CHRONIC LYMPHOCYTIC LEUKEMIA

Background:

Monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes.

It is the most common form of leukemia found in adults **Pathophysiology:**

The cells of origin in the majority of patients with CLL are clonal B cells(75%) arrested in the B-cell differentiation pathway, intermediate between pre-B cells and mature B cells.

Morphologically in the peripheral blood, these cells resemble mature lymphocytes.

B-CLL lymphocytes typically show B-cell surface antigens, as demonstrated by CD19, CD20, CD21, and CD24 monoclonal antibodies. In addition, they express CD5, which is more typically found on T cells. Because normal $CD5^+$ B cells are present in the mantle zone (MZ) of lymphoid follicles, B-cell CLL is most likely a malignancy of an MZ-based subpopulation of anergic self-reactive cells devoted to the production of polyreactive natural autoantibodies.

Recent studies have demonstrated that *bcl2*, a protooncogene, is overexpressed in B-CLL. The protooncogene *bcl2* is a known suppresser of apoptosis (programmed cell death), resulting in a long life for the involved cells. Despite the frequent overexpression of bcl-2 protein, genetic translocations that are known to result in the overexpression of *bcl2*, such as t(14;18), are not found in patients with CLL.

-An abnormal karyotype is observed in the majority of patients with CLL.

-The most common abnormality is deletion of 13q, which occurs in more than 50% of patients. Patients showing 13q14 abnormalities have a relatively benign disease that usually manifests as stable or slowly progressive isolated lymphocytosis.

-The presence of trisomy 12, which is observed in 15% of patients, is associated with atypical morphology and progressive disease.

-Deletions of bands 11q22-q23, observed in 19% of patients, are associated with extensive lymph node involvement and aggressive disease.

- More sensitive techniques have demonstrated abnormalities of chromosome 12.

-Approximately 2-5% of patients with CLL exhibit a T-cell phenotype.

CLL also should be distinguished from prolymphocytic leukemia, in which more than 65% of the cells are morphologically less mature prolymphocyte

I**ncidence**

Occur between 45-75 years

Sex

M>F 2:1

Procedures:

Bone marrow aspiration and biopsy.

-Increased mature lymphocytes in the bone marrow-normal up to 5% but in CLL up to 40 %

-Decreased myeloid, erythroid and megakaryocytic cells.

-blast transformation may occur but is lymphoid type only unlike CML. When such transformation is accompanied by **fever, weight loss, and pain**, it is termed **Richter syndrome**

Consider a lymph node biopsy if lymph node(s) begin to enlarge rapidly in a patient with known CLL to assess the possibility of transformation to a high-grade lymphoma.

Staging:

Two staging systems are in common use, the Rai-Sawitsky in the United States and the Binet in Europe.

Neither is completely satisfactory, and both have been often modified.

The Rai-Sawitsky staging system divides CLL into 5 Stages, 0-IV.

Based on lymphocytosis(0), adenopathy(1), splenomegaly(2) ,Anemia(3),Thrombocytopenia(4)

Stage 0 is lymphocytosis in the blood and marrow only, with a survival of longer than 120 months.

Stage I is lymphocytosis and adenopathy, with a survival of 95 months.

Stage II is lymphocytosis plus splenomegaly and/or hepatomegaly, with a survival of 72 months.

Stage III is lymphocytosis plus anemia (hemoglobin <10 g), with a survival of 30 months.

Stage IV is lymphocytosis plus thrombocytopenia (platelets <100,000), with a survival of 30 months.

The Binet staging system uses 3 stages,

A, B, and C.

History:

-Patients with CLL present with a wide range of symptoms and signs at presentation.

-Onset is insidious, and it is not unusual for this disorder to be discovered incidentally after a blood cell count is performed for another reason.

- ✓ Predisposition to repeated infections such as pneumonia, herpes simplex labialis, and herpes zoster
- ✓ Enlarged lymph nodes
- ✓ Early satiety and/or abdominal discomfort related to an enlarged spleen
- ✓ Mucocutaneous bleeding and/or petechiae secondary to thrombocytopenia
- ✓ Tiredness and fatigue secondary to anemia

Physical:

-Localized or generalized lymphadenopathy

-Splenomegaly (30-40% of cases)

-Hepatomegaly (20% of cases)

-Petechiae

-Pallor

Causes:

-As in the case of most malignancies, the exact cause of CLL is uncertain.

-The proto-oncogene *bcl2* is known to be overexpressed, which leads to suppression of apoptosis (programmed cell death) in the affected lymphoid cells.

-CLL is an acquired disorder, and reports of truly familial cases are exceedingly rare

Investigations

CBC count with differential

1-Absolute lymphocytosis with more than 5000 lymphocytes/ m L.

Some consider this to be a prerequisite for the diagnosis of CLL and classify cases that would otherwise meet the criteria as small lymphocytic lymphoma/diffuse well-differentiated lymphoma.

2-Anemia-normocytic normochromic

3-Thrombocytopenia

PBF

- ✓ confirm lymphocytosis
- ✓ Presence of smudge cells, which are artifacts due to damaged lymphocytes during the slide preparation.

Flow cytometry

The most valuable test to confirm CLL.

-It confirms the presence of circulating clonal B-lymphocytes expressing CD5, CD19, CD20(dim), CD 23, and an absence of FMC-7 staining.

-T-cell immunotype (CD2, CD3, and CD8)

Imaging Studies:

Liver/spleen scan may demonstrate splenomegaly. Computed tomography of chest, abdomen, or pelvis generally is not required for staging purposes. However, be careful to not miss lesions such as obstructive uropathy or airway obstruction that are caused by lymph node compression on organs or internal structures.

Patients at stages 0,1, 2 whose disease is stable require only periodic follow-up.

1.Prednisolone

-Prednisolone alone, usually in a dose of 20-60 mg daily initially, with subsequent gradual dose reduction, may be useful in patients with autoimmune manifestations of the disease.

2.**Nucleoside analogs**

-Nucleoside analogs

- Fludarabine
- Cladribine
- Pentostatin

3.**Chlorambucil and prednisone**

-Responses to treatment with chlorambucil and prednisone are observed in 38-47% of patients.

-Patients treated with fludarabine have much higher rates (80%) of overall responses and a 37% complete remission rate.

4.Rituxan (rituximab)

-Therapy with monoclonal antibodies eg an antibody directed at CD52.

Stage A requires a hemoglobin of greater than or equal to 100 g/L, platelets greater than or equal to 100 X 10^{-9}, and fewer than 3 lymph node areas involved (Rai-Sawitsky stages 0, I, II). Survival is longer than 120 months.
Stage B requires hemoglobin and platelet levels as in stage A and 3 or more lymph node areas involved (Rai-Sawitsky stages I and II). Survival is 61 months.
Stage C is a hemoglobin less than 100 g/L, platelets less than 100 X 10^{-9}, or both (Rai-Sawitsky stages III and IV). Survival is 32 months.

Chemotherapy

At the time of diagnosis, most patients do not need to be treated with chemotherapy unless they have :

- Weight loss of more than 10%
- Extreme fatigue
- Fever related to leukemia
- Night sweats
- Progressive marrow failure
- Autoimmune anemia or thrombocytopenia not responding to prednisone
- Progressive splenomegaly
- Massive lymphadenopathy
- Progressive lymphocytosis. Progressive lymphocytosis is defined as an increase of greater than 50% in 2 months or a doubling time of less than 6 months.

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CHRONIC MYELOCYTIC LEUKEMIA

Background:

-Chronic myelogenous leukemia (CML) is a myelo-proliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate.
-Consequently, the peripheral blood cell profile shows an increased number of granulocytes and their immature precursors, including occasional blast cells.

Pathophysiology:

-CML is an acquired abnormality that involves the hematopoietic stem cell.
-The Philadelphia chromosome is characterized by a cytogenetic aberration consisting of a reciprocal translocation between the long arms of chromosomes 22 and 9; t(9;22).
-The translocation result in a shortened chromosome 22.as a large portion of 22q is translocated to 9 q, and a smaller piece of 9q is moved to 22q.
-This translocation relocates an oncogene called *abl* from the long arm of chromosome 9 to the long arm of chromosome 22 in the *BCR* region.
The resulting ***BCR/ABL*** fusion gene encodes a chimeric protein with **strong tyrosine kinase activity**. The expression of this protein leads to the development of the CML.
The presence of *BCR/ABL* rearrangement is the hallmark of CML, although this rearrangement has also been described in other diseases. It is considered diagnostic when present in a patient with clinical manifestations of CML.

Sex-slight M>F

Frequency

-CML accounts for 20% of all leukemia affecting adults.
-world wide-1-1.5 per 100,000

Age

-It peaks 40-50 years.
-Although uncommon, the disease also occurs in younger individuals.
(More aggressive)Increased incidence was reported among individuals exposed to radiation

Mortality/Morbidity

Generally, 3 phases of the disease are recognized. The general course of the disease is characterized by an eventual evolution to a refractory form of acute myelogenous or, occasionally, lymphoblastic leukemia. The median survival of patients using older forms of therapy was 3-5 years.

a)**Chronic phase**

-Typical symptoms are due to increasing anemia, thrombocytopenia, basophilia, a rapidly enlarging spleen, and failure of the usual medications to control leukocytosis and splenomegaly.
-The manifestations crisis is similar to those of acute leukemia.
-Treatment results are unsatisfactory, and most patients succumb to the disease once this phase develops
-In 2/3 cases, the blasts are myeloid.
-1/3 of patients, the blasts exhibit a lymphoid phenotype, further evidence of the stem cell nature of the original disease.
-Additional chromosomal abnormalities are usually found at the time of blast crisis, including additional Philadelphia chromosomes or other translocations.

c) **Accelerated phase**

-Occurs 3-6 months before the diagnosis of blast crisis.
-Clinical features in this phase are intermediate between the chronic phase and blast crisis

.**Clinical presentation**

History:

- insidious
-discovered incidentally when an elevated WBC count is revealed by a routine blood count or when an enlarged spleen is revealed during a general physical examination.
-Nonspecific symptoms of tiredness, fatigue, and weight loss may occur long after the onset of the disease.
-Loss of energy and decreased exercise tolerance may occur during the chronic phase after several months.
-Patients often have symptoms related to enlargement of the spleen, liver, or both. The large spleen may encroach on the stomach and cause early satiety and decreased food intake.
-Left upper quadrant abdominal pain described as "gripping" may occur from spleen infarction. The enlarged spleen may also be associated with a hypermetabolic state, fever, weight loss, and chronic fatigue.
-The enlarged liver may contribute to the patient's weight loss.
-Some patients may have low-grade fever and excessive sweating related to hypermetabolism.
- Rarely, the patient will present with a clinical syndrome related to leukostasis with blurred vision, respiratory distress, or priapism

The disease has 3 clinical phases

Chronic phase

-Most patients are diagnosed while still in the chronic phase.
-The WBC count is usually controlled with medication (hematologic remission).
-This phase varies in duration depending on the maintenance therapy used.
It usually lasts 2-3 years with hydroxyurea (Hydrea) or busulfan therapy
-but it has lasted for longer than 9.5 years in patients who respond well to interferon alfa therapy.
- Imatinib mesylate has dramatically improved the duration of hematologic and indeed cytogenetic remissions.

Investigations

FBC

The hallmark of **CML** is an elevated WBC; the median white blood count at diagnosis is 150,000/uL.
-Moderate anemia (8-10 g/dl) normocytic normochromic
-Thrombocytosis

-PBF

The peripheral blood is characteristic. The myeloid series is left-shifted, with mature forms dominating and with cells usually present in proportion to their degree of maturation.
-Blasts are usually less than 5%. In chronic phase
-Basophilia and eosinophilia of granulocytes may be present.
NB. With progression to the accelerated and blast phases, progressive anemia and thrombocytopenia occur, and the percentage of blasts in the blood and bone marrow increases.

Cytochemistry

-most patients present in this phase characterized by splenomegaly and leukocytosis with generally few symptoms.
-This phase is easily controlled by medication.
-The major goal of treatment during this phase is to control symptoms and complications resulting from anemia, thrombocytopenia, leukocytosis, and splenomegaly.
-Newer forms of therapy aim at delaying the onset of the accelerated or blastic phase.

b)Blast crisis

-After an average of 3-5 years
-Marked by an increase in the bone marrow or peripheral blood blast count or by the development of soft tissue or skin leukemic infiltrates.

Transitional or accelerated phase

-Some patients to this phase to which may last for several months.
-The survival of patients diagnosed in this phase is 1-2 years. This phase is characterized by poor control of the blood counts with myelosuppressive medication and the appearance of

- ✓ Peripheral blast cells (≥15%)
- ✓ Promyelocytes (≥30%))
- ✓ Basophils (≥20%),
- ✓ Platelet counts less than 100,000 cells/ m L unrelated to therapy.

-Usually, the doses of the medications need to be increased. -Splenomegaly may not be controllable by medications, and anemia can worsen.
-Bone pain and fever, as well as an increase in bone marrow fibrosis, are harbingers of the last phase.

Acute phase, or blast crisis

- Is similar to acute leukemia, and survival is 3-6 months at this stage.
-Bone marrow and peripheral blood blasts of 30% or more are characteristic.
-Skin or tissue infiltration also defines blast crisis.
-Cytogenetic evidence of another Ph-positive clones (double) or clonal evolution (other cytogenetic abnormalities such as trisomy 8, 9, 19, or 21, isochromosome 17, or deletion of Y chromosome) is usually present.
-Bleeding, petechiae, and ecchymoses may be the prominent symptoms. In these situations, fever is usually associated with infections.

Physical: Parlor, wasted or signs of infection

-Massive Splenomegaly is the most common physical finding in patients with CML.

- ✓ -Size of the spleen correlates WBC counts, biggest spleens high WBC counts.
- ✓ -A very large spleen harbinger of the transformation into an acute blast crisis form of the disease.

-Hepatomegaly -less commonly than splenomegaly.Part of the extramedullary hematopoiesis occurring in the spleen.
-Sternal tenderness may be present as a sign of marrow overexpansion.
-Leukostasis and hyperviscosity can occur in some patients, with extraordinary elevation of their WBC counts, exceeding 300,000-600,000 cells/ m L.
-Upon funduscopy, the retina may show papilledema, venous obstruction, and hemorrhages.

Causes:

-The initiating factor of CML is still unknown, but exposure to irradiation has been implicated
Other agents, such as benzene, are possible causes
DDX

- Myelofibrosis ,Myelodysplastic Syndrome Myeloproliferative Disease
- Polycythemia Vera
- Leukemoid reactions from infections (chronic granulomatous, eg, tuberculosis)
- Tumor necrosis
- Essential thrombocytosis/thrombocythemia
- CLL ,AML

Imaging Studies:

-Leukocyte alkaline phosphatase score is invariably low and is a sign of qualitative abnormalities in neutrophils. This unlike leukamoid reactions eg infections-TB, leishmania when LAP is elevated.
-Serum vitamin B_{12} level elevated
-Markedly elevated serum vitamin B-12–binding protein (TC-I). The latter is synthesized by the granulocytes and reflects the degree of leukocytosis
- Hyperuricemia, which is a reflection of high bone marrow cellular turnover

BMA

Bone marrow is hypercellular, with left-shifted myelopoiesis.
Myeloblasts < 10% of marrow cells in chronic phase
10-30% in the transitional and >30 % in Blast crisis
-Assess Fibrosis-Many patients develop myelofibrosis in later stages of the disease
-Increased myeloid/erythroid ratio
-Increased megakaryocyes

Cytogenetics

Philadelphia chromosomes-t(9,22) abl/bcr fusion gene.
The Philadelphia chromosome may be detected in either the peripheral blood or the bone marrow. The *bcr-abl* gene may be reliably found in peripheral blood by molecular techniques.
Usually at the time of diagnosis, the Philadelphia chromosome-positive clone dominates and may be the only one detected. About 5% of cases Philadelphia chromosome-negative at the level of light microscope cytogenetics, though molecular studies demonstrate the *bcr/abl* fusion gene.
Additional chromosomal abnormalities, such as an additional or double Ph-positive chromosome or trisomy 8, 9, 19, or 21; isochromosome 17; or deletion of the Y chromosome, have been described as the patient enters a transitional form or accelerated phase of the blast crisis as the Ph chromosome persists.

Other drugs:

2.Hydroxyurea (Hydrea)

-Inhibitor of deoxynucleotide synthesis is the most common myelosuppressive agent used to achieve hematologic remission.
The initial blood cell count is monitored every 2-4 weeks, and the dose is adjusted depending on the WBC and platelet counts.
Most patients achieve hematologic remission within 1-2 months. This medication causes only a short duration of myelosuppression, so even if the counts go lower than intended, stopping or decreasing doses usually controls the blood counts.
-Maintenance with hydroxyurea rarely results in cytogenetic or molecular remissions.

3.Busulfan (Myleran)

-an alkylating agent that has traditionally been used to keep the WBC counts less than 15,000 cells/ m L
-. However, the myelosuppressive effects may occur much later and persist longer, making maintaining the numbers within normal limits more difficult.
-Long-term use can cause pulmonary fibrosis, hyperpigmentation, and prolonged marrow suppression lasting for months.

4.Interferon alfa

-was the treatment of choice for most patients with CML who are too old for bone marrow transplantation (BMT) or who do not have a matched bone marrow donor.
- Interferon alfa is given at an average of 3-5 million IU/d subcutaneously after hematologic remission with hydroxyurea

5.Leukapheresis

using a cell separator can lower WBC counts rapidly and safely in patients with WBC counts of higher than 300,000 cells/ m L, and it can alleviate acute symptoms of leukostasis, hyperviscosity, and tissue infiltration. Leukapheresis usually reduces the WBC count only temporarily and is often combined with cytoreductive chemotherapy for more lasting effects.

6..**BMT**

-should be considered early in young patients (<55 y) who have a matched sibling donor.

Typical hepatomegaly and splenomegaly may be imaged by using a liver/spleen scan.

Histologic Findings:

Diagnosis is based on the histopathologic findings in the peripheral blood and the Ph1 chromosome in the bone marrow cells is 40-50%.

Medical Care:

The 3-fold goals of treatment of CML

1) achieve a hematologic remission (normal CBC count and physical examination, ie, no organomegaly)
2) Achieve cytogenetic remission (normal chromosome returns with 0% Ph-positive cells)
3) Most recently, to achieve molecular remission (negative PCR result for the mutational *BCR/ABL* m-RNA). –attempt cure and prolongation of patient survival.

A new approach is to directly inhibit the molecular cause of the disease, ie, using a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase

1.STI-571 or ima-tinib mesylate (Gleevec)

-Inhibits **-**Proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for *BCR/ABL* and fresh leukemic cells in CML positive for the Ph chromosome.

-With imatinib at **400 mg/d orally** in patients with newly diagnosed Ph-positive CML in the chronic phase, the complete cytogenetic response rate is 70% and the estimated 3-year survival rate is 94%.

-With higher doses of **800 mg/d**, the complete cytogenetic response rate increases to 98%, the major molecular response rate is 70%, and the complete molecular response rate

NB

Lymphoid blast crisis (present in one-third of cases) should be identified because chemotherapy is less toxic and more effective.

-Therapy with daunorubicin, vincristine, and prednisone (used in treatment of acute lymphoblastic leukemia) will lead to remission¾usually short-lived¾in 70% of these cases.