CHAPTER 6

LEUKEMIAS AND MYELODYSPLASTIC SYNDROMES (M.D.S.)

LEUKEMIAS

Leukemia is a morbid condition characterised by wide spread hyperplasia of leucopoitic tissue, either myeloid or lymphatic, which is usually associated with qualitative and quantitative changes in the white cells of the circulating blood.

Exposure to ionizing radiation increases the incidence of leukemia in animals, and in man exposure to doses of 100r or over carries a definite risk of leukemia.

Leukemias are classified as

1. Myeloid Leukemia (Acute and chronic)
2. Lymphatic Leukemia (Acute and chronic)
3. Monocytic Leukemia (Acute, sub acute)
4. Atypical Leukemias:
   (a) Aleukemic leukemia
   (b) Chloroma
   (c) Plasma cells leukemia
   (d) Eosinophilic, Basophilic, mast cell leukemias
   (e) Megakaryocytic leukemia etc.

ACUTE LEUKEMIAS

Two main forms of acute leukemias are recognised: myeloid (AML), more frequent in adults (more than 20 years), and lymphoblastic (ALL), predominantly in children (<15 years) (Fig. 24 & Fig. 25).

AML: 6 types of AML (FAB classification) can be identified by morphology with help of cytochemistry. The main features of each type M_1 to M_6 are summarized in the Table. 15.

Table 15 *(FAB) French American British Classification*

Types	Main Features
M_1 (Myeloblastic)	* Blasts with few or no granules (90%) * Auer rods +
M_2 (Myeloblastic)	* Blasts (30%) * Maturation beyond promyelocytes * Abnormal neutrophils
M_3 (Promyelocytic)	* Hypergranular promyelocytes * Faggets * Bilobed nuclei * Hypogranular variant
M_4 (Myelo Monocytic)	* Blasts (30%) * Evidence of granulocytic and monocytic differentiation
M_5 (Monocytic)	(a) Monoblasts (b) Monoblasts, promonocytes & monocytes (a) & (b) 80% monocytic cells
M_6 Erythro Leukemia	* Over 50% of erythroid cells, often bizarre, Myeloblasts with Auer rods

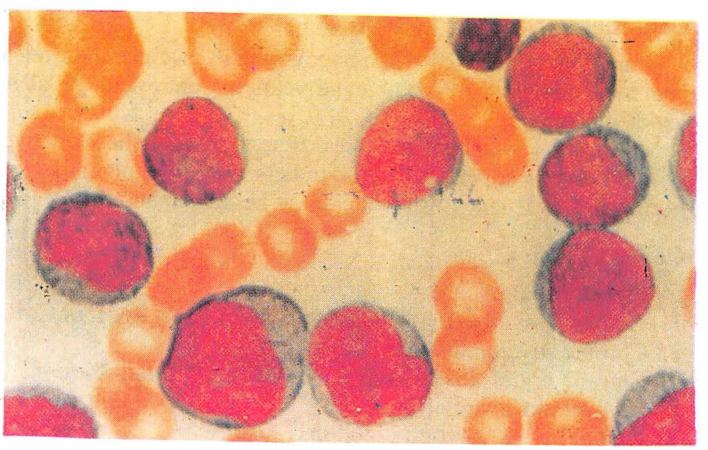

Fig. 24 Blood film of A.M.L.

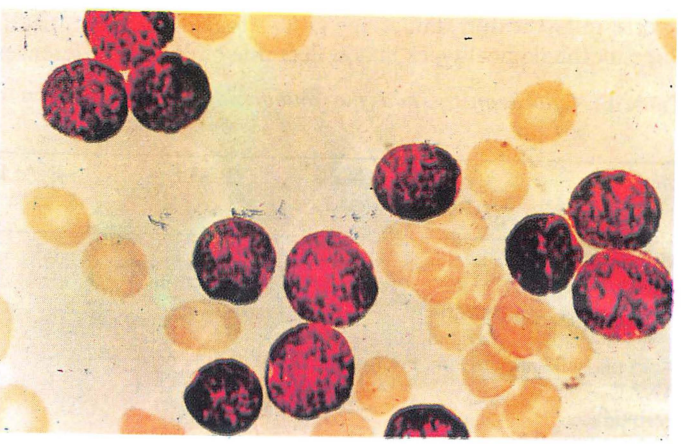

Fig. 25 Blood film of A.L.L.

CYTOCHEMISTRY OF AML

Certain cytochemical reactions are essential in distinguishing AML from undifferentiated forms of ALL (e.g. L_2). This is particularly so in cases where the cells are immature, e.g. in M_1 (myeloblastic leukemia poorly differentiated). The peroxidase, Sudan Black B and chloracetate estrase reactions reveal granulocytic differentiation in M_1, M_2, M_3 and M_4 types of AML. Whilst the non specific esterases (nephthol acetate (NASDA) and alpha-nephthol acetate esterase (ANAE) ± sodium fluoride (NaF), and the acid phosphatase and lysozyme reactions, demonstrate monocytic differentiation. Non specific esterase reactions are usually weak or negative in M_3. In erythroleukemia (M_6) the PAS (Periodic Acid Schiff) reaction may be strongly positive.

Cytochemical reactions are usually done to detect the deficiency of enzyme contents of mature neutrophils in AML, particularly in M_2 and M_6. The NAP (neutrophil alkaline phosphatase), score is often low in M_2 (myeloblastic leukemia with maturation). The peroxidase, Sudan Black B and chloroacetate reactions may also be negative in variable proportions of neutrophils in AML, more frequently in M_2 and M_6. The NAP scores are usually normal and high in ALL and M_5.

In acute megakaryoblastic leukemia, the blast cells appear undifferentiated, and may resemble lymphoblasts. The cytochemical profile of these cells is similar to that of megakaryocytes i.e. positive reactions with PAS, acid phosphatase and ANAE (NaF-sensitive as in monocyte). The cytochemical classification of some leukemias is possible by use of 7 different tests.

1. Nephthol AS-D chloroacetate esterase (NASDCA) activity.
2. Alpha-nephthyl acetate esterase (NA).
3. Alpha nephthyl butyrate esterase (NB) activity.
4. Myeloperoxidase (M.P.) activity.
5. Sudan Black B (SB) reaction.
6. Acid phosphatase (AP) activity.
7. Periodic Acid Schiff (PAS) stain.

The characteristics and interpretations are shown in microphotograph (Fig. 26 to Fig. 32).

ACUTE LYMPHOCYTIC LEUKEMIA (A.L.L.)

Three morphological types have been described by the FAB group: L_1, L_2, and L_3. The differences in age incidence (L_1 is more common in children and L_2 more frequent in adults), the strong correlation of L_3 with B-ALL (with monoclonal membrane immunoglobulins) and the difference in prognosis between L_1 and L_2 (worse in L_2) within similar age groups together suggest that the three morphological types may reflect true biological differences.

Table16. *Cytochemistry and the immunological classification of ALL.*

Method	Common-ALL	Null-ALL	T-ALL	B-ALL
Morphology	L1-L2	L1-L2	L1-L2	L3
PAS	+ or + + coarse granules	− or + +	− or +	−
Acid phosphatase	− or +	− or + +	+ + or + + +	−
ANAE	−	− or +	+ or + +	−
Peroxidase, Sudan black B, Lysozyme	−	−	−	−

L_1 lymphoblasts tend to be small and to have scanty cytoplasm; the nucleo-cytoplasmic (N:C) ratio is high in the majority and they have a small and not easily visible nucleolus; the nuclear membrane is often regular. L_2 lymphoblasts, in contrast to L1, are larger, have more abundant cytoplasm (low N:C ratio) and have one or more prominent nucleoli; the nuclear outline is irregular in over 25% of cells. The differences between L_1 and L_2 can be more easily resolved in borderline cases by the simple scoring system proposed by the FAB group. L_3 (or Burkitt type) cells, because of their resemblance to cells of the endemic African lymphoma are uniformly large, have finely stippled nuclear chromatin and, characteristically, a deep basophilic cytoplasm often associated with prominent vaculolation.

Three cytochemical tests are useful in the study of ALL; the PAS, acid phosphatase and ANAE reactions. They do not correlate with the L_1, L_2 or L_3 morphological types but they do show a relationship to the immunological subtypes of ALL.

In cases in which the cells are undifferentiated (usually L_2 blast cells in adult patients), it is important to exclude AML (usually M_1 and M_5a). For this, the peroxidase, Sudan Black B and NASDA reactions should be shown to be negative. ANAE can show in ALL a granular reaction, but this is not the strong diffuse pattern (NaF-senstive) seen in M_5. The PAS reaction is often postive in ALL — at least, in a proportion of blasts, as shown by coarse granules or blocks of positively-reacting material (usually glycogen). This pattern of reaction, particularly with a negative background, is rarely seen in AML; it is more typical of the common form of childhood ALL which can be defined by immunological tests for the ALL antigen described as non-B, non-T ALL (negative B and T markers) or common-ALL.

In T-ALL (positive T-cell markers), the PAS reaction is negative in two-thirds of cases; in B-ALL it is negative in the majority. The differences shown by the PAS reaction probably reflect the different proliferation kinetics of the immunologically-defined subtypes of ALL. For example, in B-ALL (PAS-negative) a greater number of cells are in cycle; this is also reflected in the numerous mitotic figures seen in bone marrow with L_3 morphology. The acid phosphatase test gives a consistently localized positive reaction in T-ALL and pre-T-ALL blast cells.

CHRONIC LEUKAEMIAS

Definition

Primary malignancies of haemopoietic cells in which the clinical course is measuied in months and years in contrast to the acute leukaemias.

Many of the malignant cells are differentiated and these relatively mature cells appear in large numbers in the peripheral blood, giving rise to leucocytosis which may be very marked.

Classification

I. Myeloid origin

1. Chronic granulocytic (synonymous myeloid) — CGL or CML.
2. Chronic myelomonocytic (CMML).
3. Chronic erythroleukaemia (Di Gughelmo's syndrome).

II. Lymphoid origin

1. Chronic lymphocytic (B-cell or T-cell).
2. Prolymphocytic (B-cell or T-cell).
3. Hairy cell (leukaemic reticuloendotheliosis).

THE CYTOCHEMICAL CLASSIFICATION OF SOME LEUKEMIAS IS POSSIBLE BY USE OF 7 DIFFERENT TESTS.

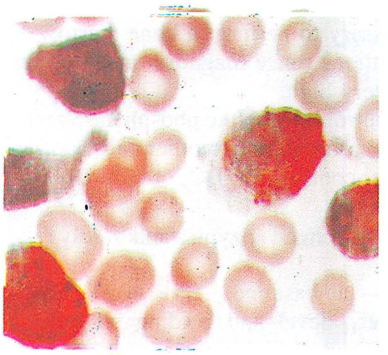

Fig. 26

NAPHTHOL AS-D CHLOROACETATE ESTERASE (NASDCA) activity is exhibited by cells of granulocytic lineage. NASDCA activity appears at differentiated myeloblast/progranulocytic stage of cellular development.

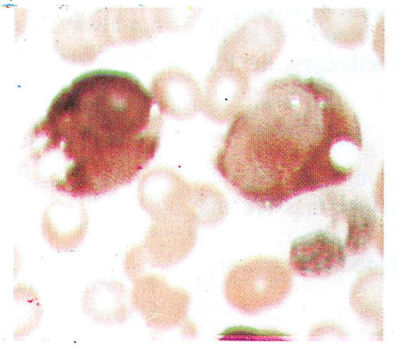

Fig. 27

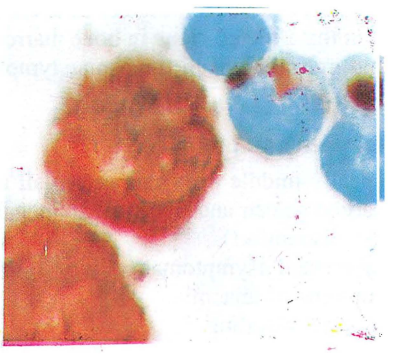

Fig. 28

α-NAPHTHYL ACETATE ESTERASE (NA) AND α-NAPHTHYL BUTYRATE ESTERASE (NB) activities are used to recognize cells of monocytic origin. At pH 7.6, NA is seen almost exclusively in monocytes and histiocytes, with occasional granules in polymorphonuclear leukocytes and lymphocytes. At this pH, megakaryocytes and erythroblasts exhibit intense NA activity. Sodium fluoride inhibits monocyte enzymes and is used to distinguish monocyte activity from other esterase activity.

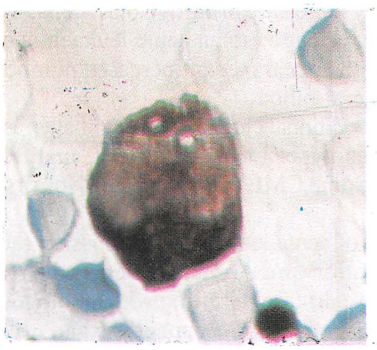

Fig. 29

MYELOPEROXIDASE(MP) is normally confined to primary granules of myeloid and monocytoid cells. However, primative blasts committed to myeloid path exhibit MP activity in the endoplasmic reticulum, paranuclear area and Golgi apparatus.

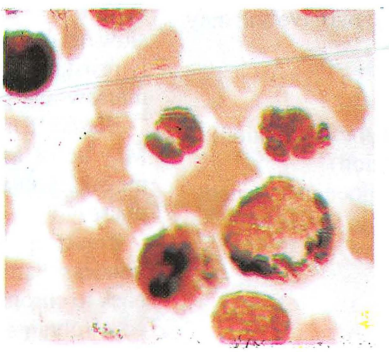

Fig. 30

SUDAN BLACK B (SB) reacts with lipid deposits in cells, paralleling the MP pattern of cellular distribution. The parallelism in not invariant since SB-positive blasts sometimes exceed those exhibiting MP. SB-positive and MP-negative blasts have been reported.

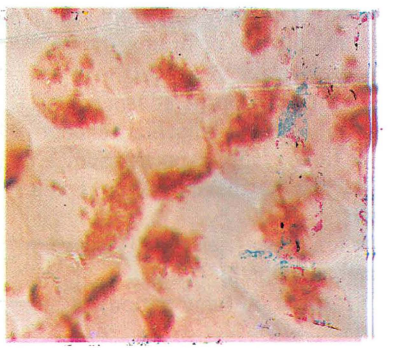

Fig. 31

ACID PHOSPHATASE(AP) is useful for differentiating sub-groups of acute lymphoblastic leukemia and delineating hairy cell leukemia from other chronic lymphoid neoplasias.

PERIODIC ACID-SCHIFF (PAS) stains glycogen and other 1, 2-glycol-containing carbohydrates. The earliest myeloid precursors are not PAS reactive, but staining increases with maturation along myeloid pathways. Normal erythroid precursors are negative while megakaryoblasts, megakaryocytes and platelets stain intensely. Diffuse or granular PAS patterns are exhibited by monocytes.

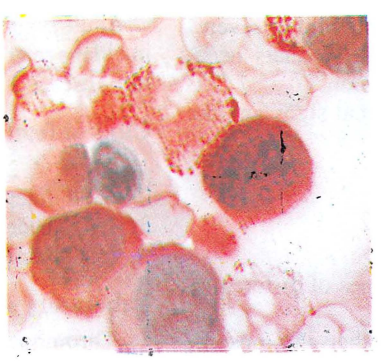

Fig. 32

I.1. Chronic Myeloid (Granulocytic) Leukaemia

Malignant clone derives from a committed stem cell and differentiates along myeloid lines. In 95% of cases the Philadelphia chromosome (Ph^1), a number 22 chromosome missing part of its long arm which has become attached to chromosome 9 [t(22;9)], is present in the affected clone in bone marrow and blood. Myeloid. erythroid, megakaryocytic and some lymphoid cells carry the Ph^1 chromosome.

Clinical presentation

1. Typically middle age, but seen in all age groups.
2. Enlarged spleen and liver (splenomegaly may be massive and cause discomfort).
3. May present asymptomatically on routine blood count.
4. Symptoms of anaemia.
5. Abnormal bleeding.
6. Weight loss, anorexia, sweats, fever, 2° amenorrhoea.
7. Hyperviscosity syndrome from leucostasis.
8. Gout.
9. De novo 'blast transformation' clinically indistinguishable from acute leukaemia.

Severe infection is rare in untreated CGL (unlike all other types of leukaemia) as the relatively mature myeloid cells seen in the blood have some bacteriocidal capabilities.

Clinical signs

1. Splenomegaly; may vary from just palpable to massive and may have audible rub or bruit.
2. Hepatomegaly.
3. Pallor, emaciation (if advanced).
4. Bruising (seldom petechial, except in blast transformation)
5. Fever (low grade, even in absence of infection)
6. Fundal haemorrhages, tortuous veins, papilloedema (leucostasis).
7. Bone tenderness, especially sternum.
8. Lymphadenopathy (rare).
9. Skin infiltration (uncommon).

Investigations

Blood count

1. Leucocytosis may be very marked, often well over $100 \times 10^9/1$. Height of leucocytosis tends to correlate with size of spleen and degree of anaemia.
2. Differential leucocyte count: whole spectrum from neutrophils (around 50%) to blasts (usually > 5%). Myelocytes common. Eosinophiis and basophils increased.
   Nucleated RBCs often seen.
3. Anaemia: normochromic, normocytic, may be mild or severe.
4. Thrombocytosis sometimes $> 1000 \times 10^9/1$. Platelets occasionally low — may herald blast transformation.

The diagnosis is often obvious from the clinical signs and the blood count alone, in classical CGL.

Bone marrow

1. Grossly hypercellular.
2. May be difficult to aspirate.
3. Gross granulocytic hyperplasia with all degrees of differentiation seen, and increased megakaryocytes.
4. Send sample for examination for Ph^1 and other chromosome anomalies (liaise with laboratory about sample — marrow or blood anticoagulated with heparin is suitable).
5. Marrow trephine to assess fibrosis; may also show pockets of blasts not detected on aspirate, in early transformation.

Note: If Ph^1 chromosome detected in peripheral blood cells it may not always be necessary to perform a bone marrow.

Additional investigations (once diagnosis made or suspected)

1. Urate — often very high.
2. NAP score — neutrophil alkaline phosphatase zero or very low in untreated CML, in contrast to other causes of leucocytosis. Tends to rise after control of WBC, or before blast transformation.
3. Liver function — deranged enzymes and mildly raised bilirubin common.
4. Renal function — as baseline.
5. Serum vitamin B_{12} level and binding proteins if available. (Transcobalamin secreted by leucocytes is raised in CML and other myeloproliferative diseases, giving rise to high serum vitamin B_{12} level.)

Disease progression

At present time CML is incurable by conventional techniques. Median survival is approximately three years. After the initial chronic phase disease in which the patient is clinically well, one of two main terminal states develop:

1. *Blast transformation:* a more malignant clone appears which gives rise to progeny which are primitive blast cells. The result is a slow or abrupt transformation to an acute leukaemia of particularly resistant type, with appearance of increased number of blasts in marrow and peripheral blood.

Blasts often have additional chromosome anomalies as well as Ph^1 May be of any phenotype: i.e. AML, ALL. undifferentiated or megakaryoblastic. Some CML patients present for first time in this phase.

Treatment is that of acute leukaemia. Remission rates and duration less than straightforward AL., and patients who respond revert back to chronic phase disease. Grafting with autologous buffy coat cells (obtained at diagnosis by leucapheresis and cryopreserved), after intensive chemotherapy or radiotherapy, has been used, but long term results poor.

2. *Bone marrow failure*: Some patients do not enter a discernible blast crisis but develop insidious marrow failure with progressive anaemia, thrombocytopenia and splenomegaly. Marrow often very fibrotic. May be natural disease process or related to chemotherapy, particularly busulphan. Patients often emaciated and hypercatabolic. Treatment is supportive only.

Juvenile Chronic Myeloid Leukaemia

Adult-type CGL does occur occasionally in childhood, usually in older age group. Juvenile chronic myeloid leukaemia is a distinct rare disease.

Clinical features

1. Age < 2 years.
2. Mild splenomegaly.
3. Lymphadenopathy.
4. Facial rash.

Laboratory features

1. Thrombocytopenia.

2. Increased monocytes and blasts in blood and marrow.
3. Many nucleated RBC.
4. High Hb F level.
5. Absence of Ph^1 chromosome.

I.2. Chronic Myelomonocytic Leukaemia

May be classified either as a type of myelogenous leukaemia or as a myelodysplastic syndrome

Clinical and laboratory features

1. Elderly patient.
2. Chronic course often over several years.
3. Leucocytosis with absolute increase in monocytes and some abnormal forms in blood and bone marrow.
4. Splenomegaly.
5. Anaemia and thrombocytopenia.

Treatment

1. Treatment is generally supportive, and many patients do relatively well.
2. Gentle chemotherapy e.g. 6-mercaptopurine or hydroxyurea may be useful in controlling very high WBC count and splenomegaly, and may improve anaemia and thrombocytopenia.

I.3. Chronic Erythroleukaemia (syn. Di Guglielmo's syndrome, chronic erythraemic myelosis)

A chronic variation of which the acute counterpart is M6 AML.

Clinical features

Chronic form usually presents with anaemia and runs a course over months and years. Splenomegaly may be present.

Laboratory features

1. Anaemia.
2. Increased reticulocytes.
3. Numerous nucleated RBC in blood.
4. Gross erythroid hyperplasia in marrow.
5. PAS + ve erythroblasts in marrow.
6. Variable dysmyelopoiesis.
7. May terminate as AML.

II. Chronic Lymphoid Leukaemias

Can be classified:
1. Clinically.
2. Morphologically.
3. Immunologically.

Generally the malignant clone has a normal counterpart in lymphocyte development, but the cells have aberrant features and are functionally defective.

II.1. B-Cell Chronic Lymphocytic Leukaemia (B-CLL)

Commonest form of leukaemia in United Kingdom. Affects mainly elderly — very rare below thirty. Often detected on routine blood count as an absolute lymphocytosis. CLL is the most common cause of persistent lymphocytosis in a middle aged or elderly patient.

Clinical features

1. Often asymptomatic with no abnormal physical signs.
2. Lymphadenopathy — all areas, soft, may be very extensive.
3. Hepatosplenomegaly.
4. Weight loss, night sweats, fatigue, recurrent infections.

Laboratory features

1. Absolute lymphocytosis $> 15 \times 10^9/1$. WBC may be very high $500–600 \times 10^9/1$.
2. 'Smudge' cells or 'smear' cells (lymphocytes ruptured on spreading film) characteristic.
3. Anaemia, neutropenia and thrombocytopenia develop as the disease progresses.

Staging

Three main staging systems based on clinical and haematological parameters. All assume diagnosis based on minimum criteria of:
1. Peripheral blood lymphocytosis $> 15 \times 10^9/1$.
2. Bone marrow lymphocytosis > 40%.

Simplest classification is as follows:

Stage A: Hb >10 g/dl. Platelets $> 100 \times 10^9/1$
< 3 lymphoid areas involved.

Stage B: Hb >10g/dl. Platelets $>100 \times 10^9/1$
3 or more lymphoid areas involved.

Stage C: Hb <10g per dl. or Platelets
$<100 \times 10^9/1$. Regardless of lymphoid areas involved.

NB: 1. A lymphoid area includes liver, or spleen or a single group of nodes e.g. neck. axillae, groins.
2. Level of lymphocyte count not considered prognostically important although counts tend to rise as disease progresses.
3. Anaemia and thrombocytopenia excludes that caused by a definite auto-immune process.

Investigations

1. Full blood count and reticulocytes, film, direct antiglobulin test.
2. Peripheral blood for lymphocyte markers, "mouse rosettes" and 'slg' (surface immunoglobulin) if available.
3. Bone marrow aspirate and trephine. A 'nodular' pattern of lymphocyte infiltration on trephine may suggest better prognosis than diffuse infiltrate.
4. Renal and liver function.
5. Uric acid.
6. Protein electrophoresis and immunoglobulin levels.
7. Chest X-ray.

Prognosis

1. Related to stage of disease.
2. Overall median survival six years.
3. Death usually associated with bone marrow failure or infection.
4. Acute transformation analogous to CGL is very rare.

T-cell chronic lymphocytic leukaemia (T-CLL)

Much less common than B-CLL in United Kingdom. Generally greater splenomegaly for same stage of disease. May occur in younger age group.

II.2. Prolymphocytic Leukaemia

Less common than CLL.

May have B or T cell characteristics.

Diagnosis based on peripheral blood appearances and immunology.

Clinical and laboratory features

1. Splenomegaly prominent.
2. Lymphadenopathy slight or absent.
3. Elderly males predominate.
4. Often very high WBC.

Prognosis

Much worse than CLL.

II.3. Hairy Cell Leukaemia (leukaemic reticuloendotheliosis)

Typically 'hairy cells' are found in peripheral blood, but may not always be apparent on light microscopy.

Clinical features

1. Usually elderly — male > female.
2. Pancytopenia.
3. Splenomegaly prominent.
4. Recurrent infections common.

Laboratory features

1. 'Hairy cells' — lymphocytes with spiky projections from cytoplasm.
2. Pancytopenia and especially monocytopenia.
3. Bone marrow aspiration often difficult. Usually hypocellular with lymphoid cells showing staining with tartrate resistant acid phosphatase.
4. Trephine biopsy often needed for diagnosis and shows excess fibrosis.

ALEUKEMIC LEUKEMIA AND LEUKEMOID REACTIONS

Aleukemic Leukemia

Aleukemic leukemia is also referred to as aleukemic lymphadenosis and aleukemic myelosis.

Aleukemic leukemia means white blood without white blood. It is a phase of leukemia in which the white cell count is normal or below normal and the differential white cell count may show only a few immature white cells.

Aleukemic leukemia occurs in 10 to 20% of all cases of leukemia. Its significance lies in the fact that, during this phase, the disease may easily by confused with other diseases such as aplastic anaemia or agranulocytosis.

With the exception of the white cells, the laboratory findings and clinical picture are the same as those which have just been described for the various leukemias.

Because the white cell count is normal or below normal, the white cells in the differential white cell count are relatively few. These white cells may be concentrated, however, and the differential white cell count run on the concentrated specimen. The concentrated specimen of white cells is called buffy coat preparation.

As previously stated, in aleukemic leukemia, the differential white cell count may not show many immature white cells. A bone marrow examination then becomes the more significant laboratory examination. This examination usually reveals large numbers of immature white cells.

Leukemoid Reactions

Leukemoid reactions are reactions which resemble leukemia. Thus, the white cell count is high and the differential white cell count shows immature white cells. But the patient does not have leukemia.

The distinction between a leukemoid reaction and true leukemia is usually made by (1) careful clinical observations of the patient, (2) a continual check for changes in laboratory examinations, and (3) a bone marrow examination.

The more commonly encountered leukemoid reactions are neutrophilic leukemoid reactions and lymphocytic leukemoid reactions. These reactions are briefly discussed below:

Neutrophilic Leukemoid Reactions

A neutrophilic leukemoid reaction is accompanied by a white cell count of 20,000 to 100,000 per cubic millimeter and a differential white cell count showing immature neutrophils such as neutrophilic metamyelocytes and neutrophilic myelocytes.

Thus, from a laboratory viewpoint, a neutrophilic leukemoid reaction may resemble granulocytic leukemia.

A neutrophilic leukemoid reaction may be found in the following conditions: tuberculosis, meningitis, diphtheria, lobar pneumonia, malaria, syphilis, haemorrhage, haemolytic anaemia, severe burns, tumors, Hodgkin's disease, myeloid metaplasia, mercury poisoning, and eclampsia.

If it is difficult to distinguish between a neutrophilic leukemoid reaction and granulocytic leukemia, the alkaline phosphatase stain may be used.

The alkaline phosphatase stain reveals values above normal in a neutrophilic leukemoid reaction and values below normal in granulocytic leukemia.

Lymphocytic Leukemoid Reactions

A lymphocytic leukemoid reaction is accompanied by a white cell count of 20,000 to 150,000 per cubic millimeter and a differential white cell count showing 35 to 95% lymphocytes.

Thus, from a laboratory viewpoint, a lymphocytic leukemoid reaction may resemble lymphocytic leukemia.

A lymphocytic leukemoid reaction may be found in the following conditions: mumps, measles, chickenpox, whooping cough, infectious lymphocytosis, and infectious mononucleosis.

Of the above conditions, infectious mononucleosis probably gives the most trouble, for it is often difficult to differentiate between infectious mononucleosis and lymphocytic leukemia.

The distinction between infectious mononucleosis and lymphocytic leukemia can usually be made by the heterophil agglutination test.

The heterophil agglutination test is usually positive in infectious mononucleosis and negative in lymphocytic leukemia.

Myelodysplastic syndromes (MDS)

Precise diagnostic criteria for the MDS were recently proposed by the FAB group. All of them are characterized by hypercellular bone marrows. Five conditions are included under the broad term MDS.

1. Refractory anaemia (RA), with erythroid hyperplasia and/or dyserythropoiesis.

2. RA with ring sideroblasts, also designated as acquired idiopathic sideroblastic anaemia (AISA), the main feature being the presence of ring sideroblasts in at least 15% of erythroblasts.
3. RA with excess of blasts (RAEB) which shows dyspoiesis in the three bone-marrow cell lineages, dysgranulopoiesis being always conspicuous. The percentage of bone-marrow blasts is between 5 and 20%; these cells may have a few or no azurophil granules.
4. Chronic myelomonocytic leukaemia (CMML), with many features of RAEB plus a significant peripheral blood moncytosis (usually over 1×10^9/l).
5. RAEB in transformation, a group close to AML, and defined by the presence of blasts in the peripheral blood (over 5%) and between 20 and 30% in the bone marrow.

In addition to staining for iron, the other cytochemical methods used in AML may be useful for the study of the MDS. They may help to define the monocytic component in CMML or the type of blasts in RAEB and they are particularly useful in demonstrating dysgranulopoiesis, e.g. by the presence of neutrophils negative for peroxidase and/or Sudan Black B reactions or giving extremely low NAP scores.