CHAPTER EIGHTEEN

HEMATOLOGICAL MALIGNANCIES

Learning objectives

At the end of this chapter, the student shall be able to:

- Describe the classification of leukemia
- Explain the diagnostic methodologies of leukemia
- Describe myelodysplastic syndrome
- Define malignant lymphoma
- Characterize multiple myeloma
- Describe myeloproliferative disorders

18.1. Leukemia

- ✓ The leukemias are a group of disorders characterized by the accumulation of abnormal white cells in the bone marrow.
- ✓ These abnormal cells may cause bone marrow failure, a raised circulating white cell count and infiltrate organs.
- ✓ Thus common but not essential features include abnormal white cells in the peripheral blood, a raise total white cell count, evidence of bone marrow failure (i.e. anemia, neutropenia, thrombocytopenia) in the acute leukemias and involvement of other organs (e.g. liver, spleen, lymph nodes, meninges, brain, skin or testes).
- ✓ Although viruses cause several forms of leukemia in animals, their role in humans is uncertain; only two viral associations are identified:
  (1) Epstein-Barr virus, a DNA virus, is associated with Burkitt's lymphoma,
  (2) human T-cell lymphotropic virus type I, called human Tcell leukemia/lymphoma virus, an RNA retrovirus, is associated with some T-cell leukemias and lymphomas, most commonly identified in Japan and the Caribbean.
- ✓ Exposure to ionizing radiation and certain chemicals (e.g., benzene, some antineoplastic drugs) is associated with an increased risk of leukemia.
- ✓ Some genetic defects (eg, Down syndrome& Fanconi's anemia) also predispose to leukemia.
- ✓ The main classification of leukemia is into acute and chronic leukemia.
- ✓ Acute leukemia is further subdivided into acute myeloid (myeloblastic/myelogenous) leukemia (AML) and acute lymphoblastic (lymphocytic) leukemia (ALL) on the basis of morphology and cytochemistry.
- ✓ AML is further subdivided into eight variants on a morphological basis according to the French-American- British (FAB) scheme.
- ✓ ALL is subdivided on a morphological basis according to the FAB classification into L1, L2, L3 types (Table 18.1). Immunophenotyping, chromosome and gene rearrangement studies are also used to distinguish AML from ALL and to subclassify them.

Table 18.1 Subtypes of AML and ALL according to the FAB group

AML Subtype	ALL subtype
M0: Undifferentiated	L1: blast cells small, uniform high
M1: Myeloid without maturation	Nuclear to cytoplasmic ratio
M2: Myeloid with maturation	L2: blast cells larger, heterogeneous,
M3: Acute promyelocytic	lowernuclear to cytoplasmic ratio

M4: Myelomonocytic L3: vacuolated blasts, basophilic
M5: Monocytic/monoblastic leukemia Cytoplasm
M6: Erythroleukemia
M7: Megakaryoblastic

- ✓ The chronic leukemias comprise two main types, chronic myeloid leukemia (CML) and chronic lymphocytic (lymphatic) leukemia (CLL).
- ✓ Other chronic types include hairy cell leukemia, prolymphocytic leukemia and various leukemia/lymphoma syndromes.

Acute leukemias

- ✓ The leukemic cell population in ALL and AML probably result from clonal proliferation by successive divisions form a single abnormal stem or progenitor cell.

- ✓ In acute leukemia, in which there are over 50% myeloblasts or lymphoblasts in the bone marrow at clinical presentation, the blast cells fail to differentiate normally but are capable of further divisions.
- ✓ Their accumulation results in replacement of the normal hemopoietic precursor cells of the bone marrow by myeloblasts or lymphoblasts and, ultimately in bone marrow failure.
- ✓ The clinical condition of the patient can be correlated with the total number of leukemic cells in the body.
- ✓ When the abnormal cell number approaches 10^{12} the patient is usually gravely ill with severe bone marrow failure. Peripheral blood involvement by the leukemic cells and infiltration of organs such as the spleen, liver and lymph nodes may not occur until the leukemic cell population comprised 60% or more of the marrow cell total.
- ✓ The disease may be recognized by conventional morphology only when blast (leukemic) cells in the marrow exceed 5% of the cell total (unless the blast cells have some particular abnormal feature).
- ✓ This corresponds to a total cell count in excess of 10^{8}.
- ✓ The clinical presentation and mortality in acute leukemia arises mainly from neutropenia, thrombocytopenia and anemia because of bone marrow failure and, less commonly, from organ infiltration, e.g. of he meninges or testes.
- ✓ The acute leukemia comprise over half of the leukemias seen in clinical practice.
- ✓ ALL is the common form in children; its incidence is highest at 3-4 years, falling off by 10 years.
- ✓ There is a lower frequency of ALL after 10 years of age with a secondary rise after the age of 40. AML occurs in all age groups.
- ✓ It is the common form of acute leukemia in adults including the elderly.

Laboratory features

- A Normocytic Normochromic anemia
- The total white cell count may be decreased, normal or increased up to $200x10^{9}$/l or more
- Thrombocytopenia in most cases, often extreme in AML
- Blood film examination typically shows variable numbers of blast cells.
- In AML, the blasts may contain Auer rods and other abnormal cells may be present, e.g. promyelocytes, myelocytes, agranular neutrophils, pseudo-Pelger cells or myelomonocytic cells.
- ALL must be differentiated from infectious mononucleosis and other caused of lymphocytosis.
- In AML M6 (erythroleukemia) many erythroblasts may be found and these may also be seen in smaller numbers in other forms.
- The bone marrow is hypercellular with a marked proliferation of leukemic blast cells which amount to over 50% and typically over 75% of the marrow cell total.

- In ALL the marrow may be difficult to aspirate because of increased reticulin fiber.
- In AML M7 the patient typically has an acute onset of Pancytopenia with marrow fibrosis.

Differentiation of ALL from AML

- In most cases, the clinical features and morphology on routine staining separate ALL from AML.
- In ALL the blasts show no differentiation (with the exception of BALL) whereas in AML some evidence of differentiation to granulocytes or monocytes is usually seen in the blasts or their progeny.
- Special test (e.g. cytochemistry, gene rearrangement studies and chromosome analysis) are needed when the cells are undifferentiated to confirm the diagnosis of AML or ALL and to subdivide cases of AML or ALL into their different subtypes.

Chronic myeloid leukemia

- Chronic myeloid leukemia (CML) comprises <20% of all the leukemias and is seen most frequently in middle age.
- In over 95% of patients there is a replacement of normal bone marrow by cells with an abnormal chromosome- the Philadelphia or Ph chromosome.
- This is an abnormal chromosome 22 due to the translocation of part of a long (q) arm of chromosome 22 to another chromosome, usually 9, with translocation of part of chromosome 9 to chromosome 22.
- It is an acquired abnormality of hemopoietic stem cells that is present in all dividing granulocytic, erythyroid and megakaryocytic cells in the marrow and also in some B and probably a minority of T lymphocytes.
- A great increase in total body granulocyte mass is responsible for most of the clinical features. In at least 70% of patients there is a terminal metamorphosis to acute leukemia (myeloblastic or lymphoblastic) with an increase of blast cells n the marrow to 50% or more.
- This disease occurs in either sex (male: female, 1.4:1), most frequently between the ages of 40 and 60 years.

- However, it may occur in children and neonates and in the very old.
- It most cases there are no predisposing factors but the incidence was increased n survivors of the atom bomb exposures in Japan.

Laboratory findings

- Leucocytosis is usually >50x109/l and sometimes >500x109/l. A complete spectrum of myeloid cells is seen in the peripheral blood.
- The levels of neutrophils and myelocytes exceed those of blast cells and promyelocytes.
- Ph chromosome on cytogenetic analysis of blood or bone marrow.
- Bone marrow is hypercellular with granulopoietic predominance.
- Neutrophil alkaline phosphatase score is invariably low
- Increased circulating basophils
- Normochromic, normocytic anemia is usual
- Platelet count may be increased (most frequently), normal or decreased
- Serum vitamin B12 and vitamin B12-binding capacity are increased
- Serum uric acid is usually raised

Chronic lymphocytic leukemia (CLL)

- Chromic lymphocytic (lymphatic) leukemia (CLL) accounts for 25% or more of the leukemias seen in clinical practice.
- The disease occurs in older subjects and is rare before 40 years.
- The male to female ratio is 2:1.

- The accumulation of large numbers of lymphocytes to 50-100 times the normal lymphoid mass in the blood, bone marrow, spleen, lymph nodes and liver may be related to immunological non-reactivity and excessive lifespan.
- The cells are a monoclonal population of B lymphocytes.
- With advanced CLL there is often bone marrow failure, a tumorous syndrome with generalized discrete lymphadenopathy and sometimes soft tissue lymphoid masses; immunological failure results from reduced humoral and cellular immune processes with a tendency to infection.

Laboratory findings

- Lymphocytosis. The absolute lymphocyte count is >5 x 109/l and may be up to 300x109/l or more. Between 70% and 99% of white cells in the blood film appear as small lymphocytes.
- Smudge or smear cells are also present.
- Normocytic, normocytic anemia is present in later states due to marrow infiltration or hypersplenism.
- Autoimmune hemolysis may also occur.
- Thrombocytopenia occurs in many patients
- Bone marrow aspiration shows lymphocytic replacement of normal marrow elements. Lymphocytes comprise 25-95% of all the cells.
- Reduced concentrations of serum immunoglobulins are found and this becomes more marked with advanced disease.
- Rarely a paraprotien is present

Hairy cell leukemia

- Hairy cell leukemia (HCL), also known as leukemic reticuloendotheliosis, is a slow growing leukemia.
- It is most common in older white males. It is an unusual disease of peak age 40-60 years and men are affected nearly four times as frequently as women. It is a type of chronic lymphoid leukemia.
- Hairy cell leukemia was first described by Bertha Bouroncle, M.D. and her colleagues at the OSU College of Medicine and Public Health at The Ohio State University in 1958.
- This disorder is characterized clinically by features due to Pancytopenia. The spleen may be moderately enlarged.
- The is a monoclonal proliferation of cells with an irregular cytoplasmic outline (‘hairy’ cells, a type of B lymphocyte) in the peripheral blood, bone marrow, liver and other organs.
- The number of hairy cells in the peripheral blood is variable; they may be rare.
- The bone marrow trephine shows a characteristic appearance of mild fibrosis and a diffuse cellular infiltrate.
- A serum paraprotein may be present and the patients may have arthritis, serositis or vasculitis.

18.2. Myelodysplastic Syndromes (Myelodysplasia)

- ✓ The myelodysplastic syndromes (MDS) are a heterogeneous group of diseases states that usually present as peripheral blood cytopenias with a hypercellular bone marrow.
- ✓ The disease is most common in the elderly and males are more commonly affected.
- ✓ There is a tendency to progress to acute myeloid leukemia, although death often occurs before this develops.
- ✓ As in the acute leukemias, the fundamental disorder is the clonal proliferation of stem cells that produce progeny that fail to mature normally.
- ✓ In the acute leukemias the maturation defect leads to the accumulation of blast cells.

- ✓ In MDS, in contrast, the maturation defect is more subtle; mature forms develop but they are often morphologically atypical (“dysplastic”) and frequently dysfunctional as well.
- ✓ The MDS are classified into five subgroups:
    1) Refractory anemia (RA)
    2) RA with ring sideroblasts (RARS)
    3) RA with excess blasts (RAEB)
    4) RAEB in transformation (RAEB-t)
    5) Chronic myelomonocytic leukemia (CMML)

Laboratory features

Peripheral blood:

- ➢ Pancytopenia is a frequent finding
- ➢ The red cells are usually macrocytic or dimorphic but occasionally hypochromic; normoblasts may be present
- ➢ The reticulocyte count is low
- ➢ Granulocytes are often reduced and may show lack of granulation. Their chemotactic, phagocytic and adhesive functions are impaired.
- ➢ The Pelger abnormality (single or bilobed nucleus) is often present and in CMML monocytes are >1.0x109/ l in the blood and the total white blood count may be >100x109/l.
- ➢ The platelets may be unduly large or small and are usually decreased in number but in 10% of cases are elevated.
- ➢ In poor prognosis cases variable numbers of myeloblasts are present in the blood

Bone marrow:

- The cellularity is usually increased
- Ring sideroblasts may occur in all five FAB types
- Multinucleated normoblasts and other dyserythropoietic features are seen
- The granulocyte precursors show defective primary and secondary granulation, and cells which are difficult to identify as either agranular myelocytes, monocytes or promonocytes are frequent.
- Megakaryocytes are abnormal with micro-, small binuclear or polynuclear forms
- Bone marrow biopsy shows fibrosis in 10% of cases

18.3. Malignant Lymphomas

- ✓ This group of diseases is divided into Hodgkin’s disease and non-Hodgkin’s lymphomas.
- ✓ In both, there is replacement of normal lymphoid structure by collections of abnormal cells, Hodgkin’s disease being characterized by the presence of Reed-Sternberg (RS) cells and the non-Hodgkin’s lymphomas by diffuse or nodular collections of abnormal lymphocytes or, rarely, histiocytes.

Hodgkin’s disease

- ➢ Hodgkin's disease (Hodgkin's lymphoma) is a type of lymphoma described by Thomas Hodgkin in 1832, and characterized by the presence of Reed-Sternberg cells.
- ➢ It is a malignant tumor closely related to the other malignant lymphomas.
- ➢ In many patients, the disease is localized initially to a single peripheral lymph node region and its subsequent progression is by contiguity within the lymphatic system.
- ➢ It is likely that the characteristic RS cells and the associated abnormal and smaller mononuclear cells are neoplastic and that the associated inflammatory cells represent a hypersensitivity response by the host, the effectiveness of which determines the pattern of evolution.
- ➢ After a variable period of containment within the lymph nodes, the natural progression of the disease is to disseminate to involve non-lymphatic tissue.

- ➢ The disease can present at any age but is rare in children.

- It has bimodal age incidence, one peak in young adults (age 20-30 years) and a second after the age of 50.
- In developed counties the ratio of young adults to child cases and of nodular sclerosing disease to other types is increased. There is an almost 2:1 male predominance.

Laboratory findings

- Normochromic, normocytic anemias is most common. With marrow infiltration, bone marrow failure may occur with a leuco-erythroblastic anemia.
- One-third of patients have a leucocytosis due to a neutrophil increase
- Eosinophilia is frequent
- Advanced disease is associated with lymphopenia
- The platelet count is normal or increased during early disease, and reduced in later stages
- The ESR is usually raised and is useful in monitoring disease progress.
- Bone marrow involvement is unusual in early disease.
- It may be demonstrated by trephine biopsy, usually in patients with disease at many sites.
- Bilateral trephine biopsy is performed in some units.
- There is progressive loss of immunologically competent T lymphocytes with reduced cellmediated immune reactions
- Infections are common, particularly herpes zoster, cytomegalovirus and fungal, e.g. *Cryptococcus* and *Candida*. Tuberculosis may occur
- Patients with bone disease may show hypercalcaemia, hypophosphataemia and increased levels of serum alkaline phosphatase.
- Serum lactate dehydrogenase (LDH) is raised initially in 30-40% of cases an indicates a poor prognosis
- Elevated levels of serum transaminases may indicate liver involvement
- Serum bilirubin may be raised due to biliary obstruction caused by large lymph nodes at the porta hepatis
- Hyperuricaemia may occur

Non-Hodgkin's lymphomas

- ✓ The clinical presentation and natural history of these malignant lymphomas are more variable that in Hodgkin's disease, the pattern of spread is not as regular, and a greater proportion of patients present with extra-nodal disease or leukemic manifestations.

Laboratory findings

- A Normochromic, normocytic anemia is usual but auto-immune hemolytic anemia may also occur.
- In advance disease with marrow involvement there may be neutropenia, thrombocytopenia (especially if the spleen is enlarge) or leuco-erythroblastic features
- Lymphoma cells ('cleaved follicular lymphoma' or 'blast' cells) with variable nuclear abnormalities may be found in the peripheral blood in some patients.
- Trephine biopsy of marrow shows focal involvement, usually paratrabecular, in 20% of cases. Diffuse infiltration often accompanied by fibrosis may also occur. Paradoxically, bone marrow involvement is found more frequently in low-grade malignant lymphomas.
- Elevation of serum uric acid may occur. Abnormal liver function tests suggest disseminate disease
- The serum LDH level is raised in more rapidly proliferating and extensive disease and may be used as a prognostic marker.

18.4. Multiple Myeloma

Multiple myeloma (myelomatosis) is a neoplastic monoclonal proliferation of bone marrow plasma cells, characterized by lytic bone lesions, plasma cell accumulation in the bone marrow, and the presence of monoclonal protein in the serum and urine (bence jones proteins). Ninetyeight percent of cases occur over the age of 40 with a peak incidence in the seventh decade.

Laboratory finding

- In 98% of patients monoclonal protein occurs in the serum or urine or both.
- The serum paraprotein is IgG in two-thirds, IgA in one-third, with rare IgM or IgD or mixed cases.
- Normal serum immunoglobulins (IgG, IgA and IgM) are depressed.
- The urine contains Bence-Jones protein in two-thirds of cases.
- The bone marrow shows increased plasma cells often with abnormal forms – 'myeloma cells'.
- Immunological testing shows these cells to be monoclonal B cells and to express the same immunoglobulin heavy and light chains as the serum monoclonal protein.
- There is usually a normochromic, normocytic or macrocytic anemia.
- Rouleaux formation is marked in most cases
- Neutropenia and thrombocytopenia occur in advanced disease
- Abnormal plasma cells appear in the blood film in 15% of patients.
- Leuco-erythroblastic changes are occasionally seen
- High ESR
- Serum calcium elevation occurs in 45% of patients.
- The blood urea is raised above 14mmol/l and serum creatinine raised in 20% of cases
- Proteinaceous deposits from heavy Bence-Jones proteinuria, hypercalcaemia, uric acid, amyloid and pyelonephritis may all contribute to renal failure
- A low serum album occurs with advance disease
- Serum β2-microglobulin (the light chain of the HLA class 1 antigens) is a useful indicator of prognosis. It partly reflects renal function. Levels less than 4mg/l imply a relatively good prognosis.

18.5 Myeloproliferative Disorders

The term myeloproliferative disorders describe a group of conditions characterized by clonal proliferation of one or more hemopoietic components in the bone marrow and, in many cases, the liver and spleen.
These disorders are closely related to each other; transitional forms occur and, in many patients, an evolution from one entity into another occurs during the course of the disease. Polycythemia vera (PV), essential thrombocythemia and myelofibrosis (increased connective tissue with decreased room for production of normal blood cells) are collectively known as the nonleukemic myeloproliferative disorders and are discussed here; chronic myeloid leukemia is discussed in leukemia subtopic.

Polycythemia vera

- Polycythemia (erythrocytosis) refers to a pattern of blood cell changes that includes an increase in hemoglobin above 17.5g/dl in adult males an 15.5g/dl in females usually with an accompanying rise in red cell count (above 6.0 x 1012/l in males and 5.5x1012/l in females and hematocrit (above 55% in males and 47% in females).
- Studies with 51Cr-labelled red cells to measure total red cell volume (TRCV) and 125I-albumin to measure plasma volume are required to establish whether the polycythemia is 'real', where there is an increase in TRCV, or 'relative', where there is no increase in TRCV but the circulating plasma volume is decreased.
- Polycythemia is considered 'real' if the TRCV is greater than 36ml/kg in mean and 32ml/kg in women.
- In polycythemia vera (polycythemia rubra vera), the increase in red cell volume is caused by endogenous myeloproliferation.
- The stem cell origin of the defect is suggested in many patients by an over production of
- granulocytes and platelets as well as of red cells.
- This is a disease of older subjects with an equal sex incidence.

Laboratory findings

- The hemoglobin, hematocrit and red cell count are increased. The TRCV is increase
- A neutrophil leucocytosis is seen in over half the patients, and some have increased circulating basophils.
- A raised platelet count is present in about half the patients
- The neutrophil alkaline phosphatase score is usually increased above normal
- Increased serum vitamin B12 and vitamin B12-binding capacity due to an increase in transcobalamin I.
- The bone marrow is hypercellular with prominent megakaryocytes, best assessed by a trephine biopsy.
- Clonal cytogenetic abnormalities may occur, but there is no single characteristic change
- Blood viscosity is increased
- Plasma urate is often increased
- Circulating erythroid progenitors are increased and grow in vitro independently of added erythropoietin.

Essential thrombocythemia

- ✓ Megakaryocyte proliferation and overproduction of platelets is the dominant feature of this condition; there
- ✓ is sustained increase in platelet count above normal ($400x10^9$/l).

- ✓ The condition is closely related to PV. Some cases show patchy myelofibrosis. Recurrent hemorrhage and thrombosis are the principal clinical features.
- ✓ Splenic enlargement is frequent in the early phase but splenic atrophy due to platelets blocking the splenic mirocirculation is seen in some patients.
- ✓ There may be anemia (e.g. due to iron deficiency from chronic gastrointestinal or uterine hemorrhage or due to
- ✓ the marrow disorder itself) or the thrombocythemia may be accompanied by polycythemia. The condition must be distinguished from other causes of a raised platelet count.

Laboratory findings

• Abnormal large platelets and megakaryocyte fragments may be seen in the blood film.
• The bone marrow is similar to that in PV. Cytogenetics are analyzed to exclude chronic myeloid leukemia.
• Platelet function tests are consistently abnormal, failure of aggregation with adrenaline being particularly characteristic.

Myelofibrosis

- Myelofibrosis, one of the myeloproliferative diseases, is the gradual replacement of the bone marrow by connective tissue. This condition has many names: (chronic) myelofibrosis, myelosclerosis, agnogenic myeloid metaplasia, or myelofibrosis with myeloid metaplasia (MMM).
- The replacement of the bone marrow tissue reduces the patient's ability to generate new blood cells resulting in
  chronic anemia.
- A prime feature is "extramedullary hematopoeisis", i.e. the remaining blood-forming cells migrate to other sites in the body, e.g. the liver or spleen.
- Patients will typically have an enlarged spleen and liver, (hepatosplenomegaly), and examination of the blood cells will show "teardrop cells".
- Typically affecting patients more than 50 years old, it is a chronic and debilitating condition.

- Hemopoietic stem cell proliferation is generalized with splenic and hepatic involvement.
- There is an increase in circulating stem cells associated with the establishment of extramedullary hemopoiesis.
- There is reactive fibrosis in the bone marrow secondary to hyperplasia of abnormal megakaryocytes.
- There is stimulation of fibroblasts probably by platelet –derived growth factor secreted by megakaryocytes and platelets and inhibition of collagenase by platelet factor IV.

Laboratory findings

- Anemia is usual but a normal or increased hemoglobin level may be fond in some patients
- The white cell and platelet counts are frequently high at the time of presentation. Later in the disease leucopenia and thrombocytopenia are common.
- A leuco-erythroblastic blood film is found. The red cells show characteristic 'tear-drop' poikilocytes.
- Bone marrow is usually unobtainable by aspiration.
- Trephine biopsy may show a hypercellular marrow with an increase in reticulin-fibre pattern; in other patients there is an increase in intercellular substance and variable collagen deposition.
- Increased megakaryocytes are frequently seen.
- Low serum and red cell folate, raised serum vitamin B12 and vitamin B12-binding capacity, and an increased neutrophil alkaline phosphatase score are usual.
- High serum urate, LDH and hydroxybutyrate dehydrogenase levels reflect the increased but largely ineffective turnover of hemopoietic cells. The serum LDH is normal in PV
- Extramedullary erythropoiesis may be documented by radio-iron studies or by liver biopsy, but these are not routine tests
- Transformation to acute myeloid leukemia occurs in 10-20% of patients.

Review Questions

1) Describe briefly the classification of leukemia
2) Explain the laboratory diagnosis of different form of leukemia
3) Define myelodysplastic syndrome and indicate the hematological findings
4) What is the features of malignant lymphoma
5) What is the characteristics multiple myeloma
6) Describe myeloproliferative disorders