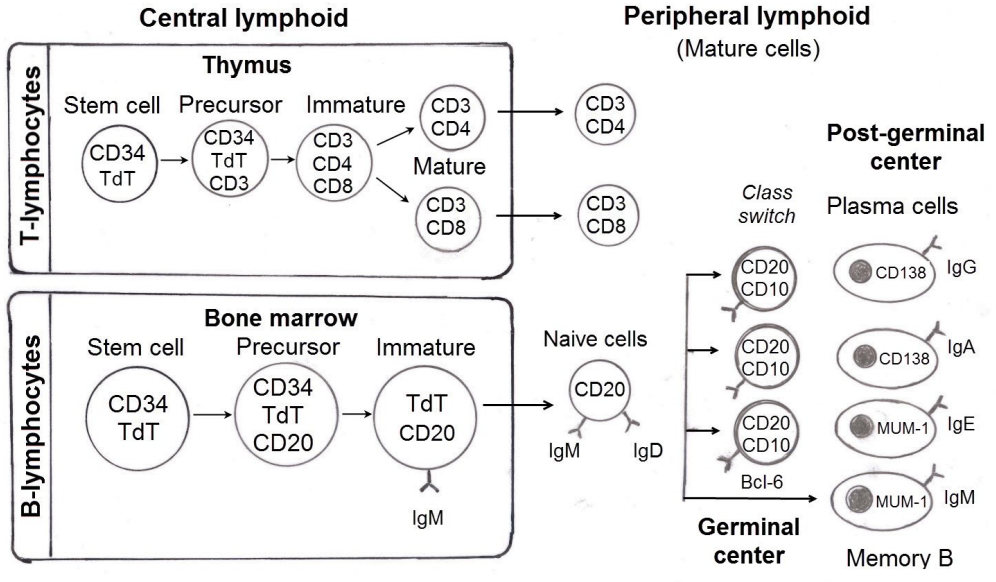

Fig 25-3 *Phenotypic changes during normal lymphocyte differentiation. An early change in both B and T lymphocyte is to acquire their specific gene rearrangement and TdT expression in precursor cells. T-cells in the thymus passes through three stages in acquiring CD4 and CD8 receptors, namely: double negative, double positive and single positive. PAX-5, a specific marker of B-cell/plasma cell lineage, is acquired in B-precursor cells and maintained throughout mature cells. B-lymphocytes assemble CD20, CD10 and Bc1-6 in germinal center, but CD10 and Bc1-6 are lost outside the germinal center with reciprocal expression of MUM-1 and Bc1-2. Immature B-lymphocytes can express IgM molecules on their surface, which on antigenic stimulation can mature to plasma cell and B-memory cell, or undergo a class switch to express IgG, IgA and IgE.*

differentiation. PAX-5 is a specific marker of B-lymphocyte/plasma cell lineage, acquired in precursor-B-cell stage and maintained throughout mature cells.

In germinal centers B-lymphocytes assemble CD20, CD10, Bcl-6 and express IgM molecules on their surface. With antigenic stimulation, B-lymphocytes modify the variable region of immunoglobulin gene by a process of *somatic hypermutation (SHM) and class switch recombination* resulting in maturation of B-lymphocytes to B-memory lymphocytes and plasma cells which produce various types of immunoglobulins (Fig 25-3). Bcl-6 function is critical in this process. Once outside the germinal center, B-lymphocytes loose CD10 and Bcl-6, with reciprocal expression of Bcl-2 and MUM-1 (multiple myeloma oncogene type 1). These phenotypic changes in B-lymphocytes during their development are made use of to differentiate germinal center lymphocytes from post-germinal center lymphocytes. Thus, the former is CD10+, bcl-6+, MUM-1-, whereas, the latter is CD10-, bcl-6- and MUM-1+. Moreover, PAX-5 is a useful marker to characterize B-lymphocyte / plasma cell lineage, both immature and mature cells.

HODGKIN LYMPHOMA (HL)

Incidence

Hodgkin lymphoma (HL) contributes 2.5% of total cancer in the Western industrialized countries, and constitutes 25% of malignant lymphomas. It has a bimodal age distribution, with a major peak at the third decade and a minor peak at the seventh decade. Males predominate in all histologic types (ratio of 1.3:1) except in nodular sclerosis type in which females predominate.

Generally, the incidence of Hodgkin's disease in developing countries is lower than in industrialized countries. Moreover, in developing countries the major age peak shifts to the pediatric age group leading to the predominance of Hodgkin's disease over non-Hodgkin's lymphoma in children. Associated with this disparity, is a predominance of unfavorable histologic types in developing than in developed countries.

Etiology

The disease is possibly an unusual effect of an infecting agent. There is association with EBV infection in 60 % of cases, with localization of the virus in Reed-Sternberg cells in 40% of cases of nodular sclerosis HD and 70% of mixed cellularity cases. Also, individuals with a history of infectious mononucleosis have a three-fold increase in the incidence of Hodgkin's disease. The association of Hodgkin lymphoma with HIV infection (AIDS patients) is also mediated through opportunistic EBV infection.

Familial clustering is reported especially in children of high social class who are generally highly susceptible to childhood infections. Other unexplained risk factors for Hodgkin's disease include: increased incidence among wood workers, after tonsillectomy and appendicectomy and its linkage with certain HLA antigens.

Reed-Sternberg Cells

Reed-Sternberg (RS) giant cells are the only malignant cells in the lesion of Hodgkin lymphoma. This is supported by its monoclonality, aneuploidy and expression of the oncosuppressor gene p53. All background cells are normal reactive in nature. Reed-Sternberg giant cells produce various cytokines which are responsible for the local cellular reactions, as well as, systemic manifestations associated with Hodgkin lymphoma (Fig 25-4).

It was recently possible by microdissection to isolate a single Reed-Sternberg (RS) cell from frozen sections immunostained for CD30 and apply molecular genetic methods. These studies revealed that the majority of classic RS cells are B-lymphocyte phenotype of germinal center origin. Thus, classic Hodgkin RS cells contain monoclonal immunoglobulin (Ig) gene rearrangement in >98% of cases and monoclonal T-rearrangement in only rare cases. However, RS cells do not produce immunoglobulin because the responsible genes are crippled by mutation or promoter inactivation.

The B-cell nature of RS cells is further supported by their immunolabeling for the B-specific activator protein (BSAP) in about 90% of cases. Also, classic RS cells are immunoreactive to the B-cell marker (CD20) in 40% of cases. Since Hodgkin disease is now known to be of B-lymphocyte origin in the majority of cases, the WHO prefers to call it Hodgkin lymphoma (HL).

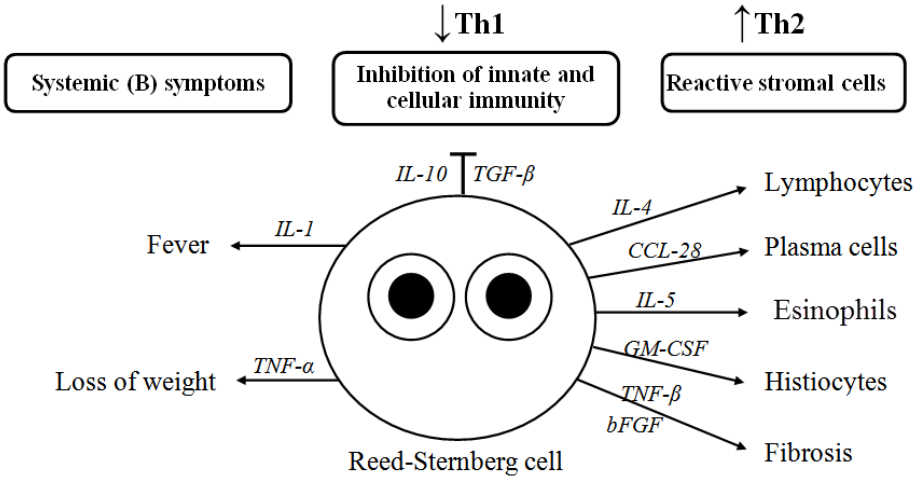

Fig 25-4 *Cytokine products of Reed-Sternberg giant cells and their biologic effects. These are responsible for the systemic B symptoms, immunosuppression and cellular reactive stromal cells characteristic of Hodgkin lymphoma. Th1 and Th2 are derivatives of CD4 helper lymphocyte.*

However, it is better to keep it as a separate entity from NHL in view of its characteristic histologic and clinical picture.

Molecular Oncogenesis

Two different molecular mechanisms are operable according to the subtype of Hodgkin lymphoma (A) *In Hodgkin lymphocyte predominance* (EBV-unrelated), The underlying mechanism is clonal rearrangement of immunoglobulin which shows multiple mutations (hypermutation) or translocations involving Bcl-6 gene with dysregulation of JAK-STAT signaling pathway. (B) *Classic Hodgkin lymphoma* (EBV-associated in 50% of cases). The central mechanism is activation of the protooncogene NF-κB, which encodes a transcription factor with proliferative and antiapoptotic activity. In EBV-negative classic Hodgkin lymphoma mutation of genes which negatively regulate NFκB is reported (e.g. TNFAIP3).

Special Features

Hodgkin lymphoma is unique among malignant tumors by the fact that neoplastic cells, (RS) cells, are a minority in the lesion. The appearance of few (RS) cells in abundant reactive cellular environment represents a battle in progress between the neoplastic process and the immune response of the host. This is in contradistinction with non-Hodgkin lymphoma in which all cellular elements in the lesion are neoplastic with very little or no host cellular reaction.

Hodgkin disease is characterized by axial lymph node affection and contiguous nodal spread, hence, the disease remains localized for a long time. There is rare primary extranodal presentation and rare involvement of Waldeyer ring (1%), mesenteric lymph node or bone marrow, as well as, no leukemic association. Involvement of the liver and bone marrow is rarely seen in the absence of splenic involvement, and affection of the spleen appears to be the key to hematogenous dissemination. Hodgkin disease appears to be a single disease entity, with minimal impact of histologic type on treatment policy. For all these reasons, the prognosis of Hodgkin lymphoma is more favorable than non-Hodgkin lymphoma.

About one third of patients with HL have systemic symptoms namely: weight loss, pyrexia and night sweats (B symptoms). Hodgkin lymphoma is also associated with a variety of hematological abnormalities, such as: anemia, hypocytopenia, raised ESR and low serum albumin.

Macroscopy

The affected lymph nodes are enlarged with a smooth surface. Hodgkin lymphoma disease unlike non-Hodgkin lymphomas, rarely invades the lymph node capsule, a fact which accounts for the discrete nature of lymphadenopathy. The cut surface is usually homogeneously gray-white. However, in some subtypes, a nodular or fibrotic appearance may be present.

Histopathology

The diagnosis of HL is only made by finding one of the variants of Reed-Sternberg giant cells in a background of reactive inflammatory cells (Fig 25-5). The host reaction is predominantly T lymphocytes (helper/inducer), histiocytes, eosinophils and plasma cells. The sole presence of mononuclear giant cells (Hodgkin cells) or apoptotic giant cells (mummified cells) is only suspicious but not diagnostic of HL. However, if the diagnosis of HL had already been established, the finding of Hodgkin cells in an appropriate cellular background is sufficient to make the diagnosis in liver or bone marrow biopsies. The histologic categories are identified according to the type of RS cell and the extent of host reaction (number of lymphocytes and quality of fibrosis). A large number of lymphocytes is associated with good prognosis, whereas, abundant RS cells and atypical histiocytes influence the prognosis adversely.

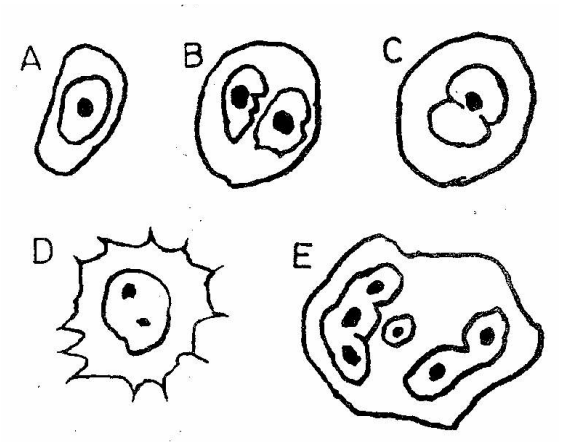

Fig 25-5 *Variants of Reed-Sternberg (RS) giant cells. A. Mononuclear type observed in all types of Hodgkin lymphoma, but not diagnostic. B. Binucleated classic RS cell found in mixed cellularity type. C. Lympho-histiocytic variant (popcorn RS cell observed in lymphocyte predominance type. D. Lacunar RS cell found in HL nodular sclerosis. E. Anaplastic variant observed in HL lymphocyte depletion.*

The recently introduced WHO classification (Table 25-1) emphasized the importance to recognize two fairly distinct variants in Hodgkin disease which have different phenotypic and biologic properties: (1) the nodular lymphocyte predominance HL, and (2) the classic HL, which includes mainly nodular sclerosis, mixed cellularity and lymphocyte depletion. Two additional subgroups are added to classic HL, namely: (1) lymphocyte rich classic HL which describes diffuse lymphocyte lesions with abundance of classic RS giant cells; and Hodgkin disease unclassifiable (Table 25-1).

The histologic types of HL remain constant over a long follow-up period in most of the cases. Thus, the histologic type is often maintained in relapse biopsies. However, when a change occurs, it is usually towards a histologically more malignant form. Moreover, certain subtypes of Hodgkin disease appear to be closely related to non-Hodgkin lymphoma. Thus, nodular lymphocyte predominance HL may progress to non-Hodgkin lymphoma (NHL) in 2% of cases. Also, HL and NHL may coexist in the same patient (composite lymphoma). Finally, the overlap between HL and NHL is demonstrated by some rare types of HL (syncytial variant of nodular sclerosis and lymphocyte depletion) which are almost indistinguishable from NHL (anaplastic large cell, peripheral T and large cell lymphoma).

Table 25-1 Comparative Frequency (%) of Hodgkin Lymphoma Subtypes in Egyptian and Western Series

Subtype	Mokhtar et al (2007)	Swerdlow et al (2008)
Nodular lymphocyte predominant	10	5
Classic Hodgkin lymphoma		
Nodular sclerosis	34	70
Mixed cellularity	48	20
Lymphocyte-rich	5	5
Lymphocyte depleted	3	<1
Hodgkin lymphoma, unclassified	-	-

Lymphocyte Predominance HL

Nodular Lymphocyte Predominance (NLPHL) accounts for 5% of cases of HL and is B phenotype. The median age is 35 years with male/female ratio of 3:1. Patients present with asymptomatic limited disease, usually with peripheral lymph node affection with sparing of the mediastinum (note similarity of pattern to NHL). More than 75% of patients are in stage I or II at the time of diagnosis. It is an indolent disease, and 90% of patients are alive 10 years later. However, late relapses are more common than in other types of HD, but these do not affect survival. In about 2% of cases, it may progress to NHL, usually large cell B phenotype.

Histologically, the RS cell variant in this disorder differs from mononuclear and classic RS cells in that they have vesicular, polylobated nuclei (P 25-1), and small usually peripheral nucleoli (lymphohistiocytic giant cell or "popcorn" cell). Classic RS cells are not found in the lesion. The background is predominantly lymphocytes, with or without epithelioid histiocyte clusters. Plasma cells, eosinophils and neutrophils are rarely seen. Progressive transformation of germinal centers are often seen in the same or other nodes. These are enlarged follicles that contain numerous small B lymphocytes of mantle zone type. This phenomenon has given rise to speculation that lymphocyte predominance may arise from a progressively transformed germinal centers.

Lesions with classic RS cells and dominance of lymphocytes should be included in the group of classic HL under the term *lymphocyte rich HL*.

The immunophenotype of lymphocyte predominance HL is characterized by positivity to CD45, CD19 and CD20 (P 25-2) but lacks Hodgkin associated antigens (CD15 and CD30). Popcorn cells also express the nuclear protein encoded by bcl-6 gene, which is associated with normal germinal center B -cell development, and the activation associated molecules (CD40 and CD86) which are involved in B-cell interaction with T lymphocytes. The background lymphocytes in the pseudonodules are mainly polyclonal B-cells and few T-cells.

Nodular Sclerosis HL

This variant is common in developed countries, constituting 60% to 70% of cases. It typically arises in young adult females with anterior mediastinal tumors. The disease is commonly limited to supradiaphragmatic sites.

Histologically, it has in most cases at least a focal nodular pattern (P 25-3A), with nodules separated by fibrous bands (birefringent under polarized light). The characteristic cell is the lacunar type RS cells. They have multilobed vesicular nuclei, small nucleoli and abundant pale cytoplasm, which retracts in formalin-fixed sections producing empty lacunae (P 25-3C). Diffuse areas and necrosis are common, and necrotic foci are often surrounded by palisaded histiocytes and lacunar cells simulating granulomas. Fibrous bands may be absent *(cellular phase of nodular sclerosis HL)*. Another variant is the *syncytial variant* in which lacunar cells grow in cohesive groups, a histology closely similar to anaplastic NHL or metastatic carcinoma (P 25-4).

Nodular sclerosis HL was graded by the British National lymphoma Investigators (BNLI) into grade 1 (75% of cases) and grade 2 (25% of cases) based on the number and atypia of lacunar cells in the nodules. This may have a potential prognostic value. However, the use of this system is declining since recent effective therapies tend to abolish histologic prognostic differences (Jaffe et al, 2011).

Mixed Cellularity HL

It accounts for about 20% of cases in the West, but 50% in developing countries. It affects mainly older age and AIDS patients who present with extensive disease. It is commonly infradiaphragmatic with involvement of abdominal lymph nodes and spleen. Systemic B symptoms are frequent.

Histologically, the infiltrate is usually diffuse without band-forming fibrosis, but fine interstitial fibrosis may be present. The classic RS giant cells are large cells with eosinophilic cytoplasm, bilobed nuclei (P 25-5) with large eosinophilic inclusion-like nucleoli (owl eyes). The background infiltrate contains mainly T-lymphocytes, epithelioid histiocytes, eo-sinophils, neutrophils and plasma cells. Mixed cel-lularity HL may be focal, involving interfollicular regions of lymph nodes, sparing follicles which may appear reactive or may show regressive changes resembling Castleman disease.

Lymphocyte Depleted HL

It contributes about 5% in the West. But recently, a low incidence of 1% was reported (DeVita, et al, 2011) since many cases were reassigned to NHL especially peripheral T and ana-

plastic large cell. It is usually encountered in the setting of relapsing disease or in patients with exhausted immunologic defenses (e.g. AIDS).

The patients present in an advanced stage with extensive disease, usually subdiaphragmatic. Histologically, the RS giant cells present are usually of pleomorphic or anaplastic variant with multiple nuclei and prominent nucleoli (Fig. 25-5). The infiltrate is diffuse and appears hypocellular with depletion of lymphocytes. Two variants are recognized: the *reticular type* shows a predominance of Hodgkin cells and atypical histiocytes; and the *diffuse fibrosis type* (P 25-6). Immunoreactivity of Reed-Sternberg cells to CD30 and CD15 is confirmatory (P 25-7).

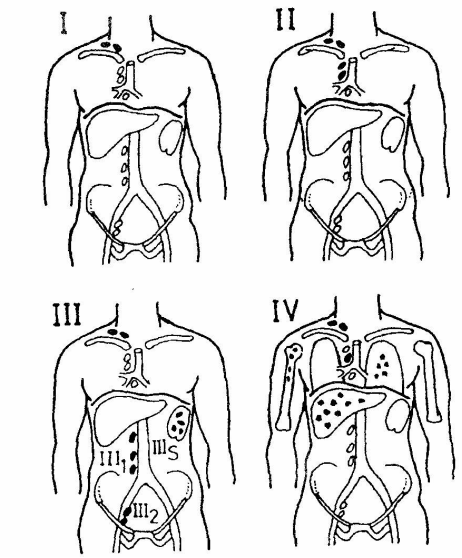

Fig 25-6 *Cotswolds revision of Ann Arbor staging system for Hodgkin lymphoma. The modification included: (1) indicating the number of lymphnode groups involved and (2) Subclassification of stage III infradiaphragmatic disease (Lister, 1990).*

Table 25-2 Cotswolds Revision* of Ann Arbor Staging System for Hodgkin's Disease (Lister, 1990)

Stage I	Involvement of a single lymph node region (stage I) or a single extralymphatic organ or site (stage I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (stage II) or localized involvement of an extralymphatic organ or site (stage II_E)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (stage III) or localized involvement of an extralymphatic organ or site (stage III_E), the spleen (stage III_S), or both (stage III_{SE}) Stage III is further subdivided into stage III_1, in which disease is limited to the upper abdomen (such as the spleen). Splenic hilar, celiac, or porta hepatis nodes, and stage III_2, in which disease involves the lower abdomen, such as periaortic, mesenteric, pelvic, or inguinal nodes
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement, with distant (non-regional) nodal involvement
SUBCLASSIFICATION FOR ALL STAGES:	
	A= Asymptomatic B= Fever, night sweats, weight loss > 10% of body weight in 6 months X= bulky mediastinal disease

*Modified by the addition of substages III_1 and III_2 and X. The number of anatomical regions involved is indicated by subscript, e.g. $II_{(3)}$.

Prognosis

A striking improvement of overall 5-year survival of HD has been accomplished during the past 6 decades; from 30% in 1950 to 83% recently (Ries, 2007). The stage of the disease is the most important prognostic factor (Table 25-2 and Fig 25-2). In stage I and II supradiaphragmatic disease without unfavorable prognostic factors, irradiation produces a 10-year cure rate of over 90% (Ries, 2007). Whereas, in stages IIIB and IVB treated with chemotherapy, the long-term survival is about 60% (Burn and, 1992). Histologic type of HL has no impact on survival.

Established unfavorable prognostic factors in HD include: (1) massive mediastinal disease with mediastinum >1/3 of thorax; (2) B symptoms, (3) more than 4 sites of lymph node involvement ; (4) bulky tumors (>10 cm) and unfavorable histology (mixed cellularity and lymphocyte depleted HD) which are usually extensive subdiaphragmatic disease. Less significant unfavorable prognostic factors are: male patients, age over 40 years, ESR over 70 and extensive splenic involvement (more than 5 nodules).

NON-HODGKIN LYMPHOMAS (NHL)

GENERAL CONSIDERATIONS

Incidence

Non-Hodgkin lymphoma (NHL) has a high incidence in the Middle East, contributing 7% of total cancer as compared to 4% in USA (SEER Data, Parker, 1997). The incidence in USA is increasing at an annual rate of 4% due to AIDS epidemic, as well as, increase in the elderly age group. Current incidence rate (ASR per 100,000) is 13.7 in USA and 8.7 in Egypt (Ferlay et al, 2010, chapter 2). Burkitt lymphoma is common in tropical Africa; and adult T-cell lymphoma leukemia (ATCL/L) in Japan and the Caribbean.

The ratio of NHL to Hodgkin lymphoma is about 3:1 (i.e. 75% of lymphomas are NHL). The predominance is reversed in pediatric patients in developing countries. The age distribution of NHL is unimodal with a median at 55 years. Male patients slightly predominate (1.3:1).

Etiology

The various etiologic factors related to NHL are listed in (Table 25-3 and Table 25-4). Viruses appear to play a major role. Thus, EBV is associated with Burkitt lymphoma and angiocentric T-cell lymphoma. Also, NHL in immunosuppressed patients is possibly related to associated oppor -tunistic EBV infection.

Table 25-3 Etiology of NHL

Immunodeficiency
Congenital
AIDS-related
Post-transplantation
Iatrogenic
Malnutrition
Autoimmune
Chemicals
Herbicides
Prior chemotherapy
Physical
Therapeutic radiation
Atomic radiation
Infections (Table 25-4)

Table 25-4 Infectious Agents in Etiology of Lymphomas

Agent	Lymphoma type
Viral	
EBV	Burkitt, Hodgkin, NHL* Angioim munoblastic
HHV-8	Castleman disease
HTLV-1	Adult T-cell lymphoma
HCV	Hepatosplenic T cell
Bacteria	
H. pylori	Gastric MALT
C. jejuni	Jejunal MALT
C. psittaci	Orbital MALT
B. burgdorferi	Skin NHL
Protozoa	
Malaria	Burkitt

*Includes AIDS-associated lymphomas.

EBV and NHL

Epstein-Barr virus is DNA virus, a member of human herpes virus (HHV-4). The virus infects nasopharyngeal epithelium and B cells, and may enter a latent phase in the latter. The virus expresses three types of proteins, namely: EBNA-1 which helps DNA integration, EBNA-2 and Latent membrane protein LMP-1 which activate other genes leading to cellular proliferation (Chapter 3).

The outcome of EBV infection is mainly dependent on the immune status of the host. Thus, normal immunocompetent individuals develop infectious mononucleosis only. Conversely, immunodeficient patients (e.g. malaria, AID or iatrogenic immunosuppression) develop lymphoma. This phenomenon is explained by a molecular model presented in (Fig 25-7).

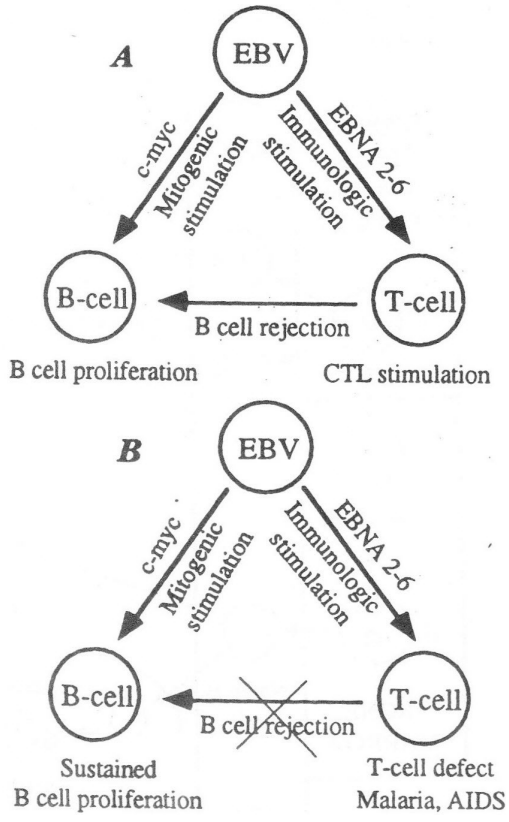

Fig 25-7 *Pathogenesis of EBV-related lymphoma. A. In immunocompetent individuals, B-cell proliferation is controlled by cytotoxic T- cell reaction and a reversible infectious mononucleosis results. B. In patient with T-cell deficiency (e.g. malaria or AIDS), B-cell proliferation is sustained resulting in lymphoma development (Klein, 1998).*

Molecular Oncogenesis

Lymphomas, like other cancers, arise from stem or progenitor cells rather than normal mature cells. The observed histologic types of lymphomas represent arrest of cells at different stages of normal differentiation (Table 25-5). In children, lymphomas of precursor cells predominate (e.g. acute lymphoid leukemia, lymphoblastic lymphoma and Burkitt lymphoma). Conversely, in adults lymphomas are commonly of mature peripheral cell type (e.g. small lymphocytic, follicular lymphoma, myeloma and mantle cell lymphoma).

The *molecular mechanism* of NHL varies according to the presence or absence of chromosomal translocation. Two alternative mechanisms were proposed to explain the primary genetic lesion:

Chromosomal translocation. This common mechanism may result in either locating a proto-oncogene in proximity of an activating promoter, or the creation of a chimeric gene with oncogenic protein product (Table 25-6). This mechanism produces a single DNA mutation which results in cellular proliferation (clonal expansion) or arrest of apoptosis or cellular differentiation (cell accumulation). Additional mutations are usually required (e.g. TP53) for temporal progression of a lymphoma from a low to high grade, or (PAX-5) mutation for the development of another different lymphoma type (composite lymphoma).

Aberrant somatic hypermutation (ASHM) defines a recently identified alternative mechanism for lymphomagenesis (DeVita et al, 2011). The genetic lesion involves abnormal gene rearrangement of non-immunoglobulin genes. This results in multiple mutations. This model is operable in 50% of cases of diffuse large B-cell lymphoma and explains the multiple mutations observed in this lymphoma subtype, with dysregulation of Bcl-6, TP53 and NFκB.

Special Features

Non-Hodgkin lymphoma, compared with Hodgkin lymphoma has the following ten characteristic features:

1. They are multiple heterogeneous diseases.
2. Malignant lymphoid cells are a majority in the lesion.
3. Peripheral lymph node affection.
4. Noncontiguous lymph node spread (85%).
5. Common primary extranodal presentation (40%).
6. Frequent involvement of Waldeyer ring

Table 25-5 Stem Cell Differentiation Lineages in Lymphomas

Stem Cell Origin	Terminal cell differentiation	Lymphoma type
Precursor B-cell	Pre- B cell	Lymphoblastic Leukemia / Lymphoma
Pre-germinal center cell	Naive B cell	Mantle
Germinal	Centrocytes and centroblasts	Follicular lymphoma Burkitt lymphoma DLBCL, SLL/ CLL Hodgkin Lymphoma
Post-germinal Center	Memory B-cell	Marginal zone (MALT) Nodal marginal DLBCL
	Plasma cell	Plasma cell myeloma

NB: Stem T-cell differentiation produces either precursor (immature) lymphomas or peripheral T/NK (mature) lymphomas. Abbreviations: DLBCL diffuse large B-cell lymphomas, SLL/CLL small lymphocytic lymphoma/Chronic lymphocytic leukemia.

Table 25-6 Genetic Lesions in Non-Hodgkin Lymphoma

Lymphoma type	Chromosomal abnormality	Oncogene	% of cases
Mantle	t(11;14)	BCL-1 / Cyclin D1	95
Burkitt	t(8;14)	C-MYC	80
Follicular	t(14; 18)	BCL-2	90
DLBCL	t(multiple)	BCL-2, BCL-6	30,45
Lymphoplasmacytic	t(9;14)	PAX-5	50
Lymphoblastic	t(multiple)	BCR / ABL, TEL / AML, PBX / EZA	25-70
MALT lymphoma	t(11;18)*	AP12-MALT-1	30
Anaplastic large	t(2;5)*	NPM / ALK	60

*

(20%), mesenteric lymph nodes and bone marrow (early dissemination).

7. Frequent leukemic association or transformation.
8. Lymphomas are commonly B phenotype (85 % of cases), except in Japan (50%) and in children (35%).
9. Significant impact of histologic type on treatment policy.
10. Therapeutic results are inferior to Hodgkin lymphoma.

Classification

Originally, NHLs were classified into low and high-grade classes according to the expected natural history. The *low-grade (or indolent lymphomas)* are characterized by a long clinical course and resistance to treatment, whereas, *high-grade lymphomas (aggressive and highly aggressive subclasses)* have a shorter course of months or weeks, but potentially curable (Table 25-7). Paradoxically, high-grade lymphomas usually have a more favorable prognosis than low-grade ones with recent effective therapy (Fig 25-8). Moreover, mantle cell lymphoma (previously considered a low-grade lymphoma) was shifted to the high-grade class when its aggressive behavior was realized.

The WHO classification of lymphomas was based on genetic abnormalities, immunophenotyping and clinical features, rather than morphology (Kleihues and Cavenee, 2001). These parameters were considered essential to identify disease entity and determine specific therapy. Accordingly, lymphomas are classified into either B or T cell types, then each is subclass -sified into immature (precursor) or mature according to cellular differentiation. This classification system had a diagnostic accuracy of 85% and reproducibility of 85% (Armitage et al, 1997). An updated WHO classification (Swerdlow et al, 2008) included a long list of 86 distinct entities, plus additional variants.

Table 25-7 Biological Classification of NHL for Therapy Guidance, Differences Between Low-grade and High-grade NHL

Feature	Low-grade NHL	High-grade NHL
Frequency	30%	70%
Clinical course	Long	Short
Response to therapy	Incurable	Curable
Growth pattern	Non destructive	Destructive
Primary extranodal	Common	Rare
CNS involvement	Rare	Common

(Abraham et al, 2010/Cassidy et al, 2010/ Kantarjian et al, 2011).

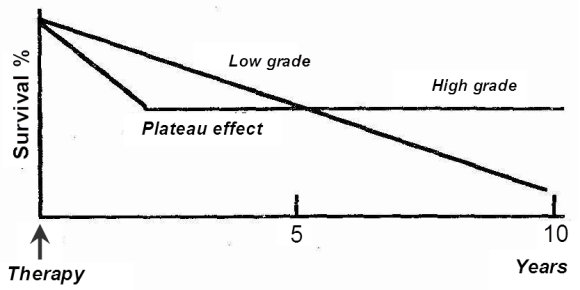

Fig 25-8 *Comparison of survival of low-grade and high-grade non-Hodgkin lymphomas. Paradoxical results were obtained in historic data with more favorable long-term survival in high-grade lymphomas than low-grade types. However, with recent therapy, more favorable outcome was reported in low-grade lymphomas.*

A modified simplified version of the WHO classification is shown in (Table 25-8). Only 22 *common types* are included, grouping them into *low and high grade*, as well as, subgrouping them into three broad categories of different *clinical presentations*, namely: disseminated, extranodal and nodal. Mantle cell lymphoma, multiple myeloma and immunodeficiency lymphoproliferative disorders are included in the high-grade class. *Rare variants* of B and T-cell lymphomas are presented in separate tables (Tables 25-9 and Table 25-10). The relative frequency of NHL subtypes differs according to age and geographic area of the world. A comparison of lymphoma profile in Egyptian and US series is shown in (Table 25-11) stratified by age.

Dynamic Pathology

The pathology of NHL is a dynamic one, characterized by the frequent leukemic association and the common transformation of one histologic type to another (Fig 25-9). Thus, lymphocytic leukemias and lymphomas represent different phases of the same disease entity and reflect the normal circulation and homing of lymphocytes between lymphoid tissue and blood. The frequency of *leukemia association* varies according to lymphoma type, being 20% in small lymphocytic lymphoma, 40% in mantle cell lymphoma and 50 in lymphoblastic lymphoma.

One type of NHL may progress to another type. *Progression* is usually from a low-grade to a high-grade lymphoma. Examples include: The progression of 5-10% of small lymphocytic lymphoma to diffuse

Table 25-8 Modified WHO Classification of Non-Hodgkin Lymphoma

Biology/Presentation	B-phenotype	T/NK Phenotype
Low-Grade	Small lymphocytic/CLL	T cell CLL
Disseminated	Lymphoplasmacytic (LPL) Hairy cell leukemia (HCL) Splenic marginal zone lymphoma	Large granular cell leukemia
Extranodal	Marginal zone lymphoma (MALT)-related	Mycosis fungoides (MF)
Nodal	Follicular lymphoma (FL) Nodal marginal zone (NMZL)	—
High-Grade	Diffuse large (DLBCL, NOS)	Peripheral T (NOS)
Aggressive	Rare variants of DLBCL Mantle cell lymphoma (MCL) Multiple myeloma (MM)	Rare variants of peripheral T Anaplastic large (ALCL)
Highly-Aggressive	Lymphoblastic leukemia/Lymphoma Burkitt lymphoma Immunodeficiency lymphoproliferative disorders	Lymphoblastic lymphoma/leukemia HTLV-1 adult leukemia/lymphoma

(Swerdlow et al, 2008/Abraham et al, 2010/Kantarjian et al, 2011). Abbreviations: CLL chronic lymphocytic leukemia, MALT mucosa- associated lymphoma, DLBCL diffuse large B-cell lymphoma, NOS not otherwise specified.

Table 25-9 Other Rare Variants of Diffuse Large B-cell lymphoma (DLBCL)

T-cell rich DLBCL
Intravascular DLBCL
Lymphomatoid granulomatosis LYG
Primary thymic DLBCL
Primary effusion DLBCL
ALK+ DLBCL
DLBCL with Chronic inflammation
DLBCL with Castleman disease
DLBCL with Hodgkin features
DLBCL with Burkitt features
DLBCL with Plasmablastic features

(Swerdlow et al, 2008)

Table 25-10 Rare Variants of Peripheral T-cell Lymphomas (PTL)

Epithelioid rich PTL (Lennert)
Angioimmunoblastic lymphoma (AITL)
T/NK cell lymphoma (Nasal type)
Enteropathy-associated EATL (Coeliac disease)
Hepatosplenic HSTL
T-cell lymphoma with hemophagocytic syndrome
Panniculitis-like PTL
Sezary syndrome

(Swerdlow et al, 2008)

large cell lymphoma (Richter syndrome), 30% of follicular lymphoma to diffuse lymphoma and the progression of classic mantle cell lymphoma to the more aggressive blastoid mantle cell lymphoma (Swerdlow et al, 2008). Biologically, this phenomenon represents tumor progression resulting from additional muta-tions (TP53, RB, MYC and BCL-2) with the evolution of a more aggressive tumor subclone.

The occurrence of different types of lymphomas in separate sites in the same patient is termed *discordant lymphoma*. However, rarely, two distinctly different lymphomas may be present in the same lymph node (Mokhtar, 2007), thus, creating a mixed tumor named *composite lymphoma*. This phenomenon is explained by the plasticity of lymphoid stem cells, with PAX-5 gene playing a key role. PAX-5 gene is essential for early B-cell differentiation. Mutation of this gene may lead to transdifferentiation of B-cell to Reed Sternberg cell, T-lymphocyte or even histiocytic cell.

Table 25-11 Comparative Frequency (%) of Adult and Pediatric NHL in Egyptian and Western Series

NHL type	Mokhtar et al. (2007)	Shipp and Harris (1997)
ADULTS		
B-cell lymphomas		
Follicular lymphoma	5	35
Diffuse large B-cell lymphoma	56	30
Mantle cell lymphoma	0.7	5
B-CLL/SLL	6	5
Immunocytoma/Waldenstrom MALT -type/monocytoid B-cell	-	1
All others	5	1
T-cell lymphomas	9	8
Peripheral T-cell lymphomas	3	5
Anaplastic large-cell lymphoma	2	5
Angioimmunoblastic lymphoma	-	2
Lymphoblastic T	4	2
ALL others	6	1
CHILDREN		
B-cell lymphoma		
Burkitt's lymphoma	44	29
Diffuse large B-cell lymphoma	14	5
Follicular lymphoma	-	0.5
Lymphoblastic B	-	0.5
T-cell lymphomas		
Lymphoblastic T	25	45
Anaplastic large cell-lymphoma	3	15
Peripheral T-cell lymphomas	3	5
Others	11	-

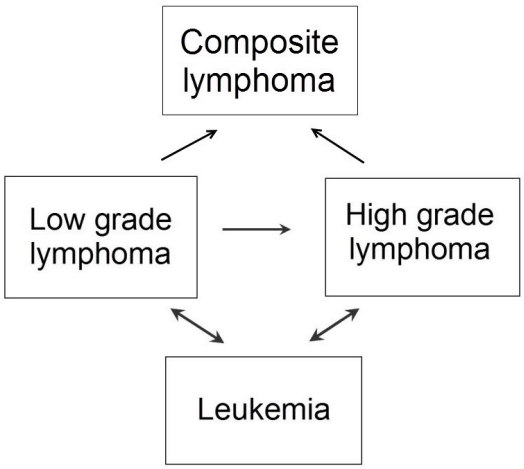

Fig 25-9 *The dynamic pathology of non-Hodgkin Lymphoma. This includes: the association with or conversion to leukemia, progression of a low-grade to high grade lymphoma and the development of two different lymphoma types in the same patient or the same tumor (discordant and Composite lymphoma respectively).*

Borderline Lymphoproliferative Disorders

The WHO recognized a separate group of monoclonal lymphoid proliferations which are self-limited and lack histologic or clinical progression. The following are seven examples:

1. Monoclonal B lymphocytosis. About 3% of healthy adults have circulating high count of monoclonal B lymphocytes with genetic abnormalities, yet they rarely progress to chronic lymphocytic leukemia.

2. Follicular and mantle lymphoma in situ. These lesions are only focal in otherwise normal lymph node or intestine. Usually, an incidental finding that usually does not progress to disseminated lymphoma.

3. Early gastric MALT lymphoma (Helicobacter associated). This hyperplastic lymphoid tissue lacks genetic alterations and 75% of cases regress with anti-Helicobacter therapy.

4. Monoclonal follicular hyperplasia. This involves CD10 germinal center B cells. In children it is not considered neoplastic.

5. Lymphomatoid papulasis. This cutaneous CD30 positive T-cell lymphoma usually regresses in 4 to 6 weeks.

6. Pediatric follicular and marginal zone lymphomas. They tend to be localized and have an excellent prognosis in this age group. Follicular lymphoma in children lacks t(14;18) and BCL-2 expression.

7. Iatrogenic post-transplant lymphomas. These are etiologically related to immunosuppressive therapy. The lymphoma is usually reversible when the immunosuppressive drug is discontinued.

Prognosis

Several factors may influence the prognosis of NHL, either when used singly or in combination. The following seven factors are clinically relevant:

1. Histologic type. Difference in survival is more apparent when we compare 10-year rather than 5-year survival in large series such as SEER data (Ries, 2007). It is possible to stratify NHL subtypes into 4 different prognostic groups, namely most favorable, favorable, unfavorable and most unfavorable (Table 25-12).

2. Age. Patient age at diagnosis strongly influences prognosis. Survival of pediatric lymphoma/Leukemia is much more favorable than that of adults in view of the major advances made in treatment in this young age group (Pulte et al, 2008). Thus, the 10-year relative survival rate for pediatric NHL is 87%, whereas, that of adults is 51%. Also, the 10-year survival of pediatric acute lymphoblastic leukemia is 84%, whereas, in adults if is 60% (Tables 25-12 and Table 25-13).

3. Site. In general, primary cutaneous T-cell lymphomas are more favorable (10-year survival about 80%), as well as, gastrointestinal B-cell MALT lymphomas. (10-year survival 60%). Nodal localization has an intermediate outcome (50%). The most unfavorable sites are: primary brain NHL (10%), as well as, disseminated bone marrow involvement and the rare variants of lymphomas at unusual sites which have no long-term survival (Table 25-12).

4. Immunophenotyping. Nodal B-cell lymphomas are more favorable than nodal T-cell lymphomas (Table 25-12). Thus, the 10-year survival of B-cell lymphomas (both small and large cell types) is about (50%). Conversely. The comparable survival of peripheral T-cell lymphoma NOS is 33%. The expression of

Table 25-12 Survival Groups of Non-Hodgkin Lymphomas According to Histologic Type

Group / Type	5-year (%)	10-year (%)
Most favorable		(80-100)
Hairy cell Leukemia	92	92
Mycosis Fungoides	88	83
Favorable		(50-80)
Cutaneous T-cell	84	78
Pediatric lymphoblastic	80	77
Marginal zone cell	84	64
Follicular lymphoma	76	62
Adult lymphoblastic	62	60
Small lymphocytic	60	51
Unfavorable		(20-50)
Large B-cell (NOS)	50	46
Lymphoplasmacytic	65	46
Burkitt lymphoma	45	45
Anaplastic T-cell *	54	44
Mature T-cell (NOS)	38	33
Most unfavorable		(0-20)
Multiple myeloma	30	12
AIDS-related	15	0
Other rare variants **	0-7	0

(Ries, 2007, US SEER data, 61,214 adult non-AIDS patients with NHL). * The 8-year survival of ALK positive is 82% (Sibon, 2012). ** Includes: Primary effusion lymphoma, intravascular lymphoma, lymphoma complicating Castleman, Enteropathy-associated T-cell, Sezary syndrome, adult T-cell, leukemia lymphoma and hepatosplenic T-cell lymphoma.

Table 25-13 Survival Trends of Pediatric Lymphomas

Lymphoma type	1990-1994		2000-2004	
	5-y	10-y	5-y	10-y
Acute lymphoblastic Leukemia	80	73	88	84
Acute non-Lymphoblastic Leukemia	42	39	60	59
Non-Hodgkin lymphoma	77	73	88	87

(Pulte et al, 2008, 6,957 US children younger than 15 years, 1990-2000)
NB. Relative survival rates for Hodgkin disease remained stationary at around 95%.

other markers such as p53 and mast cell tryptase is associated with unfavorable prognosis in large B-cell lymphoma (Zayed et al, 2003 and EL-Bolkainy et al, 2007).

5. Molecular profiling, Gene expression studies using cDNA microarrays have identified molecular prognostic groups in diffuse large B-cell lymphoma (Alizadeh et al, 2000). Initially, two subgroups were recognized, namely: germ center B (GCB) and activated B cell (ABC), but a third group was subsequently added (type 3). Prognosis is more favorable in patients with GCB lymphomas. However, this technology is not used in routine practice due to cost limitation and the need of fresh samples. Immunostains (at lower expenses) can be used to determine molecular subtypes of DLBCL and predict survival (Hans et al, 2004). A panel of only 3 immunostains are used (CD10, Bcl-6 and MUM-1). Germ center B lymphoma (CD10+, Bcl6+, MUM-1-) has an overall 5-year survival of 76%, compared with only 34% survival for non germinal ABC lymphoma (CD10-, Bcl-6- and MUM-1+).

6. Ki-67 index (MIB-1). Quantitation of cell proliferation by Ki-67 nuclear labeling can predict prognosis in DLBCL. High values (>50%) were associated with unfavorable prognosis (EL-Bolkainy et al, 2007). In another report, a cut-off value of 45% can separate low from high-grade lymphomas (Broyde et al, 2009). In follicular lymphoma, the Ki-67 index is higher in grade 3 (>30%) than grade 1 and 2 lymphomas (<20%), the former is more aggressive (Jaffe et al, 2011). Ki-67 index is low (23%) in small lymphocytic lymphoma and very high (>90%) in Burkitt, lymphoblastic and anaplastic T lymphomas.

7. International Prognostic index (IPI). The IPI is generally adopted to subclassify DLBCL into prognostic groups (Shipp, 1994). It has the advantage of combining 5 clinical parameters (each given one score), namely: age >60 years, performance status >2, LDH >normal, stage III or IV, and extranodal involvement more than one site. These scores were added together into a total score (the IPI) which is a useful guide to therapy and predict prognosis (Table 25-14). More precise survival data can be obtained by combining the histologic type of lymphoma and IPI (Table 25-15).

Table 25-14 International Prognostic Index (IPI) for (DLBCL)

IPI Score *	Original risk groups (Shipp et al, 1994)	Overall 5-year survival (%)
0>1	Low	73
2	Low-intermediate	51
3	High-intermediate	43
4>5	High	26

IPI Score	Revised risk (Sehn et al, 2007)	Overall 5-year survival (%)
0	Low	94
1,2	Intermediate	79
3,4,5	High	55

*The sum of 5 factors (each worth one point): age >60, LDH above normal, performance status ≥2, Stage III or IV and extranodal disease ≥2 sites.

Table 25-15 Survival of NHL by Combining Histologic Type and IPI

Histologic type	% of cases	Overall 5-y survival (%)	
		IPI 0/1	IPI 4/5
Follicular	22	84	17
Mantle	6	57	0
Marginal (MALT)	8	89	40
Marginal nodal	2	76	50
Small lymphocytic	7	76	38
Diffuse large	31	73	22
Primary mediastinal	2	77	0
Burkitt	2	71	0
T-lymphoblastic	2	29	40
Peripheral T	7	36	15
Anaplastic large	2	81	83

(Armitage et al, 1997), Abbreviations: NHL Non-Hodgkin lymphoma, IPI international prognostic index MALT mucosa associated lymphoid tissue lymphoma.

SPECIAL CONSIDERATIONS

Low-grade lymphomas

These are composed of predominantly small lymphoid cells with low growth fraction and long natural history, measured in years. They are common in elderly patients. Many show early dissemination, but others, presenting at extranodal sites, appear localized and show trafficking and homing of neoplastic lymphocytes. Privileged sites, as the brain and testis, are not involved. The disease is continuously relapsing after therapy, hence, survival curves lack a plateau effect (Fig 25-8). However, temporary spontaneous remission occurs in 10% of cases. Three clinical groups are recognized, namely: disseminated, extranodal and nodal

Disseminated lymphoma/leukemia

1. B-small lymphocytic lymphoma (SLL/CLL) accounts for less than 5% of NHL, affecting mainly elderly patients, with leukemic association (CLL) at initial presentation in 20% of cases. It is composed mainly of small lymphocytes with round nuclei and condensed chromatin (P25-8 and P25-9). Clusters of larger lymphoid cells (proliferation centers) may be evident. Patients often have hypogammaglobulinemia with infective complications and autoimmune phenomenon. In about 5% of cases, there is abrupt transformation to a large cell aggressive lymphoma (Richter syndrome). The tumor cells have faint sIgM, and B-cell-associated antigens (CD19, CD20) are positive. Tumor cells characteristically express both CD5 and CD23, the latter is useful in distinguishing small lymphocytic lymphoma from mantle cell lymphoma.

2. Lymphoplasmacytic lymphoma (LPL) is a biclonal lymphoma of both small lymphocytes and plasma cells (P25-10). There may be associated monoclonal serum paraprotein of IgM type (P 25-11), with or without Hyperviscosity syndrome (Waldenstrom macroglobulinemia).

3. Hairy cell leukemia (HCL) is a distinctive variant of CLL that is named for the filamentous projections or "hairs" on the surface of neoplastic cells. A B-lymphocyte lineage is almost always demonstrated. HCL is uncommon, comprising only 2% of all leukemias. The disease occurs most commonly in middle aged to elderly men (median age 50 years). The male to female ratio is 4:1. Patients present with splenomegaly and peripheral blood cytopenia as a result of infiltration of spleen and bone marrow. The lymphocytes show fine irregular cytoplasmic projections. The tartrate-resistant acid phosphatase (TRAP) stain is positive in 95% of cases. Modern therapy by interferon has prolonged survival and achieved clinical cure in a substantial number of cases (92%).

4. Splenic marginal zone lymphoma (SMZL) is a recently described entity accounting for only 1% to 2% of chronic lymphoid malignancies. It is a neoplasm of monocytoid B-cells which involves the spleen, bone marrow and usually the peripheral blood.

Extranodal lymphomas (MALT) (Marginal zone Lymphoma)

Mucosa associated lymphoid tissue (MALT) lymphomas occur in the gastrointestinal tract, lungs, salivary glands, lacrimal glands, conjunctiva, thyroid and breast. The pathogenesis is related to either autoimmune disease such as Sjogren's syndrome and Hashimoto's thyroiditis, or to bacterial infection (Helicobacter gastritis in case of gastric MALT lymphoma).

MALT lymphoma is of marginal B-cell origin (slg+, CD19+, CD20+). It is localized in 70% of

cases due to the homing phenomenon of neoplastic lymphocytes. Histologically, it is characterized by: (a) predominant infiltrate of small monocytoid lymphocytes, as well as, few centroblasts and immunoblasts mainly affecting the marginal zone; (b) preservation of germinal centers which may be infiltrated (colonized) by monocytoid cells; (c) infiltration of the epithelium forming so called lymphoepithelial lesions; and (d) associated polyclonal plasmacytosis in the lamina propria (P 25-12).

Nodal Lymphomas

1. Follicular lymphoma (FL) is composed of follicular center cells, usually a mixture of centrocytes (cleaved cells) and centroblasts (large non-cleaved cells) and exhibits a follicular pattern (P25 -13 and P25-14). It is the most common adult lymphoma in the West, comprising 34% to 40% of all NHL. Follicular lymphoma is graded into three grades according to the number of large lymphocytes (centroblasts) per high power microscopic field (HPF) (Table 25-16 and P25-15). Follicular lym-phoma progresses to diffuse large B -cell lymphoma in about 50% of cases.

The cytogenetics of follicular lymphoma is characteristic. Translocation t(14; 18) is present in 95% of cases, and results in expression of bcl-2 antiapoptosis gene, which is normally switched off in germinal center cells. Expression of the bcl-2 protein permits accumulation of long-lived centrocytes. This marker is valuable in the differential diagnosis of follicular lymphoma (positive) and reactive follicular hyperplasia (negative).

2. Nodal marginal zone B-cell lymphomas (NMZL) are monocytoid cell lymphomas reported in patients with Sjogren's syndrome and represent nodal involvement by a MALT lymphoma. Others have been reported as a composite lymphoma.

Table 25-16 Follicular Lymphoma Grading

Grading	**Definition**
Grade 1-2 (low grade)	0-15 centroblasts per hpf
1	0-5 centroblasts per hpf
2	6-15 centroblasts per hpf
Grade 3	>15 centroblasts per hpf
3A	Centrocytes present
3B	Solid sheets of centroblasts
Reporting pattern	**Proportion follicular**
Follicular	>75%
Follicular and diffuse	25-75%*
Focally follicular	<25%*
Diffuse	0%**

(Swerdlow et al, 2008) NB. 3B and diffuse areas Containing >15 centroblasts per hpf are reported as diffuse large B-cell lymphoma.

Low-grade T-cell lymphomas

They include the rare T-cell CLL (about 5% of cases), large granular cell leukemia (of NK cell origin) and mycosis fungoides which is a primary T-cell lymphoma of the skin (chapter 22).

High-grade Lymphomas

These are defined as tumors that are likely to be fatal in a matter of months if left untreated. They affect adults, as well as, children. They differ from indolent lymphomas in being localized at their early phase, and in being curable with current therapeutic modalities. Survival curves after therapy show a plateau effect, with 5-year survival of about 60%. In general, aggressive lymphomas are composed of large cells, immunoblastic or mixed cell population, with high growth fraction.

1. Diffuse large B-cell lymphoma (DLBCL) constitutes 30% of NHL in adults and about 5% of NHL in children. This lymphoma can be stratified into low and high-grade subtypes according to: IPI index (Fig 25-10), Ki-67 index and DNA microar-

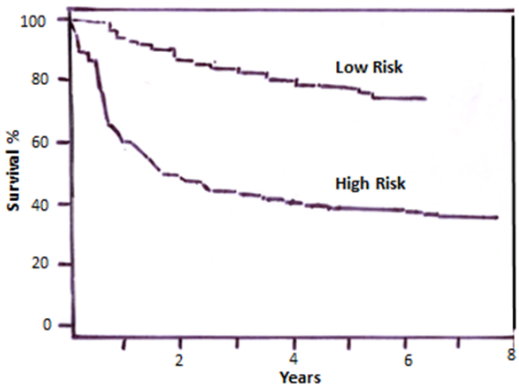

Fig 25-10 *Survival curves of diffuse large cell non-Hodgkin lymphoma stratified according to the International Prognostic index (IPI). The 5-year overall survival with R-CHOP treatment is 80% for low-risk and 40% for high-risk (Swerdlow et al, 2008).*

ray. The histopathology is characterized by a mixture of large cells, namely: centroblasts, immunoblasts and large cleaved cells (P 25-16).

Some cases may be rich in small reactive T-lymphocytes in the stroma (P 25-17). Primary mediastinal (thymic) large B-cell lymphoma is a distinct clinicopathologic entity within the broad category of diffuse large B-cell lymphoma. Large B-cell lymphomas often express slg, and one or more of B-cell associated antigens (CD 19, CD20). The bcl-2 gene is rearranged in 30% of cases.

2. Mantle cell lymphoma (MCL) comprises about 5% of adult NHL in the West and corresponds to the small-cleaved type. It is a tumor of older adults, with a marked male predominance. The course is aggressive, and lacks a plateau effect after therapy (Fig 25-11). The median survival is about 5 years (3 years in the more aggressive blastoid variant). Abrupt transformation to large-cell lymphoma does not occur.

The genetic features include immunoglobulin heavy and light chain gene rearrangement. In most of the cases, the t (11;14) translocation results in overexpression of PRAD-1 (cyclin Dl), which is a cell cycle associated protein. Histologically, it is composed of small lymphocytes with cleaved or indented nuclei (coffee bean shaped). Mitotic activity is higher (Ki67 >30%) than other indolent lymphomas (P 25-18). Some cases show numerous mitosis and fine dispersed chromatin (blastoid variant). The cells express B-cell associated antigens (CD 19, CD20); coexpress CD5 but lack CD23. Immunohistochemical staining for cyclin Dl is useful in distinguishing MCL from other indolent B-cell lymphomas.

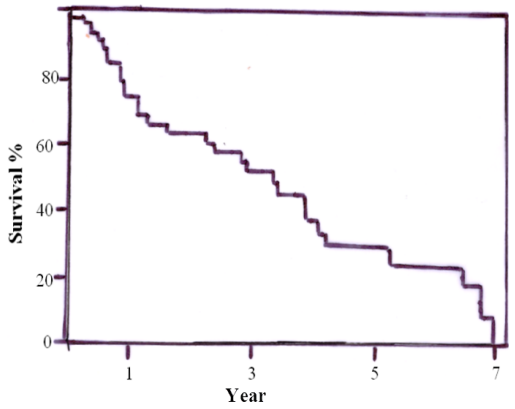

Fig 25-11 *Survival curve of mantle cell lymphoma demonstrating its high-grade aggressive nature revealed by long-term survival analysis. The 10-year survival is only 34% (Ries, 2007).*

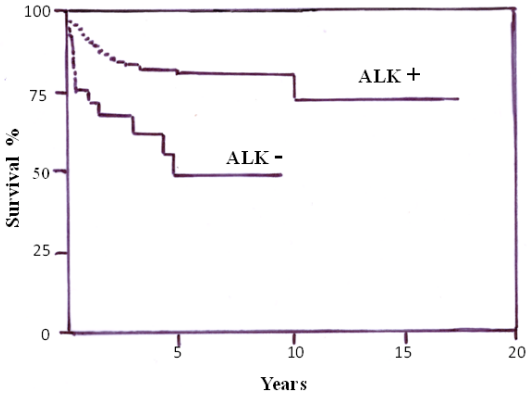

Fig 25-12 *Survival curves of anaplastic large cell Non-Hodgkin lymphoma stratified according to Immunoreactivity to anaplastic lymphoma kinase (ALK). ALK positive tumors have a more favorable prognosis. The overall 5-year survival is about 80% in ALK+ patients in contast to 40% in ALK-Cases (Swerdlow et al, 2008).*

3. Anaplastic large cell lymphoma (ALCL) constitutes 5% of NHL in adults and 15% of lymphomas in children. It has a bimodal age distribution, one peak in childhood and another in adulthood. Clinically, there are two forms of the disease: one in adults limited to the skin, and the other in children with systemic spread including skin and lymph nodes. Histologically, it is composed of sheets of large cells with pleomorphic horseshoe-shaped nuclei, sometimes multiple, with prominent nucleoli, abundant basophilic cytoplasm and sinusoidal pattern (P25-19). The lesion simulates Hodgkin lymphoma or carcinoma. The immunophenotype is characteristic, CD45+, CD30+, Pan-T (CD3, CD45RO)+ and cytokeratin negative. The majority of cases have T-cell receptor (TCR) rearranged. Genetic features also include t(2;5) translocation which results in fusion of the nucleophosmin (NPM) gene on chromosome 5 to a novel tyrosine kinase gene on chromosome 2 called ALK (anaplastic lymphoma kinase). ALK+ lymphomas have a more favorable prognosis (Fig 25-12).

4. Peripheral T-cell lymphoma constitutes about 10% of NHL. They typically contain a mixture of small, large and immunoblastic cells (P25-20). Eosinophils and epithelioid histiocytes may be numerous (P25-20). The non-specified category (NOS) includes heterogeneous diseases that require further definition. However, several rare variants are recognized as distinct entities (Table 25-10): (a) angioimmunoblastic lymph-

adenopathy; (P25-21) (b) nasal type T/NK-cell lymphoma (P25-22 and P 25-23), formerly called angiocentric lymphoma; (c) intestinal T-cell lymphoma complicating celiac disease; and (d) hepatosplenic T-cell lymphoma. The lymphoid tumor cells in most cases express pan-T antigens (CD2 +, CD3+) and nasal type lymphoma P 25-22 will express in addition natural killer antigen (CD56+). (e) Lennert lymphoma, is epithelioid rich T-cell lymphoma (P 25-24).

Highly Aggressive Lymphomas

Highly aggressive lymphoid neoplasms, or acute lymphomas, are defined as tumors that are likely to be fatal in a matter of weeks if left untreated. They are common in pediatric patients contributing 80% of their lymphomas. They are composed of small cells with extremely high growth fraction. Early dissemination with invasion of bone marrow, peripheral blood, CNS and testis is common. However, survival curves after intensive therapy show a plateau effect, with a long-term cure rate of about 80%.

1. Lymphoblastic leukemia (LBL) is defined as more than 20% lymphoblasts in bone marrow. The phenotype is 80% B and 15 % T. Most B-LBL are positive for pre- B markers (CD10 or common acute lymphoblastic leukemia antigen CALLA) and terminal deoxyribonucleotide transferase (TdT+).

2. Lymphoblastic Lymphoma (LBL) is the tissue equivalent to ALL, but 85% of cases are of T-cell lineage. It consti-tutes about 40% of pediatric lymphomas. Patients are predominantly adolescent, and typically present with mediastinal (thymic) masses and/or peripheral lymphadenopathy. CNS involvement is common. Untreated T-LBL is rapidly fatal, usually terminating in acute leukemia.

Histologically, it is composed of intermediate size cells with irregular nuclei, dispersed chromatin, indistinct nucleoli and active mitosis (P 25-25). A single cell file infiltration pattern may be present. Expression of TdT is useful in distinguishing precursor T lymphoblastic lymphoma from peripheral T tumors and Burkitt lymphoma (which are negative).

3. Burkitt's lymphoma is most common in children, contributing about 30% of pediatric lymphomas. It is observed in 3 clinical settings: (a) African or endemic Burkitt lymphoma, affects children, common in jaws and neck, EBV association is high (95%); (b) sporadic or non-endemic Burkitt lymphoma, affects mainly adults, with common abdominal localization specially the ileocecal region, and EBV association is low (5-15%); and (c) immunodeficiency- associated Burkitt lymphoma, particularly AIDS patients.

Histologically, it is composed of medium-sized cells with rounded nuclei, coarsely reticulated chromatin, multiple nucleoli, and basophilic scanty cytoplasm. There is extremely high rate of cell proliferation, as well as, a high rate of apoptosis. A starry sky pattern is usually present, imparted by numerous benign macrophages that have ingested apoptotic tumor cells (P 25-26). In adults, Burkitt-like lymphomas may be observed and typically show more cellular pleomorphism and prominent central nucleoli. It is at present included as a variant of diffuse large B-cell lymphoma. Burkitt lymphoma is a B-phenotype, expressing sIgM, (CD 19 +, CD20 +), as well as, CD10+, but are CD5-ve, CD23-ve, TdT-ve and Ki-67 index > 90%.

4. Adult T-cell lymphoma/leukemia (ATL/L) is defined as a T-cell neoplasm caused by HTLV-1 virus, affecting mainly adults. Most cases occur in Japan and the Caribbean. It is manifested by leukemia, lymphadenopathy, heaptosplenomegaly, hypercalcemia, lytic bone lesions and skin rashes. Survival is only a few months. The histology is variable, usually there is a mixture of small and large atypical lymphoid cells, rarely multinucleated giant cells may be present simulating Hodgkin lymphoma.

5. Immunodeficiency-associated lymphoproliferative disorders. The WHO (Swerdlow et al, 2008) recognizes 4 clinical settings of immunosuppression: (1) primary immunodeficiency syndromes, (2) infection with HIV virus (AIDS), (3) post-transplant immunosuppression and (4) iatrogenic immunosuppression associated with methotrexate treatment in rheumatoid patients, or other autoimmune diseases as psoriasis.

Three main mechanisms are operable in lymphomagenesis, namely: (1) defective immune surveillance to oncogenic viruses (e.g. EBV and HHV-8), as well as, chronic antigenic stimulation (in congenital immune deficiency, AIDS and organ transplant recipients), (2) defective DNA repair (as in ataxia telangiectasia), and (3) defective apoptosis due to FAS mutation.

Lymphoma development passes through three stages. (1) *Early reactive stage* rich with plasmacytoid cells and T cells, but preserved architecture. (2) *Polymorphic stage* rich with immunoblasts, plasma

cells and lymphocytes with loss of normal nodal pattern. (3) A final *monomorphic stage* of Lymphoma with loss of architecture. Diffuse large B-cell lymphoma (immunoblastic) is the most common type (but less commonly T-cell, Burkitt or Hodgkin lymphoma). The sites of tumors may be nodal or extranodal (gastrointestinal, lung or brain). Prognosis is most unfavorable in AIDS-related lymphoma (Table 25-12), but favorable in iatrogenic lymphoma when immunosuppressive therapy is discontinued.

PLASMA CELL NEOPLASMS

These are monoclonal neoplasms with plasma cell differentiation which usually secrete monoclonal immunoglobulin (M protein or paraprotein). Plasma cell tumors contribute about 15% of deaths from lymphoma and are classified according to clinical presentation, as well as, the type and level of paraprotein (Table 25-17).

Biochemical Background

Immunoglobulins are antibody molecules (glycoproteins) that are produced by plasma cells as a highly specific response to an antigenic challenge. The basic immunoglobulin molecule (chapter 8, Fig. 8-7) is a 4-chain monomer consisting of: (1) two heavy chains, (2) two light chains (either kappa or Lambda, polypeptides), (3) Variable "V" domains which have great variation in amino acid sequence between immunoglobulins, and have short segments of hypervariable regions, (4) FAB (fragment antigen binding), the paratope or antigen binding site occurs when the loops bearing the hypervariable regions of the light and heavy chains come together in space, (5) Constant "C" domains in which the amino acid sequences are relatively conserved, and (6) FC (fragment crystalline) is formed from constant domains and regulates the effector functions (including binding to cell surface receptors and complement fixation), leading to elimination of the bound antigen (chapter 8 Fig 8-7). There are 5 types (isotypes) of immunoglobulins (Ig G, A, M, E, D). They differ from each other by the type of the heavy chain and size of molecule e.g. Ig A is a dimer of IgG and IgM is a pentamer of IgG (Fig 25-13).

Table 25-17 WHO Classification of Plasma Cell Neoplasms

1. Monoclonal gammopathy of undetermined Significance (MGUS)
2. Plasma cell myeloma
   - Symptomatic myeloma
   - Asymptomatic (smoldering) myeloma
   - Nonsecrtory myeloma
   - Plasma cell leukemia
3. Solitary plasmacytoma
   - Osseous plasmacytoma
   - Extraosseous plasmacytoma
4. Monoclonal immunoglobulin deposition disease (MIDD)
   - Primary amyloidosis
   - Systemic light and heavy chain deposition diseases
5. Osteosclerotic myeloma (POEMS Syndrome)
6. Lymphoplasmacytic neoplasms
   - Waldenstrom (SLL)
   - Marginal zone (MALT)

(Swerdlow et al, 2008)

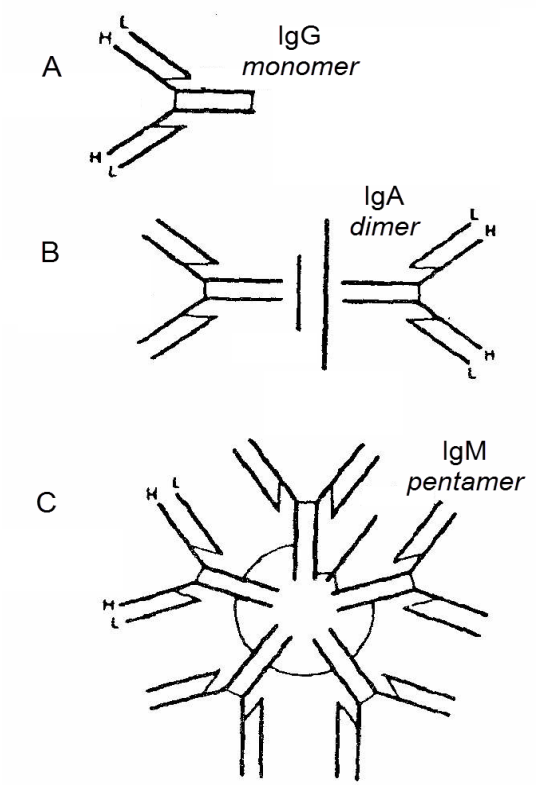

Fig 25-13 *Biochemical structure of immunoglobulins. A. IgG exist only as a monomer with the basic structure of two light and two heavy chains (Chapter 8, Fig 8-7), but other Immunoglobulins may exist as polymers. B. IgA can exist as a high-order dimer molecule C. IgM, a pentamer of five IgG molecules. Gammopathies secreting this large molecule (e.g. Waldenstrom lymphoma) may be associated with hyperviscosity syndrome (Murray et al, 2006).*

Immunoglobulin production is under genetic control. The molecule is encoded within three separate chromosomes, namely: (1) chromosome 14 for heavy chain, (2) chromosome 2 for κ light chain, and (3) chromosome 22 for *X* light chain. The primary immune response is of the IgM isotype, whereas, IgG and IgA responses develop later. This switching requires gene rearrangement with T lymphocyte help. Normally, each individual is capable of generating different antibodies directed against perhaps one million different antigens. This property of antibody diversity depends on gene rearrangement of immunoglobulin genes. The produced antibodies are polyclonal with characteristic electrophoretic pattern, namely: a broad-based curve with high albumin value.

Zone electrophoresis is useful in the diagnosis of human paraprotein disorders. In these diseases an electrophoretically restricted monoclonal protein spike (M protein or monoclonal component) usually occurs in the γ-globulin or β-globulin regions. This abnormal spike is usually associated with reduction in the normal globulins. With immunoelectrophoresis, it is possible to identify the specific type of immunoglobulin causing the spike and this has a diagnostic valve. Thus, in multiple myeloma the paraprotein is IgG, IgA or light chain, in Waldenstrom disease it is IgM and in IPSID it is α heavy chain IgA.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

MGUS is the most common plasma cell dyscrasia, affecting about 3% of patients older than 50 years and 5% of patients older than 70 years. It is characterized by M protein <30g/L, plasma cells <10% in bone marrow, normal blood picture asymptomatic and no endorgan damage. About 2% of patient/year will progress to multiple myeloma, so MGUS is considered an early stage of multiple myeloma (premyeloma). The 10-year survival, compared to normal population, is reduced by about 10%.

Multiple Myeloma

This is a multifocal disseminated plasma cell neoplasm associated with monoclonal protein (M protein) in serum and/or urine, and usually fatal due to endorgan destruction (especially renal). It is classified by WHO under the high-grade highly aggressive B-cell lymphoma.

Molecular Oncogenesis

Multiple myeloma develops from clonal proliferation of a stem cell with postgerminal plasma cell differentiation. The most common chromosomal abnormalities include chromosome 14 (the site of heavy chain locus) and chromosome 13. Myeloma cells secrete IL-6 and MIP-1a which lead to activation of plasma cells and osteoclasts respectively, resulting in bone resorption and hypercalcemia.

Diagnosis

The updated WHO diagnostic criteria of multiple myeloma allows early application of therapy and is based on a combination of pathologic, radiologic, clinical and laboratory features (Table 25 -18 and P 25-27). The types and frequency of the secreted monoclonal (M protein) is presented in (Table 25-19 and Fig 25-14). Three multiple myeloma variants are recognized: (1) *Asymptomatic or smoldering* myeloma, the plasma cell count in bone marrow smears is 10-30%, serum M protein >30 g/L, but the patient is asymptomatic. About 75% of patients will progress to multi-ple myeloma in 15 years. (2) *Non-Secretory myeloma* (3% of cases) there is lack of M protein, hence less risk of endorgan damage and hypercalcemia. Immu-noglobulins are made, but not secreted outside the plasma cells. (3) *Plasma cell leukemia*, an aggressive variant in which monoclonal plasma cell count in peripheral blood exceeds $2x10^9$/L or is 20% of the leukocytic differential count, besides other features of multiple myeloma.

Table 25-18 The Revised WHO Diagnostic Criteria of Multiple Myeloma

Eary Dissease
1. The presence of one of the following: plasma cells ≥60% in marrow biopsy or smears, light chain (≥100 mg/L), or more than one focal bone lesion on MRI (>5mm).
2. Plasma cells (>10%) and high M protein (IgG>30 g/L or IgA>25 g/L).
Advanced Disease
End-organ failure including: hypercalcemia, renal failure, anemia, amyloidosis and destructive bone lesions.

International Myeloma Working Group (RajKumar et al, 2014)

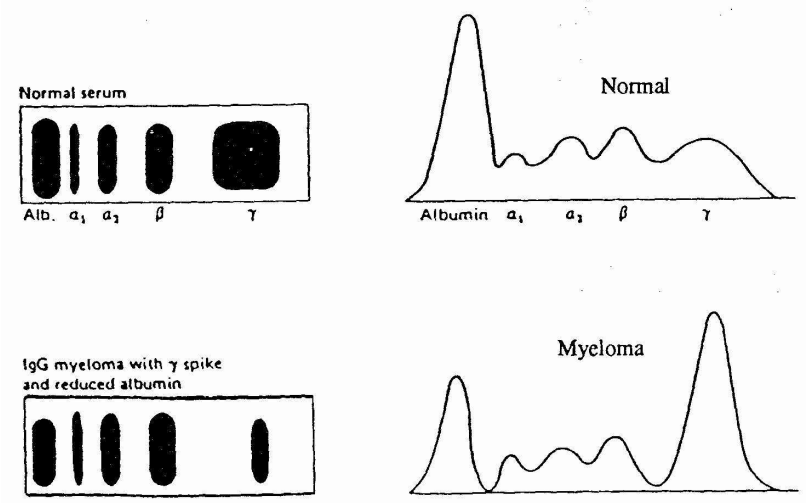

Fig 25-14 *Serum protein electrophoresis. A. Normal human serum showing high albumin and broad-based globulin curves B. serum of IgG multiple myeloma showing an abnormal paraprotein (Spike) in the γ-globulin region with reduced albumin.*

Table 25-19 Frequency of Monoclonal (M)

M protein	%
IgG	60
Light chain (Bence Jones)	20
IgA	17
IgD	2
Biclonal	1

(Rodgers and Young, 2010)

Pathology

Well-differentiated tumors show a pure population of small uniform plasma cells, not associated with lymphocytes and atypical binucleated plasma cells may be observed (P 25-28). Immunoglobulin inclusions may be found in the nucleus (Ducher bodies) or cytoplasm (as single Russel bodies, or grap-like structure or Mutt cell). Amyloid may be seen in the stroma. In anaplastic or poorly-differentiated variants, plasmablasts have prominent nucleoli. Immunostains are confirma-tory. Myeloma cell is reactive to CD38, CD138, CD56 but negative for CD19 and LCA. Conversely, normal plasma cell is negative for CD56 but positive for CD19. Electron microscopy reveals the characteristic crystalline structure of immunoglo-bulin.

Clinical

Symptomatic multiple myeloma is characterized by manifestations of endorgan damage. A useful acronym for tissue damage is CRAB (hypercal-cemia, renal insufficiency, anemia and bone lesions). Renal failure is the main cause of death and results from toxic effect of light-chain protein on renal tubules and amyloid deposits in glomeruli.

Other complications of myeloma include inter-current infections due to reduced normal immu-noglobulins, hyperviscosity syndrome and IgG cryoglobulinemia and heart failure from cardiac amyloidosis.

Prognosis

Multiple myeloma is included in the most unfavorable class of NHL (Table 25-12) with 5-year survival (30%) and 10-year survival (12%). The median survival with treatment is 4 to 6 years. Bone marrow transplantation may prolong life, but not curable. Unfavorable prognostic factors are chro-mosomal deletions (13 and 17) and serum β2 -microglobulin >5.5 μgm/L (Table 25-20).

Solitary Myeloma

Solitary myeloma (plasmacytoma) contributes about 4% of plasma cell tumors. It presents as a solitary localized mass in bone or respiratory sys-tem, usually not associated with M protein. Osseous plasmacytoma invariably progresses to multiple my-eloma in 15 years. Conversely, extraosseous plasma-cytoma are cured by local excision.

Table 25-20 International Staging System for Multiple Myeloma and Related Median survival

Stage	β_2 Microglobulin mg/L	Median survival (months)
I	<3.5	52
II	3.5-5.5	44
III	>5.5	29

(Swerdlow et al, 2008)

Monoclonal Immunoglobulin Deposition Disease (MIDD)

This neoplasm is characterized by deposition of paraprotein in tissues without other features of multiple myeloma. Two types are recognized according to the chemical nature of the paraprotein:

Primary amyloidosis (AL amyloid). So named because the amyloid deposit is immunoglobulin light chain (mainly lambda chain). It is positive for Congo red stain with greenish bifringence on polarized light and electron microscopy shows amyloid fibrils.

Monoclonal light and heavy chain deposition disease. The paraprotein deposits are mixture of light chain (mainly kappa) and heavy chain. The M protein, as a result of mutation undergoes structural changes making it different from AL amyloid for this reason the amyloid in this disease is negative for Congo red and electron microscopic structure is nonfibrillary.

Osteosclerotic Myeloma (POEMS Syndrome)

A rare plasma cell tumor characterized by fibrosis and osteosclerotic changes in bone associated with lymphadenopathy (Castleman-like), as well as, a syndrome of polyneuropathy, endocrinopathy, monoclonal gammopathy and skin changes (POEMS).

Lymphoplasmacytic tumors

These neoplasms are biphasic, with monoclonal proliferation of both B-lymphocytes and plasma cells, hence are classified in the low-grade class of non-Hodgkin lymphomas (P 25-29). They include: Waldenstrom disease (=phasmacytoid small lymphocytic lymphoma) and marginal zone lymphomas (nodal or extranodal MALT). The prognosis is unfavorable (10-year survival of 45%).

NHL IN EGYPT

At NCI-Cairo, lymphoma and leukemia constituted 12% of all cancers, and ranked the third after bladder and breast cancers (Sherif and Ibrahim, 1987). Non-Hodgkin lymphoma (NHL) contributed about 6% and the lymphoma to leukemia ratio was 2:1. NHL predominated over Hodgkin in adults with a ratio of 2.5:1, but not in children with a ratio of 0.6:1 (El-Bolkainy, 1994). Primary extranodal lymphomas constituted 34% of all NHL. The mean age was 40 years with the pediatric patients (16 years or less) contributing 17% of cases (Fig. 18-9). Male patients predominated with a sex ratio of 1.9:1. Recent incidence rate of NHL Egypt in 8.7/100,000 (chapter 2). The high incidence of NHL in Egypt is possibly related to the exposure of population, at a young age, to various bacterial, parasitic and viral infec-tions which result in a sustained stimulation of the lymphoid system. Epstein-Barr virus (EBV) association was evident in 73% of Burkitt's lymphoma in Egyptian patients (Anwar et al, 1995). Moreover, immunologic deficiency, as a result of malnutrition, may also be involved in the pathogenesis of lymphoma.

Malignant lymphomas in Egyptian patients present special unfavorable features which are distinctly different from those reported in the Western literature. Thus, in Egypt diffuse aggressive lymphomas (high grades) predominate and constitute 87% of cases in adults and 100% in children. Phenotyping studies reveal a high incidence of B-cell lymphomas (82.6%), overexpression of p53 (34.6%) and bcl-2 oncogene positivity (44.2%), but 64.5% in follicular lymphoma (Mokhtar, 1994). Expression of multidrug resistance (MDR-1) gene, (assessed by p-glycolprotein immunoreactivity), is evident in 80% of cases. The patients present at advanced stages, with 85% of cases in stages III and IV of Ann Arbor classification. They also present with bulky disease which is invariably associated with high serum level of lactic dehydrogenase (LDH). The malnutrition and anemia, commonly associated with the disease in Egyptian patients, also have a negative impact on hematologic recovery after chemotherapy, as well as, the performance status of the patient. The majority of patients belong to a high-risk international index score of 4 or more.

Survival data were analyzed for adult NHL patients treated at the Department of Medical Oncology, NCI during the years 1975-1986. The 10-year survival was 34.5% for COP therapy

and 22.7% for CHOP therapy (Gad-El-Mawla, 1991). However, in pediatric patients, the 5-year survival was 75% (Gad-El-Mawla, 1998).

Recent reports on the long-term survival of Egyptian patients with NHL are lacking. The only study is a 2-year survival analysis after CHOP therapy, reporting an overall survival of 82% and disease free survival of 69% (Abdelhamid et al, 2011). Moreover, there are also, so far, no reports on the use of Rituxan-CHOP combination in Egyptian patients, a protocol at present considered a standard treatment for DLBCL. The high cost of the monoclonal antibody may be an explanation, but not an excuse.

DIAGNOSTIC APPROACH TO LYMPHOMA TYPING

I- DIFFERENTAL DIAGNOSIS FROM OTHER LYMPHOMAS

An accurate typing of lymphoma requires careful evaluation of three important pathologic features, namely: (1) *Pattern* of lymphoma (follicular or diffuse), (2) *Cell size*, small, intermediate or large and (3) Confirmatory *immunophenotyping* (Fig 25-15 and Table 25-21).

Follicular Pattern

The size of follicles varies in different lymphomas (Fig 25-16). Follicular lymphoma is characterized by small crowded follicles (back-to-back) which may invade the perinodal fat. Larger follicles are observed in progressive transformation of germinal centers and Hodgkin lymphocyte predominance. The latter shows vague nodularity with ill-defined margins. The largest nodules are observed in nodular sclerosis Hodgkin lymphoma, which also shows dense fibrotic bands around the nodules.

Diffuse Small Cells

The main differential diagnosis of diffuse small cell lymphoma is between: small lymphocytic (CD23+, Cyclin D1-), mantle cell (CD23-, Cyclin D1+), marginal zone lymphoma (CD23-, Cyclin D1-) and plasma cell myeloma (CD38+, CD138+).

Intermediate Sized Cells

The main differential diagnosis is between lymphoblastic lymphoma (TdT+), Burkitt lymphoma (TdT-, Ki67-index 90-100%) and blastoid mantle cell lymphoma (TdT-, Cyclin D1+).

Diffuse Large Cells

Diffuse large B-cell lymphoma (DLBCL) is CD20+ PAX-5+, whereas, peripheral T-cell lymphoma is CD20-CD3+. Anaplastic large T-cell lymphoma is CD3+, CD30+ and commonly ALK-1+.

Diffuse small and Large Cells

The presence of a mixed cell population of a mixed cell population of variable sizes raises the possibility of classic Hodgkin lymphoma, peripheral T-cell lymphoma and T-cell rich B-cell lymphoma. Immunoreactivity of the large cells helps in the differential diagnosis. Hodgkin lymphoma is CD30+ CD15+, peripheral T-cell lymphoma is CD3+ and T-cell rich B-cell lymphoma is CD20+.

Lymphomatoid granulomatosis (LYG) is a rare NHL which simulates T-cell rich B-cell lymphoma (large CD20+ cells and small CD3+ cells) but differs by the following features: (1) extranodal location, (2)

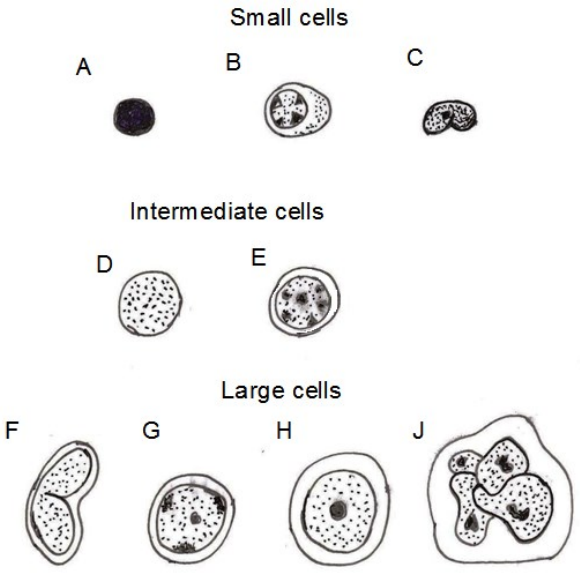

Fig 25-15 *Classification of Non-Hodgkin lymphoma into three groups according to nuclear. size. In large cell lymphomas, their nuclei are equal to or slightly larger than the nuclei of macrophages or twice the size of a normal lymphocyte. In small cell lymphomas, their nuclei are equal in size to a normal lymphocyte. A. Small lymphocyte, B. Plasma cell, C. Small cleaved, D. Lymphoblastic, E. Burkitt. F. large cleaved, G. Lange non-cleaved (centroblast), H. Immunoblast J. Giant cell.*

Table 25-21 Diagnostic Approach of Lymphomas and Histiocytic Tumors According to the Pattern, Cell size and Immunophenotype

Pattern	Cell size*	Diagnosis	Immnuophenotype
Nodular	Variable	Follicular lymphoma (FL)	CD20+, bcl-2+, CD10+,CD23-, CD5-
		Hodgkin, nodular sclerosis (NSCHL)	CD15+, CD 30+,CD 3-, CD20-
		Nodular lymphocyte predominance Hodgkin lymphoma (NLPHL)	CD20+, CD3-, CD30-, CD15-
			CD21+, S100-, CD1a-, CD68-
		Follicular dendritic sarcoma (FDC)**	CD20+, CD43+, CD5-, CD23-
		Nodal marginal zone lymphoma (MZL)	CD20+, CD 5+, cyclin D1+, CD23-
		Mantle cell lymphoma (MCL)	
Diffuse	Small	Small lymphocytic lymphoma (SLL/CLL)	CD20+, CD23+, CD5+, CD3-
		Mantle cell lymphoma (MCL)	CD20+, CD5+, cyclin D1+, CD23-
		Marginal zone lymphoma (MZL)	CD20+, CD 43 + 50%), CD5-, CD23-, cyclinD1-
		Lymphoplasmacytic lymphoma (LPL)	CD20+, CD5-, CD23-
		Plasma cell myeloma (MM)	CD38+, CD138+, CD56+, CD19-
	Intermediate	Burkitt's lymphoma (BT)	CD20+, CD10+, TdT-, Ki-67 100%
		Lymphoblastic Lymphoma (LBL)	TdT+, CD20+ or CD3+
	Large	Diffuse large B-cell lymphoma (DLBCL)	CD20+,CD3-
		Anaplastic large cell lymphoma (ALCL)	CD3+,CD30+, ALK±, CD15-
		Peripheral T-cell lymphoma (PTCL)	CD3+, CD20-
		Hodgkin lymphoma, lymphocyte depletion (LDCHL)	CD15+, CD30+
	Mixed	Hodgkin lymphoma, mixed cellularity (MCCHL)	CD30+, CD15+
		Peripheral T-cell lymphoma (PTCL)	CD3+, CD20-
		T-cell rich B-cell lymphoma (TCR-LBCL)	CD20+, CD3 (large cells -, small cell +)
		Histiocytic Sarcoma (HS)	CD68+, CD 21-

*Nuclear size: small <10 microns, Intermediate 10-15 microns and large 15-20 microns.
**MZL includes: Nodal, splenic and extranodal marginal zone lymphomas (MALT).

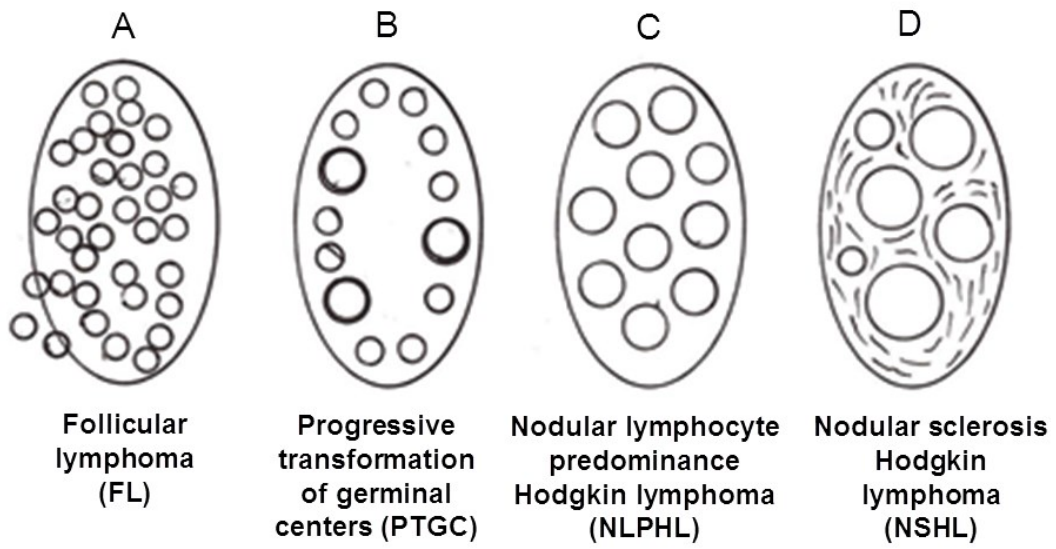

Fig 25-16 *Comparison of follicular patterns in lymphomas. A. Follicular lymphoma shows small closely-packed follicles (back to back) and may invade perinodal fat. B. Progressive transformation of germinal centers appears as large follicles among smaller normal germinal centers C. Hodgkin, Lymphocyte predominance is vaguely nodular with illdefined margins. D. Hodgkin nodular sclerosis present as very large follicles surrounded by thick fibrotic bands.*

angiocentric pattern, (3) focal necrosis, (4) consistent EBV association and (5) spontaneous regression in 27% of cases.

II- DIFFERENTAL DIAGNOSIS FROM REACTIVE LYMPHADENOPATHY

Diagnostic pitfalls between lymphoma and some reactive lymphoid hyperplasia are not uncommon. Such misdiagnosis is serious, since the patient will be subjected to an unnecessary aggressive therapy. The following are six examples of common reactive lymphadenopathies that may be misdiagnosed as follicular or diffuse NHL.

Follicular lymphoma

1. Follicular hyperplasia (P 25-30).
2. Castleman disease (P 25-31 and P25-32).
3. Progressive transformation of germinal centers (P 25-33).
4. Toxoplasmosis (P 25-34).

Diffuse lymphoma

1. Infectious mononucleosis (P 25-35).
2. Kikuchi necrotizing lymphadenitis (P 25-36).

III-DIFFERENTIAL DIAGNOSIS FROM OTHER MALIGNANCIES

Failure to distinguish lymphomas for other malignant tumors of similar histology will subject the patient to ineffective treatment. This error must be avoided by all means.

Small Cell Lymphomas

Some NHLs of small cell size may simulate other high-grade neuroendocrine tumors such as: small cell undifferentiated carcinoma, neuroblastoma and small cell malignant melanoma (P 25-37). Metastatic lobular carcinoma in axillary lymph node may also present a similar diagnostic problem, but, immunostains (cytokeratin and LCA) will help to avoid this pitfall.

Large Cell Lymphomas

Large cell carcinoma may be misdiagnosed as lymphomas in certain locations as the nasopharynx or lung (P25-38). Also, large cell lymphomas with focal pattern and Hodgkin nodular sclerosis (syncytial type) may be mistaken for carcinoma. Moreover, anaplastic T-cell lymphoma may be misdiagnosed as carcinoma in view of its pleomorphic and giant cells and focal sinus pattern, but, immunostains (CD3+, CD30+, ALK+, CK-)

will solve the diagnostic problem.

Mixed Cell Lymphomas

Extramedullary hematopoiesis, a reactive compensatory condition (P 25-39) must not be misdiagnosed as lymphoma. Malignant tumors with polymorphous cells of variable size may be mistaken as mixed cell lymphoma. A classic example is myeloid leukemia/ sarcoma (P 25-40). Other examples include histiocytosis, Langerhans and non-Langerhans subtypes (P 25-41) and follicular dendritic cell sarcoma (Chapter 26).

THE BONE MARROW

Hematopoiesis

Hematopoiesis refers to the process of formation of the formed elements of the blood. This process originates from hematopoietic stem cells (HSCs), which have the ability of self-renewal, as well as, to differentiate into all mature blood lineages. The property of self-renewal (due to telomerase activity) hence, immortality of stem cells, assures a constant source of reserve undiffer -entiated cells for hematopoiesis.

HSCs are rare, occurring at a frequency of one stem cell per 2000 bone marrow cell. Under steady state, HSCs are dormant (noncycling or G0 phase of cell cycle). However, when activated they have one of four fates namely: (1) asymmetrical division to one differentiated cell and another HSC, (2) symmetrical division into two HSCs, (3) apoptosis, and (4) migration to blood to start extramedullary hematopoiesis elsewhere (e.g. spleen or lymph nodes).

A stem cell (pleuripotential) initially gives rise to two committed multipotential progenitor lineages (Fig 25-17), namely: common lymphoid progenitors (LP) and common myeloid progeny-tors (MP). These progenitors will further divide into unipotential blast cells with restricted differentiation into only one cell type. Only blast cells and differentiated mature blood cells are recognizable by routine cytomorphology. Three distinct cell lineages are usually identified namely: myeloid, erythroid and lymphoid.

Hematopoiesis is under control by several growth factors which are rather specific to their target cells. Stromal cells are the major source of these growth factors, with the exception of erythropoietin (made in the kidney) and thrombo-poietin (made in the liver). Growth factors may be classified into the following 3 main groups accor-ding th their target cells:

1. *Acting on stem cells*: Including stem cell factor (SCF or C-Kit legand), FLT3 and VEGF (causing stem cell proliferation) and GCSF (activating stem cell migration).

2. *Acting on progenitor cells*: Including IL-3, IL-6 interleukins and GM-CSF (granulocyte monocyte colony stimulating factor).

3. *Acting on blast cells* to activate proliferation and differentiation: Including G-CSF, M-CSF, IL-5 (eosinophil colony stimulating factor), erythro-poietin (acting on erythrocytes) and thrombo-poietin (acting an megakaryocytes).

The biologic effects of growth factors (cell proliferation, differentiation and apoptosis) are mediated through activation of 3 main signal transduction pathways, namely: (1) the Janus asso-ciated kinase JAK/STAT pathway, (2) mitogen-activated protein kinase (MAPK) pathway and (3) posphoinositole-3 kinase PI-3K/AKT pathway (Chapters 6 and 8).

Signal transduction will liberate a variety of transcription factors which will largely determine the fate of hematopoietic cell. For example, NOTCH-1 and GATA-2 activate stem cell proli-feration, whereas, GATA-3 and PU-1 induce dif-ferentiation, but GATA-1 activate stem cell migra -tion into the blood. It is noteworthy, that some cytokines such as transforming growth factor beta (TGF-β) and interferon gamma (γ-interferon), can exert a negative effect on hematopoiesis and may play a role in anaplastic anemia.

Blood Counts

The normal blood counts for Egyptians at different ages is presented in (Table 25-22). How-ever, the production of normal blood cells is affected by various disorders which may be a reversible adaptive condition or a serious neoplastic disease. Practically it is best to classify these disorders into two main groups, namely: those associated with high blood counts and those with low blood counts.

High Blood Counts

1. *Neutrophilia*: This is defined as a unilineal increase of neutrophil cell count >7x10^9/L. This is observed with infections, infarcts, autoimmune and malignant disease. In infections, some increase of immature cells may be observed (shift to the left).

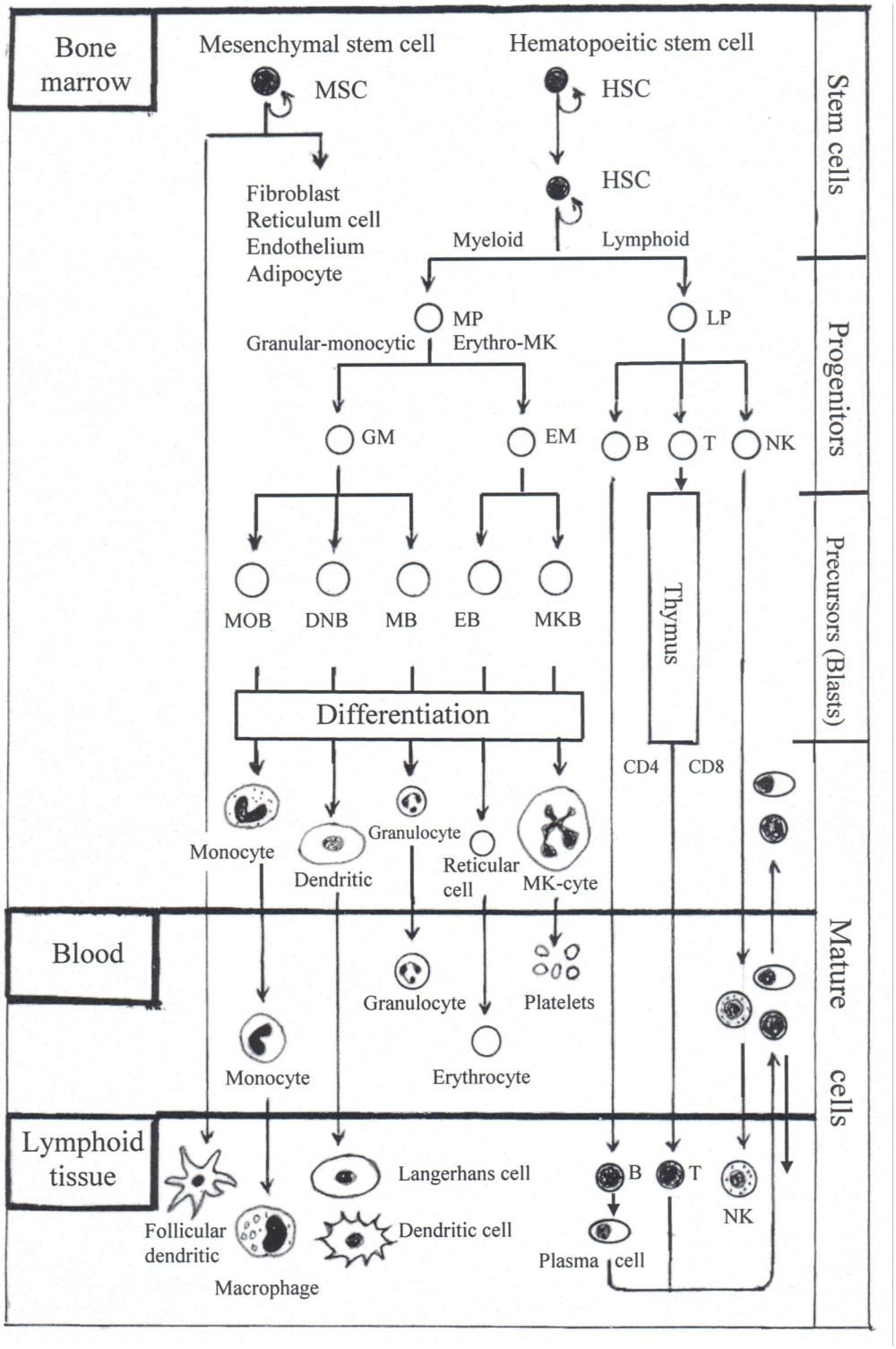

Fig 25-17 *Normal differentiation and maturation of hematopoietic cells. Abbreviations: MSC mesenchymal stem cell, HSC hematopoietic stem cell, MP myeloid progenitor, LP lymphoid progenitor GM granular monocytic, EM erythromegakaryocytic, NK natural killer, MOB monoblast, DNB dendritic blast, MB myeloblast, EB erythroblast, MKB megakaryoblast.*

Table 25-22 Complete Blood Count (CBC), Normal Values for Egyptians

Age	WBC	Neut	Lymph	Mono	Eos	Bas	RBC	Plat
			(70%)	**(17%)**	**(4%)**	**(2%)**		
1-6 days	9-29	2.3-18.8	1.4-20-3	0.27-4.9	1.2	0.58	**4.1-6.7**	**140-440**
			(60%)	**(12%)**	**(4%)**	**(2%)**		
7-30 days	5-21	0.75-9.5	1-12.6	0.1-2.5	0.84	0.42	**3.9-6.4**	**140-440**
			(75%)	**(15%)**	**(6%)**	**(2%)**		
1 m - 2 y	6-14	1.1-5.5	2-8.9	1.5	0.7	0.2	**3.8-5.4**	**140-440**
			(68%)	**(14%)**	**(6%)**	**(2%)**		
3-6 y	4-12	1.5-5.5	2-5.8	1.0	0.5	0.2	**4-5.3**	**140-440**
			(50%)	**(12%)**	**(6%)**	**(2%)**		
7-10 y	4-12	2-7.5	1.5-4	1.0	0.5	0.5	**4-5.3**	**140-440**
			(50%)	**(12%)**	**(6%)**	**(2%)**		
11-16 y	4-10.5	2-7.5	1.1-3.5	1.0	0.5	0.2	**4.2-5.6**	**140-440**
			(45%)	**(12%)**	**(6%)**	**(2%)**		
17 y	4-10.5	2-6.5	1.1-3.5	1.0	0.5	0.2	**4.2-5.6**	**140-440**
			(45%)	**(12%)**	**(6%)**	**(2%)**		
Adults	4-10.5	2-6.5	1.5-35	1.0	0.5	0.2	**4.4-5.7**	**140-440**

(EL-Saify, 2012) N.B. Absolute counts in thousands (/μL) and differential counts as percentages (%).

2. *Lymphocytosis*: This is seen in virus infections (EBV, Herpes and HIV), chronic lymphocytic leukemia and lymphoma.

3. *Monocytosis*: This is defined as monocyte counts >800/μL and is observed with hematologic disorders and lymphomas.

4. *Eosinophilia*: A high eosinophilic cell count is common with allergic, parasitic disease and Hodgkin lymphoma.

5. *Polycythemia*: This is associated with hematocrit value (HCT >60% in males and >55% in females). The cause may be primary (polycythemia vera/JAK2 mutation) or secondary to hypoxia.

6. *Essential thrombocytosis*: Platelets count >450 x10/L, seen in child birth, major hemorrhage or inflammation.

Low Blood Count

1. *Neutropenia*: This is defied as an absolute neutrophil count <1.5x10^9/L. Causes: Congenital, idiopathic, irradiation, chemotherapy and autoimmunity.

2. *Pancytopenia*: This denotes bone marrow failure with significant reduction of all cell elements of blood (Hgb<10^9/d L, neutrophils <1.5x10^9/L and platelets <100x10^9/L). Important causes are: aplastic anemia, hairy cell leukemia, hypersplenism, myelodysplasia, and bone marrow replacement (by metastases, leukemia and myelofibrosis).

3. *Anemia* is reduction in hemoglobin <12 g/dL) hematocrit (<35%) and red blood cell count (<4x1^6/μL). Causes: Blood loss by hemorrhage or hemolytic anemias), impaired production (iron deficiency, B12 and folic acid deficiency) and megaloblastic anemia.

4. *Thrombocytopenia*: It is defined as platelet counts (<150,000/μL) which is associated with increased risk of bleeding. Causes: idiopathic thrombocytopenic purpura, or secondary to bone marrow failure or hypersplenism.

Normal BM Histology

The bone marrow (BM) is the space inside bone trabeculae. It is composed of three main components, namely: hematopoietic cells, stromal cells and extracellular matrix (ECM).

The *hematopoietic cells* include: hematopoietic stem cells, myeloid series, erythroid cells, megakar yocytes and lymphocytes, Their relative frequency in marrow and their immunophenotypic characterization is presented in (Table 25-23 and Table 25-24). These cell types, normally, have a characteristic distribution pattern in marrow. Thus, erythroid cells and megakaryocytes are perisi-

Table 25-23 Relative Frequency of Normal Adult Bone Marrow Cells

Fat cells	50 ± 15%
Myeloid to erythroid ratio	1:1 to 3:1
Myeloid series	40% to 65%
Erythroid series	10% to 20%
Megakaryocytes	2-5/high power field
Plasma cells	< 3% of nucleated cells
Lymphocytes	< 20% of nucleated cells
T-cells in BM biopsy	22%
T-cells in BM smears	46%

Table 25-24 Immunophenotyping of Bone Marrow Cells

Cell type	antibody
Blast cell	CD34
Myeloid cell	CD117, myeloperoxidase
Erythroid cell	HbA, Glycophorin A
Megakarocyte	CD41, CD61, Factor VIII
Lymphoid precursor	TdT
T-lymphocyte	CD3, CD4, CD8
Natural killer (NK)	CD56
B-lymphocyte	CD20, CD10, Kappa, Lambda
Reed-Sternberg cell	CD30
Normal plasma cell	CD38, CD138, CD19+ CD56-
Malignant plasma cell	CD38, CD138, CD19- CD56+
Langerhans cell	CD207, S100, CD1a
Macrophage	CD163, CD68, Lysozyme
Follicular dendritic	CD21
Fibroblast	Actin
Mast cell	Tryptase

nusoidal, whereas, granular cell precursors are paratrabecular in location, with an empty zone separating the cells from bone trabeculae (Fig 25-18).

Stromal cells include: Sinusoids (endothelial cells and adventitial mesenchymal cell), fat cells, fibroblasts, osteoblasts, osteoclasts and macrophages. Stromal cells secrete several growth factors which control stem cells and their derivatives.

The extracellular matrix is also secreted by stromal cells and includes: collagen (Type I and III), elastic fibers, glycoproteins (fibronectin and thrombospondin), as well as, hyaluronic acid and chondroitin derivatives.

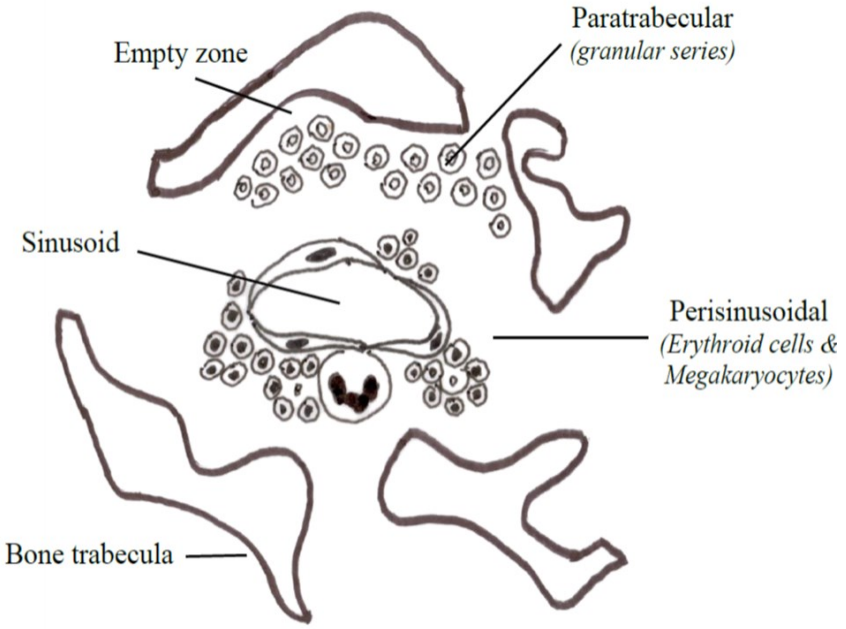

Fig. 25-18 Histologic structure of normal bone marrow. Stromal cells include sinusoids (endothelial and adventitial cells), fibroblasts, and macrophages. The normal distribution pattern of granular cell precursors are para-trabecular, whereas, erythroid cells and megakaryocytes are perisinusoidal

Bone Marrow Biopsy

Tissue core biopsy from the iliac crest allows preparation of tissue sections, as well as, Giemsa-stained smears for evaluation. The combined study of both preparations is essential since they complement each other. Thus, tissue biopsy is ideal to assess cellularity, myelofibrosis and focal lesions, whereas, smears are superior to study cytomorphologic details. The evaluation of bone marrow biopsy must be conducted in a systematic way (Table 25-25) with coverage of the following ten items:

1. *Adequacy of sample*. The tissue core must be at least 15 mm long and should contain a minimum of cortical bone.

2. *Cellularity*. This denotes the proportion of hematopoietic cells relative to fat cells. Bone marrow cellularity decreases with age, hence cellularity can be roughly obtain ed by subtracting patient age from 100 (100-age = cellularity).

3. *Topographic distribution*. An abnormal localization of immature precursors (ALIP) denotes dysplasia or malignancy.

4. *Predominance of any cell lineage*. This is determined by the myeloid erythroid (M:E) ratio, which is increased (>3) in myeloid leukemia and decreased (<1) in polycythemia.

5. *Cellular dysplasia*. Cytomorphologic features of atypia in myeloid and erythroid cells (Fig 25-21) is indicative of myelodysplastic syndromes.

6. *Blast count*. (assisted by CD34 immuno-staining). Counts (5-20%) indicate preleukemia (myelodysplastic syndrome and myeloproliferative tumors). But values (>20%) confirms the diagnosis of acute leukemias (both myeloid and lymphoblastic type). However, for the diagnosis of chronic lymphocytic leukemia (CLL) a count of mature lymphocytes (>30%) is needed to make the diagnosis.

7. *Stroma*. Special stains (silver Gomori stain) for reticulin and (trichrome) for collagen are done to confirm early or late stages of myelofibrosis.

8. *Focal lesions*. These include metastases, lymphomas, histiocytosis and granulomas.

9. *Bone trabeculae*. There are examined for evidence of osteoporosis (senile or cortisone

Table 25-25 Systematic Examination of Bone Marrow Biopsy

1. Adequacy of sample
2. Cellularity (fat : cell ratio)
3. Topographic distribution of cell lineages
4. Predominance of any cell lineage (Myeloid: Erythroid ratio)
5. Cellular dysplasia
6. Blast count (CD34+ %)
7. Stroma (reticulin and collagen)
8. Focal lesions: metastases, lymphomas or granulomas
9. Bone trabeculae (osteoporosis or osteosclerosis)
10. Histochemistry and Immunostains

effect) and asteosclerosis (sclerotic metastases and late stages of myelofibrosis).

10. *Immunohistology* or flow cytophotometry, for confirmatory phenotyping (Table 25-24).

In addition, (cytogenetic studies) for chromosomal changes, and (molecular genetic studies) by FISH and PCR (for mutations and fused genes) are required for precise WHO typing and prognostic risk assessment.

MYELOID NEOPLASMS

The WHO classified myeloid neoplasms into five main groups with characteristic clinical and genetic features, namely: myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), myeloid and lymphoid neoplasms with eosinophilia (MLNE) and acute myeloid leukemia (AML). The first 4 aleukemic members of myeloid neoplasms have a common feature of low blast count (<20%), but, differ from each other by their molecular genetics, blood picture, frequency of organomegaly (splenomegaly and hepatomegaly) and the risk of blast crisis to AML (Fig 25-19).

Myelodysplastic Syndromes (MDS)

These are clonal myeloid disorders characterized by ineffective hematopoiesis (hypercellular marrow associated with paradoxical blood cytopenias and dysplastic cell cytomorphology). This paradox, of cellular marrow and cytopenia, is explained by the development of apoptosis in the proliferating dysplastic bone marrow progenitor cells (Fig 25-20).

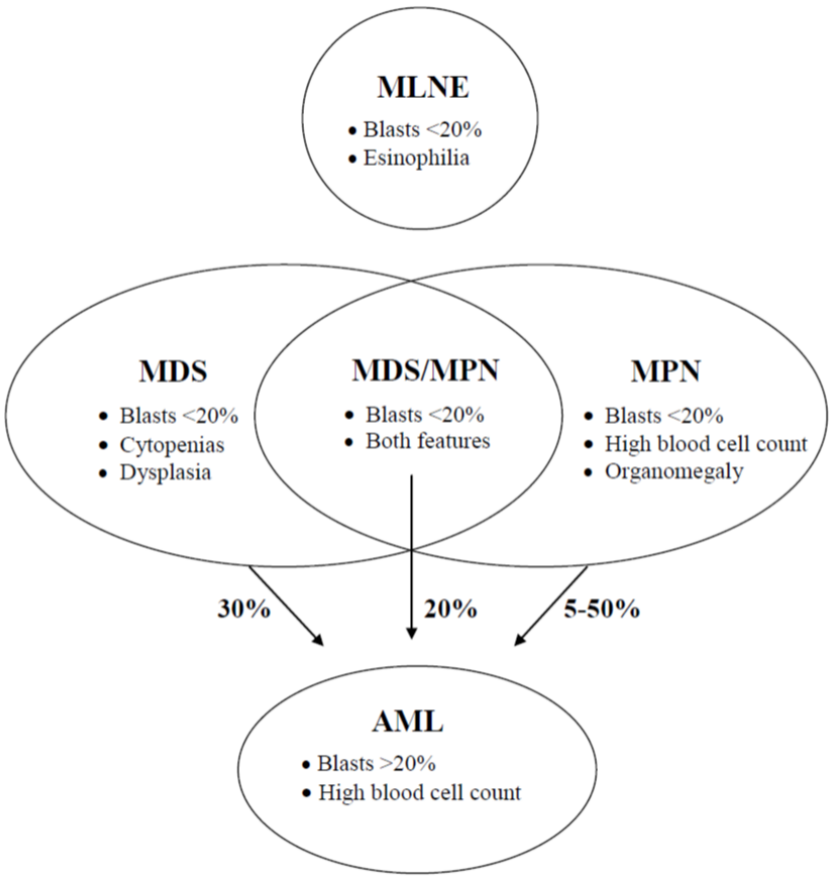

Fig 25-19 *Myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN) and Acute myeloid leukemia (AML) inter-relations. MLNE refers to myeloid and lymphoid neoplasm with eosinophilia and abnormalities of PDGFRH, PDGFRB, or FGFR1. MLNE is not associated with leukemic transformation. The blast crisis of MPN is low (5%), intermediate in myelofibrosis and high (50%) in chronic myeloid leukemia. The blast crisis in CML is AML in 70% of cases and B-lymphoblastic in 30%. (Swerdlow et al, 2008/ Rodgers and Young, 2010).*

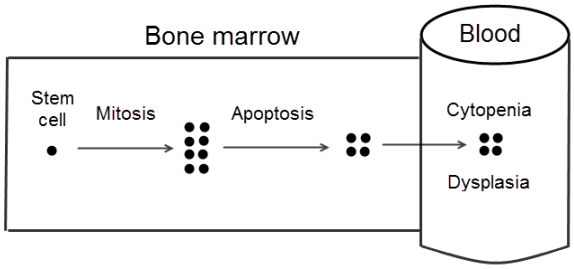

Fig 25-20 *The pathogenesis of myelodysplastic syndromes. The paradox of bone marrow hypercellularity associated with cytopenia in blood is explained by cellular proliferation is followed by cell loss through apoptosis. This ineffective hematopoiesis is also characterized by cytomorphologic dysplastic features in the produced cells.*

Dysplastic changes affect all types of myeloid cells (granular, erythroid and megakaryocytic) and are more evident in bone marrow smear preparations (Fig 25-21) The WHO classification recognizes 6 subgroups based on the lineage involved and the specific cytogenetic abnormality (Table 25-26). Myelodysplastic syndromes will ultimately terminate into (AML) in about 30% cases, hence, they may be considered a precursor or preleukemic disorders.

To summarize, the cardinal features of MDS) are: (1) ineffective hematopoiesis (cellular marrow with cytopenia), (2) dysplasia in all myeloid cells (3) Absence of organomegaly, and (4) the cytogenetic basis is chromosomal deletions or duplication, (monosomy 7, trisomy 8 and trisomy 21) but translocations are rare.

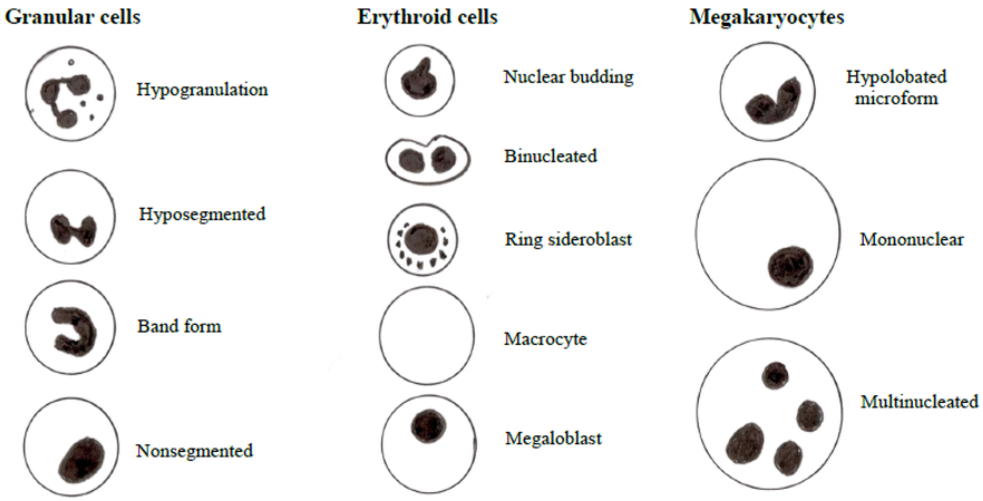

Fig 25-21 *Myelodysplastic syndrome, atypical cytomorphological changes in hematopoietic cells in peripheral blood and bone marrow smears.*

Table 25-26 WHO Classification of Myelodysplastic Syndromes

Refractory cytopenia with unilineage dysplasia (RCUD)
Refractory anemia (RA)
Refractory neutropenia (RN)
Refractory thrombocytopenia (RT)
Refractory anemia with ring sideroblasts (RARS)
Refractory cytopenia with multilineage dysplasia (RCMD)
Refractory anemia with excess blasts (RAEB)
Myelodysplastic syndrome with isolated del (5q)
Myelodysplastic syndrome, unclassifiable (MDS,U)
Childhood myelodysplastic syndrome
Provisional entity: Refractory cytopenia of childhood (RCC)

(Swerdlew et al, 2008)

Myeloproliferative Neoplasms (MPN)

These are defined as clonal myeloid neoplasms characterized by effective hematopoiesis, hence, the hypercellular marrow is associated with increased cell counts in peripheral blood, without any dysplastic cytomorphologic features. The neoplasms affect mainly adults, and are commonly associated with organomegaly and variable risk (5-50%) of acute leukemia crisis.

The genetic basis of (MPN) is mainly chromosomal translocation, leading to the formation of fusion genes with oncogenic products. The WHO classified (MPNs) according to these genetic findings into eight subtypes (Table 25-27).

1. *Chronic myeloid leukemia* (CML). This is invariably associated with t(9;22) creating the *Philadelphia chromosome* with BCR-ABL-1 fusion gene which codes for an oncogenic tyrosine kinase protein product. The disease passes through 3 stages as determined by blast count in bone marrow smears, namely: (a) *chronic phase*, count 5-10%, (b) *accelerated phase*, count 10-19% and (c) *blast crisis*, count >20%, which may be AML phenotype(70%) or ALL phenotype (a phenomenon of transdifferentiation).

2. *Chronic neutrophilic leukemia (CNL).* Characterized by sustained peripheral blood neutrophilia, negative Philadelphia chromosome and BCR-ABL -1 fusion gene, and bone marrow hypercellularity.

3. *Polycythemia vera (PV).* Characterized by increase of red blood cell production, hemoglobin >18.5 g/DL in men, >16.5 g/DL in women, and or JAK2 mutation.

4. *Primary myelofibrosis (chronic idiopathic myelofibrosis CIMF).* This is a clonal myeloproliferative neoplasm, a result of JAK2 mutation, characterized by reactive deposition of reticulin in bone marrow in early stage and fibrosis, as well as, osteosclerosis in the late stages. Platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β) produced by megakaryocytes play a key etiologic role (Kuter et al, 2007). Bone marrow biopsy reveals atypical megakaryocytes and erythroid cell proliferation in early stage and fibrosis later with blast court <20% (P25-42). The disease is associated with cytopenia in peripheral blood and extramedullary hematopoiesis in the spleen The main differential diagnosis is from secondary myelofibrosis which is related to a known cause (inflammatory, neoplastic or therapy-induced).

5. *Essential thrombocythemia (ET)* is defined as proliferation of megakaryocytic cell lineage, with increase of platelets (thrombocytosis) >450x10^9/L and/or JAK2 mutation.

6. *Chronic eosinophilic leukemia (CEL).* This is characterized by proliferation of eosinophils and their precursors with negative Philadelphia chromosome and BCR-ABL-1 fusion gen. The eosinophils count is >1.5x10^9/L and is persisting for at least 6 months.

7. *Mast cell disorders*. Mast cells originate from bone marrow myeloid progenitor cell, migrate in immature form to peripheral tissues where they mature in situ. A common location is the upper dermis with perivascular distribution. Histologically, they appear as ovoid small cells with cytoplasmic granules. The cells are immunoreactive to tryptase, and the granules are more apparent with Giemsa or toluidine blue stains.

Mast cells secrete several products (histamine, heparin and prostaglandins), hence they play a key role in various pathologic processes such as (a) IgE- mediated allergic reaction, (b) autoimmune diseases and (c) ultraviolet-induced cutaneous malignancies.

Table 25-27 WHO Classification of Myeloproliferative neoplasms (MPN) and their associated Mutation or Rearrangement of Tyrosine Kinase Genes

Neoplasm	Gene
Chronic myelogenous leukemia, (CML)	BCR-ABL1
Chronic neutrophilic leukemia (CNL)	-
Polycythemia vera (PV)	JAK2
Primary myelofibrosis (PMF)	JAK2, MPL
Essential thrombocythemia (ET)	JAK2, MPL
Chronic eosinophilic leukemia, NOS (CEL, NOS)	PDGFR, FGF
Mastocytosis	KIT
Myeloproliferative neoplasm, unclassifiable (MPU,U)	-

(Swerdlow et al, 2008)

Clonal proliferation of mast cells (mastocytosis) may present clinically in one of 3 forms: (a) *urticarial pigmentosa*, a cutaneous localized favorable disease, (b) *systemic mastocytasis* with multiorgan affection and unfavorable prognosis and (c) *mast cell leukemia*, a rare unfavorable hematologic malignancy.

8. *Unclassified myeloproliferative neoplasms (MPNU).*

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN)

The WHO classified this class of myeloid neoplasms into 4 subtypes (Table 25-28). This group is characterized by an overlap of both features of MDS and MPN. An example is *chronic myelomonocytic leukemia* (CMML). There is ineffective erythropoiesis and megakaryopoiesis with dysplasia, but, granutopoiesis is effective with leucocytosis lacking dysplatic features.

LEUKEMIAS

Definition

Leukemia is defined as a clonal proliferation of white blood cells, with their accumulation in bone marrow and blood to a high level resulting in serious complications. The two main hazards are: (1) *bone marrow failure* (infections and hemorrhage), and (2) *vital organ failure* due to infiltration of brain or liver by leukemic cells. Acute leukemias are rapidly fatal if left untreated.

Incidence

In US SEER Registry (Ries, 2007), the incidence per 100,000 is 1.3 for acute lymphoblastic leukemia (ALL), 4.3 for chronic lymphocytic leukemia (CLL), 3.4 for acute myeloid leukemia (AML) and 1.8 for chronic myeloid leukemia (CML).

Two age peaks are observed in leukemia incidence. The first is pediatric (1-4 years) related to ALL, and the other adult peak (over 60 years) related to chronic leukemias.

Etiology

The cause of leukemia is unknown in most cases (*idiopathic or primary leukemia),* but, it may be related to exposure to a known leukemogenic agent such as radiation or chemotherapy (*secondary leukemia*). The following are five recognized etiologic factors for leukemia:

1. *Radiation.* This may be radiation in utero for pediatric leukemia, postradiotherapy in adults and survivors of atomic explosions.

2. *Chemicals*. This includes exposure to benzene in rubber industry, tobacco smoking, and chemotherapy especially alkylating agents.

3. *Viral infections*. This includes EBV infection in ALL and HTLV-1 infection in adult T-cell leukemia in Japan.

4. *Hereditary syndromes*. There is usually 4 times increased risk to develop leukemia. The etiology may be related to congenital immunodeficiency (Wiscott-Aldrich syndrome), a defect in DNA repair (Fanconi syndrome, bloom syndrome and ataxia telangiectasia), and other hereditary syndromes as Down syndrome, Klinefelter syndrome and neurofibromatosis.

5. *Preleukemic hematologic disorders* as myelodysplastic syndromes and myeloproliferative neoplasms which are precursors of ALL.

Pathogenesis

Leukemias arise from malignant transformation of hematopoietic stem cells or early lineage committed progenitor cells. *In acute leukemia,* progeny cells proliferate but fail to differentiate and blast cells replace normal hematopoietic cells which become markedly reduced in number (but cyto-

Table 25-28 WHO Classification of Meyelodysplastic/Myeloproliferative Neoplasms (MDS/MPN)

Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia, BCR-ABL1 negative (aCML)
Juvenile myelomoncytic leukemia (JMML)
Myelodysplastic/Myeloproliferative neoplasm, unclassifiable (MDS/MPN,U)
Provisional entity: Refractory anemia with ring sideroblasts and thrombocytosis (RAPS-T)

(Swerdlow et al, 2008)

morphology remains normal contrary to myelodysplastic syndrome). However, in *chronic leukemias* precursor cells proliferate and also differentiate, hence, blast count is <20% and normal blood cells >80% and the clinical course is prolonged and uncomplicated.

Each leukemia subtype has its own genetic lesion (rearrangement or mutation) which determines its entity and forms the basis of WHO classification of leukemias (Table 25-29).

Despite the marked genetic diversity among leukemias, a unified *molecular oncogenesis* model is generally operable. Thus, chromosomal translocation, which is the main primary event, will result in activation of a proto-oncoge by one of two mechanisms, namely: (1) *fusion gene* formation with oncogenic potential (e.g. BCR-ABL-1 with tyrosine kinase activity enhancing cell proliferation, or PML-PARA fusion gene which causes arrest of cell maturation, and (2) *gene activation* at the translocation site by an immunoglobulin enhancer locus (e.g. t(14;18) with bcl-2 expression and t(12;21) in pediatric AML).

It is noteworthy that additional mutations are required in case of progression of chronic leukemias to acute types (blast crisis), as well as, in the development of the rare biphenotypic leukemias (transdifferentiation among myeloid and lymphoid lineages). Other mechanisms of leukemia genesis occur in chronic lymphocytic leukemia (e.g. mutation of B-cell receptor (CD79) or Ig gene).

Classification

The main classification of common leukemias is into 4 types, lymphocytic and myeloid, and each is divided into acute and chronic. Acute leukemias are common in children, whereas, chronic leukemias are common in adults. The relative frequency of these subtypes is presented in (Table 25-30). Acute myeloid leukemia (AML) is subdassified by WHO according to specific genetic abnormality or its relation to previous therapy or syndromes whether myelodysplastic or hereditary (Table 25-31). Acute lymphocytic leukemia (ALL) is subclassified according to phenotype into B, T, and Burkitt features. The main differences between AML and ALL is summarized in (Table 25-32).

Diagnosis

A multidisciplinary approach is necessary for the accurate diagnosis of leukemias, based on morphology, immunophenotyping, cytogenetic and molecular genetic studies.

1. Blast count

This is facilitated by immunostaining of blasts with CD34. A blast count in bone marrow smears (>20%) will establish the diagnosis of acute leukemias (both myeloid and lymphoblastic). In chronic myeloid leukemia, blast count helps to stage the disease into chronic phase (count 5-9%), accelerated phase (count 10-19%) and blast crisis (count > 20%). Conversely, in chronic lymphocytic leukemia, the diagnosis is established by the counts of mature lymphocytes (absolute lymphocytosis in blood >$5x10^9$/L or counts of lymphocytes >30% in bone marrow smears).

2. Cytomorphology

This is best studied by Giemsa-stained bone marrow smears (P25-43). Acute myeloid leukemia (ALL) is classified into 8 morphologic subtypes by the French-American-British (FAB) system (Table

Table 25-29 The Genetic Basis of Leukemogenesis

Leukemia type	Cytogenetics	Molecular genetics
Lymphocytic Pediatric (ALL)	t(12;21)	TEL-AML1 fusion, IgH rearrangement
Adult (ALL)	t(9;22) 25%	BCR-ABL-1 fusion
Chronic lymphocytic (CLL)	del 13q, t (14;18)	CD79, Bcl-2, IgH rearrangement, ZAP-70 expression
Myeloid Pediatric AML	t(8;21), t(15;17), inv(16)	CRFIoc, C-kit, FLT-3
Promyelocytic (PML)	del 5 and 7	
Promyelocytic (PML)	t(15;17)	PML-PARA fusion
Chronic myeloid (CML)	t(9;22) 100%	BCR-ABL-1 fusion (Philadelphia chromosome)

(DeVita et al, 2011)

Table 25-30 Relative Frequency of Leukemias, US SEER data, 42, 678 patients 1988-2001

Type	Frequency (%)	Relative Survival (%)	
		5-year	10-year
Lymphocytic leukemia	(50.5)		
ALL Pediatric (<19y)	10.4	80	77
ALL Adults (>20y)	5.4	62	60
Chronic lymphocytic	30.8	75	54
Other lymphocytic leukemia*	3.9	-	-
Myeloid leukemia	(43.9)		
Acute myeloid leukemia	26.8	17	16
Acute monocytic leukemia	1.7	22	21
Chronic myeloid leukemia	14.1	38	22
Other myeloid leukemias	1.2	-	
Other leukemias	6.0	-	

(Ries, 2007) * Includes: hairy cell leukemia, T-cell leukemia, Burkitt and plasma cell leukemias.

25-33). Cell population of AML can be predominantly eosinophilic, basophilic, monocytic erthrocytic, megakaryocytic, neutrophils or a combination of these cells. Some cases may express *lineage infidelity* by expressing two paradoxical markers (biphenotypic B and T, or lymphocytic and myeloid). These rare complex neoplasms are called *leukemias of ambiguous lineage*.

3. Immunophenotyping

The three cell lineages of acute leukemias develop from a common stem cell through a process of differentiation by acquiring specific cell markers (Fig 25-22). Immunohistochemistry is usually adopted for phenotyping of leukemias, using three different methods according to the sample (immunocytology, immunohistology and immunoflowcytometry). The latter is the most rapid and accurate method.

Stem cells are positive for CD34. Lymphoblasts are positive for TdT, but myeloblasts are negative. T- phenotype is confirmed by CD3 and B-phenotype by CD20 and CD19, whereas myeloid series are reactive to CD117. The markers CD13 and CD33 are usually used in flow cytometry to confirm the myeloid lineage.

4. Cytochemistry

Cytochemistry was used in the past for leukemia phenotyping: (1) myeloperoxidase (MPO) and Sudan black B (SBB) for myeloid series, (2) nonspecific esterase for myelomonocytic leukemia, (3) PAS for acute lymphoblastic leukemia and erythroid leukemia, (4) leucocyte alkaline phosphatase (LAP) for chronic myeloid leukemia and (5) tartrate resistant acid phosphatase (TRAP) for

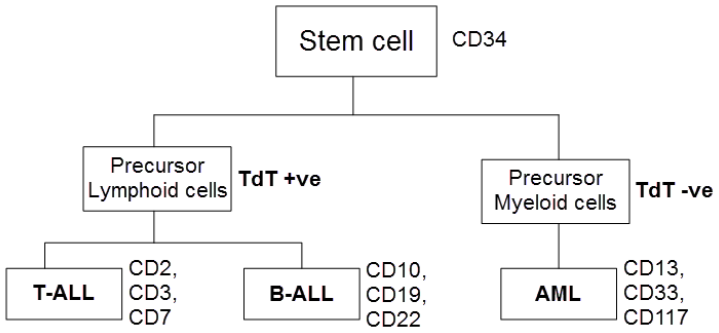

Fig 25-22 *The development of three main types of acute leukemias from marrow stem cell and their diagnostic phenotype. Three different markers, are needed to characterize each type of acute leukemia (Hoffbrand and Moss, 2011).*

Table 25-31 WHO Classification of Acute Myeloid Leukemia and Related Myeloid neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); RUNX1-RUNXIT1
AML with inv(16)(p13. 1q22) or t(16;16)(p13. 1;q22); CBFB-MYH11
APL with t(15;17)(q22;q12); PML-RARA
AML with t(9;11)(p22;q23); MLLT3-MLL
AML with t(6;9)(p23;q34); DEK-NUP214
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute mononblastic/monocytic leukemia
Acute erythroid leukemias
Pure erythroid leukemia
Erythroleukemia, erythroid/myeloid
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma (chloroma)
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasms

hairy cell leukemia. These methods at present, have been replaced by immunostains.

5. Genetic Analysis

Both cytogenetics (chromosomal abnormalities) and molecular genetics (gene abnormalities by FISH or PCR methods) are essential in leukemias for 4 main reasons: (1) to discover a specific genetic alteration needed for precise typing by WHO classification, (2) to detect a fusion gene abnormality that may guide targeted therapy (e.g. antityrosine kinase therapy for BCR-ABL-1 fusion and retinoid derivatives for PML-PARA fusion, in CML and PML leukemias respec-tively, (3) to detect any genetic change associated with unfavorable prognosis (high-risk factors), and (4) to detect minimal residual disease (MRD) after therapy.

Prognosis

Acute lymphoblastic leukemia (ALL) is a model for advances accomplished in the therapeutic outcome of pediatric oncology over the past 4 decades. It has evolved from being an incurable disease in the 1960s to a curable one (5-year disease free survival approaching 80%), thanks to intensive multiagent chemotherapy. Advances were also made in other leukemias with the use of targeted therapy, especially antityrosine kinase (Glevec) in CML and retinoid acid derivatives (ATRA) in premyelocytic leukemia (PML).

The largest series reporting short and long-term survival of leukemias came from the US-SEER Registry (Ries, 2007), presented in (Table 25 -30). The various genetic and clinical high-risk prognostic factors are outlined in (Table 25-34).

Table 25-32 Comparison of Acute Myeloid Leukemia (AML) and acute Lymphoblastic Leukemia (ALL)

Feature	AML	ALL
Percent of leukemias	27%	16%
Age group	Adults	Pediatric
Disease entity	Multiple	Single
Cell size	Moderate	Small
Chromatin	Coarse	Fine
Nucleoli	Prominent (1-4)	Indistinct
Cytoplasm	Moderate	Minimal
Cytoplasmic granules	+	-
Auer rods	+ (60%)	-
Immunostains	TdT-, CD117+ Myeloperoxidase	B(85%) CD19+, TdTt, CD20+ t(15%) CD3+
Cytogenetics	t(8;21), Inv. (16)t(1;16), t(15,17) del. 5 and 7	t(12;21), t(4;11), t(1;19)
5-year Survival	20%	80%

Table 25-33 The French-American-British (FAB) Cytomorphologic Classification of Acute Myeloid Leukemia (AML)

M0	Undifferentiated
M1	Myeloblastic with no differentiation
M2	Myeloblastic with differentiation
M3	Promyelocytic (APL) M3v microgranular variant
M4	Myelomonocytic M4E0 with eosinophilia
M5	Monocytic
M6	Erythroleukemia
M7	Megakaryoblastic (AMKL)

N.B. M2, M3 and M4E0 are favorable subtypes.

Table 25-34 High Risk Prognostic Factors in Leukemias

Leukemia type	Cytogenetics	Molecular genetics
ALL	t(8;22), t(4;11) t(1,19), hypodiphloid	Complex rearrangement (>3) FLT3 internal tandom repeat
CLL	Trisomy 129, del (119), del (139)	NF-κB, ATM unmutated EgvH
AML*	del(17p) complex karyotyping del 5, del 7, t (6;9) t(6;11), t(11;19)	TP53 FLT3
CML**	-	-

*Other unfavorable prognostic factors for AML are age >6 years and blast count >20% after the first course.** The main high-risk factors for CML are high leucocytic count (>100,000 per cu ml), massive splenomegaly constitutional symptoms, accelerated phase or blast crisis. (Rodgers and Youring, 2010, Hoff brand and Moss, 2011, Abraham et al, 2010).

BONE MARROW INVOLVEMENT BY LYMPHOMAS

Incidence

The overall incidence of bone marrow involvement by lymphomas at initial presentation is about 45% (EL-Bolkainy et al, 2008), being highest in follicular lymphoma (65%), intermediate in large cell lymphoma (30%) and lowest in Hodgkin lymphoma (10% in classic HL and only 1% in lymphocyte predominance).

Patterns

Five histologic patterns were described (Arber and George, 2005), namely, paratrabecular, nodular, diffuse, interstitial and mixed (Fig 25-23). In the paratrabecular pattern, the neoplastic lymphocytes obliterate the empty zone around the trabeculae and come in direct contact with bone (P 25-44). Immunostains (CD20) may play a confirmatory role, especially if the lymphoma is known to be a B-phenotype. Bone marrow involvement by lymphomas is considered stage IV and carries an unfavorable prognosis. Moreover the diffuse pattern with small lymphocytic lymphoma (SLL/CLL) is considered a high-risk prognostic factor.

Differential Diagnosis

The main differential diagnosis of lymphoma infiltrate in bone marrow biopsies is the reactive lymphoid aggregates which are usually encountered in about 30% of elderly individuals. The following are 6 helpful diagnostic features of these benign lymphoid aggregates: (1) perivascular non-trabecular distribution (2) usually small in size and few (<3), (3) well-circumscribed, (4) may show germinal center (5) biphenotypic B and T, the latter predominates, and (6) polyclonal.

THE SPLEEN

Structure

The spleen is composed of two distinct regions: The red pulp (75%) and white pulp (25%) also known as malpighian corpuscles (Fig 25-24).

The red pulp includes two components namely: splenic sinuses and the cords of Billroth. Sinuses have an incomplete lining of special endothelium (Littoral cells) with one micron gaps in between to allow blood cells to pass through. The splenic cords are rich in fibroblasts, smooth muscle and histiocytes.

The white pulp is a periarteriolar collection of lymphocytes, 1-2 mm in size, with an inner zone of T-lymphocytes and outer zones of B-lymphocytes, arranged in 3 distinct areas: the germinal center, mantle and marginal zone (Fig 25-24). Perifollicular tissue is rich in macrophages and dendritic cells.

The spleen has a closed and open blood circu-

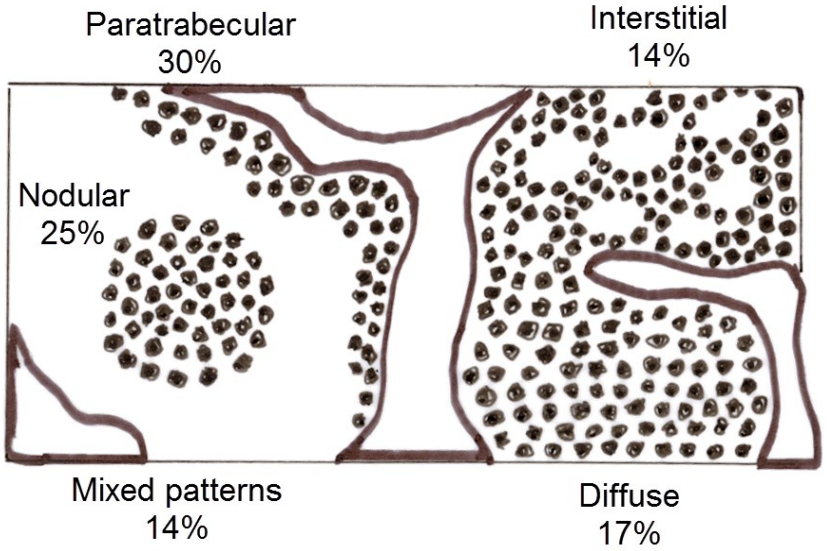

Fig 25-23 *Patterns of bone marrow involvement by non-Hodgkin lymphoma (El-Bolkainy et al, 2008/Arber and George, 2005).*

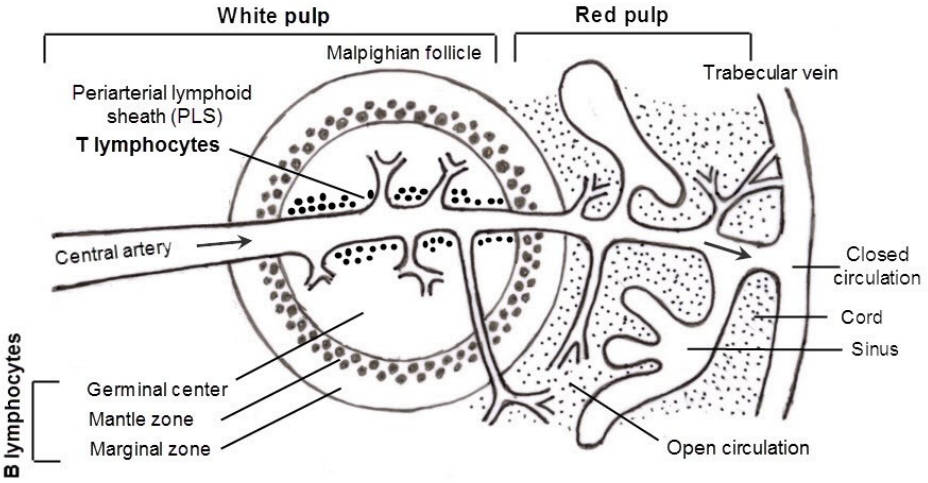

Fig 25-24 Histologic structure of the spleen. It is composed of two compartments, the red pulp and white pulp, two circulations, open and closed circulations, and two functions, phagocytic and immune functions. The red pulp is composed of sinuses and cords, lined by an incomplete layer of endothelium (phagocytic littoral cells). The white pulp is composed of lymphocytes with central arteriole. In the lymph follicle, T-cells are centrally located (periarteriolar), whereas, B-cells are peripheral (mantle and marginal zones).

lations. In the *closed circulation* (rapid, 1-2 min), blood passes directly from the arterial side through capillaries to the venous side (Fig 25-24). Conversely, the majority of blood passes through the *open circulation* (slow, 30-60 min), blood including cellular components passes through the interendothelial spaces of the sinuses, enter splenic cord, then exit back.

Function

1. *Filter function*. The spleen control red cell integrity by removing aged or damaged cells. Moreover, it eliminates nuclear remnants, siderotic granules and bacteria through phagocytosis in splenic cords. The flexibility of aged or damaged red cells is impaired, hence, they can enter the splenic cord, but cannot leave it, hence are trapped and become phagocytosed by macrophages (Fig 25-25).

Normally, only 5% of red cells and 30% of platelets are present in the spleen, but, in cases of congestive splenomegaly, up to 40% of red cells and 90% of platelets are sequestrated in the spleen mainly in the open circulation of red pulp. The cells are subjected to phagocytosis in splenic cords (hypersplenism), resulting in serious cytopenia. Splenectomy will correct this disorder and restore the normal blood picture.

2. *Immunologic function*. Macrophages and dendritic cells in the marginal zone initiates an immune response by presenting antigens to T and B-lymphocytes to start an adaptive immune response. This represents an important defense against infections, particularly encapsulated bacteria (Staph pneumonia, Hemophylus influenza, and Neisseria meningitides), hence the susceptibility of patients after splenectomy to infection by these organisms.

3. *Hematopoietic function*. The spleen undergoes a transient period of hematopoiesis during fetal life. In adults, extramedullary hematopoiesis may occur

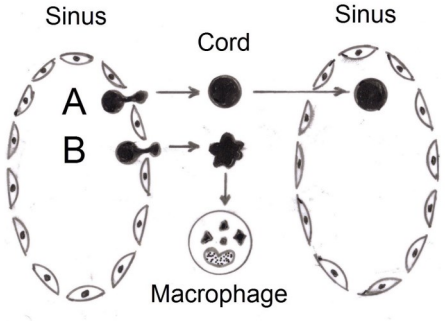

Fig 25-25 *The ingenious filter mechanism of red pulp to select and eliminate damaged blood cells. The space inbetween endothelial cells is only one micron, blood cells have to deform and squeeze to pass through. A. A viable cells can enter and exit the sinus, but, B. A senile or damaged blood cell can enter, but, get trapped and phagocytosed in the cord.*

in case of bone marrow failure. Blood cell formation in the spleen may result either from reactivation of dormant stem cells in the spleen or homing of hematopoietic stem cells from bone marrow to spleen.

Splenomegaly

Etiology

The spleen may be enlarged in a wide range of conditions (Table 25-35). These vary from simple developmental disorders (e.g. cysts and hamartomas), infections, portal hypertension, systemic diseases, hemolytic anemias, to neoplastic disease (both benign and malignant). It is noteworthy that the spleen, in contradistinction to the liver is a rare site of metastases (unfavorable soil theory).

Pathology

Splenomegaly is best classified on the basis of distribution pattern of the lesion in the spleen, particularly in relation to the red and white pulps (Table 25-36). This topographic classification is helpful in reaching a correct pathologic diagnosis by correlating gross and microscopic features. According, lesions causing splenomegaly are classified into three main groups:

1. *Red pulp involvement*: The spleen appears diffusely dark red in color with attenuated or abolished white pulp. Common examples are: (a) chronic venous congestion (P 25-45), hemolytic anemias (P 25-46 and P 25-47), myelodysplasia (P 25-48) and chronic leukemias (P 25-49 and P 25-50).

2. *White pulp involvement (Miliary pattern)*: Examples are: (a) chronic lymphocytic leukemia (P 25-51) and marginal zone lymphoma (P 25-52).

3. *Focal lesions*: These appear as localized lesions, unrelated to the white or red pulp. Examples include benign vascular tumors (P 25-53 and P 25-54) and lymphomas, such as Hodgkin lymphoma (P 25-55) and diffuse large cell non Hodgkin lymphoma (P 25-56).

Table 25-35 Etiological Classification of Splenomegaly

Infections
Infectious mononucleosis
Cytomegalovirus
Typhoid
Malaria
Leishmaniasis
Brucellosis
Schistosomiasis
Echinococcosis
Vascular
Cirrhosis
Portal or splenic thrombosis
Rt sided heart failure
Splenic infarcts
Autoimmune
Lupus erythematosis
Rheumatoid
Sarcoidosis
Primary amyloidosis
Storage diseases
Gaucher
Nieman-Pick
Hemolytic anemia
Spherocytosis
Autoimmune anemias
Thalassemia
Sickle cell anemia
Neoplastic
Leukemia / Lymphoma
Polycythemia vera
Systemic mastocytosis
Vascular and stromal tumors

Table 25-36 Pathological Classification of Splenomegaly

Gross pattern	Non-neoplastic	Neoplastic
Red pulp involvement (Diffuse dark red)	Congestion Hemolytic anemia Extramedullary hematopoiesis Storage disease Hemophagocytic syndrome Amyloidosis (Lardaceous spleen) Castleman disease (plasma cell type)	Leukemias (except CLL) Hepatosplenic T-cell lymphoma Myeloid metaplasia Peripheral T-cell lymphoma
White pulp involvement (Miliary pattern, 3-5 mm)	Reactive follicular hyperplasia Marginal zone hyperplasia Miliary tuberculosis Amyloidosis (sago spleen) Castleman (hyaline vascular)	Small lymphocytic lymphoma /CLL Marginal zone lymphoma Follicular lymphoma Hodgkin lymphocyte predominance Systemic mastocytosis
Focal involvement (nodular whitish mass)	Cysts (hydatid, mesothelial) Infarcts Hamartoma	Classic Hodgkin lymphoma Diffuse large B-cell lymphoma Vallcular tumors Inflammatory pseudotumor Follicular dendritic sarcoma Metastases

(Jaffe et al, 2011)

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