CLINICAL CASES AND PEARLS IN MEDICINE

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Dedicated to

Pujya Pita Diwan Sajanmal and Pujya Mata Pari Devi
&
My Loving Grand Daughters
Mishka, Ishita, Anaya & Myra
Preface

The origin of this book is based on the students behavioral patterns and their increased nervousness during practical examination. The percentage of success rate in medicine practical is lower than theory examination. For theory examination, the student has to remember the facts by reading a standard textbook of medicine, recall and reproduce the facts to answer the questions to the point. But, in practical examination, the student should have an expertise in bedside clinical methods to elicit proper history, clinical signs in the allotted time in long, short and spot cases to arrive at a proper diagnosis. Here, he is being observed particularly in short and spot cases by the examiners; hence, he has to follow the correct bedside methods of eliciting signs. He has to present the cases and answer the viva voce including demonstration of signs in the allotted time. He has to race against the time.

For sharpening their bedside clinical methods, I recommend the students to read Manual of Clinical and Practical Medicine by GS Sainani, VR Joshi and Rajesh G Sainani along with this book. Unfortunately, these days, students have developed wrong practices and slipshod methods of eliciting history and carrying out physical examination with the result that they are not able to elicit and demonstrate clinical signs in the examination.

In the book, I have discussed 203 clinical cases and described 101 pearls in medicine befitting the title of the book Clinical Cases and Pearls in Medicine. Pearls are nothing but important messages of clinical medicine which will help students to face the viva voce during practical examination. Each clinical case covers all important aspects of the case which the student is expected to know for practical. The book is enforced with 309 illustrations (relevant sketch diagrams and clinical photographs of the patients). Every important case is followed by the relevant viva voce.

The purpose and scope of the book is to help the student prepare for the medicine practical at final MBBS, MD, DNB and MRCP level. I strongly feel that this book should justifiably prove to be a key companion to the students appearing for medicine practical.

With my teaching experience of nearly 6 decades in clinical medicine at various medical colleges of Maharashtra, private teaching hospitals, at 10 foreign universities (mostly in USA), having taught MRCP students at Hammersmith and St Mary’s Hospitals, London and having been examiner for final MBBS, MD (at 18 Indian universities) and DNB medicine several times, I can say that any student will find these 203 cases more than adequate for his long, short and spot cases. Also, for the viva voce on cases and table viva voce, the textual matter given in cases and pearls in medicine will suffice so that the student will not have to read any other book before appearing for the medicine practical.

The book is written in simple English and mostly in points which covers a mammoth collection of important facts about clinical medicine and as it is supplemented by 309 illustrations, it makes it easy in reading, revising and remembering the clinical cases.

The book is envisaged to disseminate knowledge of clinical medicine not only to students appearing for practical examination but also serve as a ready-reckoner for a busy family physician and even consultants in medicine and its allied branches.

I would appreciate receiving a feedback and criticism from all our readers which will help me to improve further in the next edition.

GS Sainani
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The foundation of the book was laid during a family trip with my wife (Dr Pushpa Sainani) to visit my daughter (Dr Renuka Bathija) in Melbourne. I utilized that time by working on my book and my son-in-law (Mr Ravi Bathija) who is a software engineer helped type 70 clinical cases which were then edited by my daughter. Even my wife lent a helping hand in this family effort such that when I returned to Mumbai, the book had started to take shape with 70 clinical cases beautifully typed and spiral bound. This book has come a long way since then and I am grateful to my loving family who have always supported me in every way in all my endeavors.

My special thanks to Elsevier and my co-authors of Manual of Clinical and Practical Medicine, Dr VR Joshi and Dr Rajesh G Sainani who gave me the permission to use some of the figures from the Manual. I have taken 14 original figures from the Manual. Quite a few pictures from the Manual have been modified by Mr Manoj Pahuja (Senior Graphic Designer, M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India) and some by Mr Lokesh Uchil. I am grateful to both of them.

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**Pearls in Medicine**

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Oncology

Outlines

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BASIC CONSIDERATIONS

Oncological diseases are also labeled as hematological malignancies. These occur when the mechanism controlling proliferation of stem cells go wrong in blood cells. When primitive stem cells are involved, the cell can develop the higher growth resulting in all human neoplasms such as rapidly progressive life-threatening diseases like acute leukemia or high grade lymphomas. Involvement of pluripotent stem cells result in the most dangerous acute leukemia.

But if mature differential cells are affected, the cells will grow slowly and produce low grade lymphomas or chronic leukemia with relatively better prognosis.

Hematological malignancies mostly affect elderly persons. However, acute leukemia affects mainly children and Hodgkin’s lymphoma affects adults in the age group of 20–40 years.
INTRODUCTION

There are two main types of acute leukemia—acute myeloblastic leukemia (AML) and acute lymphoblastic leukemia (ALL).

SALIENT CLINICAL FEATURES

- Blast cells (myeloblast and lymphoblast) accumulate in bone marrow and they also appear in peripheral smear. If not treated in time, course is rapid and fatal. ALL occurs in children and elderly whereas AML affects young adults and middle aged.
- Onset is acute and patients present with fever, anemia, generalized pain, tenderness, weakness, bleeding from gums, ecchymosis, petechiae, epistaxis, hepatosplenomegaly, pain and tenderness of bones (because of bone marrow involvement) and lymphadenopathy (more common in ALL). Meninges may be involved which cause headache, nausea, vomiting, papilledema and neurological deficit particularly cranial nerves involvement.

INVESTIGATIONS

- Red blood cells (RBCs) counts, mean corpuscular volume (MCV) and Hb low
- White blood cells (WBCs) count elevated (40,000 to 100,000)
- Peripheral smear will show blast cells and lymphoid or myeloid premature cells depending upon whether it is ALL or AML. Myeloblast may show Auer rods in some cells (Figs 7.1 and 7.2).
- Platelets count low (thrombocytopenia)
- Bone marrow shows that more than 30% of normal cells are replaced by blast cells (lymphoblasts or myeloblasts) (Fig. 7.3)
- Due to fast turnover of cells, there is elevation of uric acid, lactate dehydrogenase (LDH) and alkaline phosphatase
- Renal profile (Serum creatinine, blood urea is done to detect renal failure)
• Cerebrospinal fluid (CSF) should be examined in all ALL cases to evaluate CNS affection
• To detect mediastinal lymphadenopathy, chest X-ray and CT chest are done in all cases
• Chromosomal studies
• Immunotyping and define lineage type whether B or T cells.

**MANAGEMENT PRINCIPLES**

**Chemotherapy**

The treatment is targeted to kill the leukemic clone of cells without destroying the normal stem cells. There are three stages: (1) Induction, (2) Consolidation, (3) Maintenance.

**Induction Phase**

One uses combination chemotherapy to destroy bulk of abnormal cells. During the treatment severe bone marrow hyperplasia occurs, which warrants supportive therapy. The drugs used are oral prednisolone, IV vincristine, IV daunorubicin, intrathecal methotrexate in cases of acute lymphocytic leukemia. For acute myeloid leukemia, IV daunorubicin, IV cytarabine an etoposide (IV and oral are used).

**Consolidation Phase**

If remission occurs, residual disease is managed by drugs during consolidation phase. For ALL—daunorubicin IV, cytarabine IV, methotrexate IV and for AML—cytarabine IV, amsacrine IV, mitoxantrone IV are used. One may have to give number of courses of chemotherapy, which will also cause bone marrow depression.

**Maintenance Phase**

If at the end of consolidation phase, patient of ALL is still in remission; one may use maintenance therapy for ALL by administering prednisolone (oral), vincristine IV, and methotrexate oral. In cases of ALL, it is essential to give prophylactic treatment to CNS by combination of radiotherapy and intrathecal chemotherapy. After that chemotherapy is discontinued and patient is observed.

• Administer RBC packed cells and platelet transfusions to treat anemia and thrombocytopenia
• Antibiotics for prophylaxis and treatment.
INTRODUCTION

- Chronic myeloid leukemia (CML) is a clonal disorder of pluripotent stem cell involving erythroid, myeloid, megakaryocytic and lymphoid cells. Normal stem cells are not affected as they can emerge after suppression of CML clone with chemotherapy. In majority of cases CML progresses to an accelerated phase and then finally blast crisis occurs.
- About 90–95% cases have reciprocal translocation between long arms of chromosomes 9 and 22, which is a cytogenetic abnormality. The translocated piece of chromosome 9 contains oncogene c-Abl. This and BCR gene on chromosome 22 fuse with formation of ABL-BCR fusion gene. This abnormal 22 chromosome is known as Philadelphia chromosome (Ph).
- In survivors of atomic bomb, higher prevalence has been reported. Patients undergoing radiation treatment have greater risk. Exact cause is not known.

SALIENT CLINICAL FEATURES

- More common in elderly (40–70 years)
- There is initial period where patient is asymptomatic and that may be diagnosed accidentally on routine checkup
- Patient presents with fever, loss of weight, sweats at night, generalized weakness and tiredness
- Physical examination reveals pallor, slight liver enlargement, moderate spleen enlargement and tenderness over bones particularly sternum
- In late stages, lymphadenopathy occurs and skin is involved, and these foretell poor prognosis
- Accelerated phase follows, which is characterized by anemia and thrombocytopenia and defective granulocytes
- The final stage of blast crisis reveals myeloblast (60% patients), lymphoblast (30% patients) megakaryoblast (20% patients). Additional chromosomal abnormalities are frequent. Blast cell tumors may develop at extramedullary sites. This stage resembles acute leukemia.

INVESTIGATIONS AND DIAGNOSIS

- High leukocytosis (WBC > 50,000 to few lakhs/mm³) in symptomatic patients
- Hb low (normocytic normochromic anemia)
- Initially platelet count is raised, later it becomes low
- Peripheral smear is diagnostic as it contains all myeloid cells—promyelocyte, myelocyte and metamyelocyte (> 30%) and myeloblast (< 10%). Eosinophils are also present (Fig. 7.4).
- Bone marrow (BM) is full with myeloid series as seen in peripheral smear. In majority (90%) Ph is present. In some cases myelofibrosis is also seen
- B₁₂ levels and LDH are elevated. Low leukocyte alkaline phosphatase.

![Peripheral smear from a case of chronic myeloid leukemia showing myelocytes, metamyelocytes, mature neutrophils, eosinophils and other cells](Fig. 7.4)
DIFFERENTIAL DIAGNOSIS

- **Myeloid leukemoid reaction** reveals absence of eosinophilia and basophilia, along with elevated leukocyte alkaline phosphatase
- **Myelofibrosis**: In this nucleated RBC, and teardrop RBC, anemia and thrombocytopenia are seen and these are diagnostic.

MANAGEMENT

**Palliative/Symptomatic**

- Interferon gamma (IFN gamma)
- Hydroxyurea (0.5–2 g) daily for induction and maintenance
- Radiation to spleen in refractory cases
- Splenectomy relieves abdominal discomfort or when other treatment cannot control hypersplenism. It may relieve thrombocytopenia and patient’s requirement of blood is reduced
- Busulfan, hydroxyurea and IFN-gamma are used to treat ABL-BCR negative patients, patients after relapse and blast crisis. These achieve only symptomatic relief. Hydroxyurea (0.5–2 g) is administered as per response. Now-a-days Busulfan is not recommended.

**Curative Treatment**

- The drug of choice is Imatinib, which achieves complete clinical and cytogenic remission of Ph positive CML. It also works in accelerated phase. When there is resistance to **Imatinib**, newer agents like dasatinib and nilotinib are good alternatives.
- **Bone marrow transplant**: First eradicate leukemia clone with chemotherapy and radiotherapy and then allogeneic BM transplant is carried out to restore normal hemopoiesis; however, with newer agents mentioned above (Imatinib, dasatinib and nilotinib) the need for BM transplant has become less.
- **Blast crisis**: Here management is like acute leukemia, the regime will depend upon type of blast crisis transformation (myeloblastic or lymphoblastic). In some cases novel new drugs imatinib or dasatinib with enhanced dose can be tried.

VIVA VOCE

Q1. Tell the anatomical location of spleen and what is your comment when spleen is just palpable?
- Remember that spleen must be at least twice its size to be just palpable
- Remember that the spleen in normal persons does not extend beyond the anterior axillary line and lies along the 9th, 10th and 11th ribs. **The spleen percussion sign is a useful diagnostic technique.**

Q2. What are the causes of massive splenomegaly?
- Malaria
- Kala-azar
- Chronic myeloid leukemia
- Myelofibrosis
- Gunther’s disease
- Hodgkin’s disease.

Q3. Describe the terms myeloid metaplasia and extramedullary hemopoiesis.
- These two words are used interchangeably. Have process of ectopic hematopoietic activity, which may occur in any organ (liver, spleen). It may or may not be associated with myelofibrosis.
INTRODUCTION

- In the west, this is the most common type of leukemia with long life span
- It comprises 25% of all types of leukemia. It is relatively less common in India.
- It originates from a clone of mostly CD5 B lymphocytes.

SALIENT CLINICAL FEATURES

- It is seen in early childhood or elderly persons (60 years and above)
- Males suffer more than females. Male: Female ratio is 2:1
- It is usually asymptomatic (70% of patients) and detected during routine check-up
- Lymphocytes increase and they accumulate in BM, blood, lymph nodes, liver and spleen. In later stages BM gets fully saturated till it fails
- In initial stages, generalized lymphadenopathy, mild enlargement of liver and spleen and anemia are common
- In late stages, anemia, neutropenia, thrombocytopenia and reduced Ig production develop because of extensive BM involvement. There is also increased susceptibility to infections, which is due to granulocytopenia and hypogammaglobulinemia. Hence, patient presents with chest infections and fever
- Patients are also susceptible to autoimmune diseases, autoimmune hemolytic anemia and slightly more risk of developing other cancers.

INVESTIGATIONS

- BM and peripheral smear are packed with lymphocytes (> 30%) (Fig. 7.5) and more than 5000/mm³ is the absolute lymphocyte count
- Autoimmune hemolytic anemia occurs in 18% cases—hemoglobin is reduced
- Hypogammaglobulinemia
- In few cases monoclonal band is seen on protein electrophoresis
- Beta cell type chronic lymphatic leukemia (CLL) is the most common subtype having CD5 and CD23 as surface markers.

STAGING OF CHRONIC LYMPHOCYTIC LEUKEMIA

RAI Staging

- Stage 0: Absolute lymphocytes greater than 10,000/mm³ in blood and in BM, absolute lymphocytes > 30%
- Stage I: Lymphocytosis plus lymphadenopathy
- Stage II: Lymphocytosis plus lymphadenopathy plus liver and spleen enlargement
- Stage III: Lymphocytosis plus lymphadenopathy with anemia (Hb < 11 g) plus splenomegaly or hepatomegaly may be present
- Stage IV: Lymphocytosis with lymphadenopathy with thrombocytopenia plus splenomegaly or hepatomegaly may be present
Clinical Cases in Medicine

**Modified RAI Staging as per Risk**
- **Low risk:** Stage 0
- **Intermediate risk:** Stages I and II
- **High risk:** Stages III and IV.

**DIAGNOSIS**
- Diagnosis is confirmed by high lymphocyte count in peripheral smear and BM packed with lymphocytes.

**Differential Diagnosis**
- Reactive lymphocytosis seen in viral infections (one may see atypical lymphocytes in peripheral smear)
- Lymphocytic lymphoma
- **Sezary syndrome**
- **Hairy cell leukemia.**

**PROGNOSIS**
- Overall median survival is 10 years. However, patients with stage 0 to II usually live up to 20 years with no treatment and ultimately die of unrelated diseases.
- Some patients may develop second malignancy especially skin cancer
- Broadly one-third patients do not require treatment and die of unrelated diseases. In other third, disease is very aggressive from the onset and needs immediate treatment. In the remaining the disease is initially indolent followed by rapid progression.

**MANAGEMENT**
- Asymptomatic patients, no specific treatment but they should be offered supportive treatment like blood transfusions, treatment of infections with antibiotics, gamma globulin for patients having hypogamma-globulinemia with frequent infections.
- In symptomatic patients, specific treatment is advised in stage I with high lymphocyte count (> 100,000 mm³) or in patients with massive splenomegaly and lymphadenopathy.

**Specific Chemotherapeutic Treatment**
- Chlorambucil (0.1–0.2 mg/kg BW) daily for 1–2 weeks each month along with corticosteroids
- Combination of cyclophosphamide, vincristine and prednisolone (CVP regimen) used particularly in chlorambucil resistant patients
- Purine analogs—Fludarabine, 2-chlorodeoxyadenosine (2CdA) and 2-deoxycoformycin (DCI) interfere with purine degradation and are highly lymphocytotoxic
- Monoclonal antibody—Rituximab and alemtuzumab are very effective and can be combined with chemotherapy
- Steroids for autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP)
- In some cases local radiation can be tried
- Bone marrow transplant (allogeneic) done in few cases.

**Note:** As CLL is an indolent disease and the response to BM transplant is not good, one should not take the risk of BM transplant.

**VIVA VOCE**

**Q1. Explain causes of anemia in CLL.**
- Bone marrow infiltration
- Autoimmune (Coomb’s test positive)
- Hemolysis.

**Q2. Describe Binet staging of CLL.**
It evaluates the enlargement of spleen, liver and lymph nodes in the head and neck, axillae and groin. It has three stages A–C:
A. Less than three areas of lymph node enlargement and there is neither anemia nor thrombocytopenia.
B. Three or more lymphoid areas involved and there is neither anemia nor thrombocytopenia.
C. Regardless of the number of areas of lymphoid enlargement, but there is either anemia and/or thrombocytopenia.

Q3. **Describe Richter syndrome.**  
When, an isolated lymph node in chronic lymphocytic leukemia gets converted into a large cell lymphoma. The prognosis is very poor and the median survival is less than 1 year after its appearance.

Q4. **Describe lymphomas, which convert to leukemia.**  
- **Burkitt’s lymphoma** may get converted to B cell acute lymphoblastic leukemia  
- Lymphoblastic lymphoma can get transformed to T cell acute lymphoblastic leukemia  
- Small cell lymphoma may sometimes get converted to chronic lymphocytic leukemia.
INTRODUCTION

- It is the most common plasma cell disorder. It is a clonal disorder of plasma cells, which secrete only one type of immunoglobulin (monoclonal immunoglobulin). IgG in about 55% of cases, IgA in about 20%, IgD in 1% and light chains in about 15–20% cases.
- Since abnormal immunoglobulins are produced without antigenic stimulation, there is reduced production of normal immunoglobulin, which makes patients more prone to infections.
- Bone marrow is fully packed with plasma cells with the result that bone is eroded resulting in pathological fractures. Osteoclastic activity of myeloma cells is due to osteoclast activating factor (cytokines) released by myeloma cells. That results in osteoporosis or osteolytic lesions. Common sites are skull, pelvis, ribs and spine.
- In 65% cases, light chains either k or λ appear in urine (Bence Jones proteins).
- Renal damage occurs due to Bence Jones proteinuria, hyperuricemia and amyloidosis. Calcium is released from bones causing hypercalcemia and hypercalciuria and nephrocalcinosis.
- Hyperviscosity syndrome due to abnormal immunoglobulins presents as anorexia, weakness, retinal and neurological abnormalities. BM invasion by plasma cells results in myelophthisic anemia, thrombocytopenia and leukopenia. In majority, plasma cells are also seen in peripheral blood (buffy coat preparation).

SALIENT CLINICAL FEATURES

- Men have higher prevalence, present between 50 and 70 years of age. About 20% are asymptomatic and are detected during routine checkup.
- Onset is insidious and present with backache, body ache, pain in joints, pathological fractures, infections particularly chest infections are seen.
- Some patients may present with neurological features like compression myelopathy, amyloid peripheral neuropathy, and carpal tunnel syndrome.
- Liver enlargement (40%), spleen enlargement (20%) and lymphadenopathy is seen.
- Renal failure due to extensive cast formation in the tubules, tubular atrophy and interstitial fibrosis may occur.
- Because of immunodeficiency, pneumonia and herpes zoster occur.
- Secondary amyloidosis is seen in 10% particularly in patients with Bence Jones proteinuria.
- Hyperviscosity symptoms, polyuria, polydipsia (secondary to hypercalcemia) may be present.

INVESTIGATIONS

- **Blood:** Normocytic, normochromic anemia, neutropenia, thrombocytopenia, coagulation defects, hyperviscosity features and rouleaux formation are seen in peripheral smear (Fig. 7.6)
- **X-ray of skeleton:** Osteoporosis or osteolytic lesions in skull, pelvis, vertebrae, ribs, clavicle and pathological fractures (Fig. 7.7)
**Clinical Cases in Medicine**

**Erythrocyte sedimentation rate (ESR) is very high (> 100 mm/hour), a typical feature**

- Hypercalcemia
- Increased serum β2 microglobulin levels (reflect plasma cell mass)
- Protein electrophoresis for M band in serum and urine
- Urine for Bence Jones proteins
- BM shows plasma cells with eccentric nucleus, which constitute greater than 10% of total nucleated cells.

**DIAGNOSIS**

- Typical features: Suspect multiple myeloma if following features are present:
  - Unexplained bone pains (particularly at night)
  - Elevated serum protein with M band protein on electrophoresis
  - Hypercalcemia
  - Anemia
  - Renal insufficiency
- Very high ESR (> 100 mm/hour)
- **Bence Jones proteinuria.** M band on serum immunoelectrophoresis of serum and urine
- **X-ray skull and bones:** Punched out lesions
- Bone marrow examination increased plasma cells greater than 10% is diagnostic

- Light chain myeloma in 20% (K or λ. Bence Jones protein), M band in serum present in 85%.

**PROGNOSIS**

- It runs a prolonged course with 3–4 years survival

**Fig. 7.7 X-ray skull showing osteolytic lesions in multiple myeloma**

**Poor prognosis, if following are present:** Hb less than 7 g/dL, blood urea greater than 80 mg/dL, low albumin, high levels of M protein, raised β2 microglobulin, hypercalcemia and diffuse bone lesions.

**MANAGEMENT**

- Intermittent courses of melphalan (0.15 mg/kg/day) with prednisolone (60 mg) daily after breakfast for 4 days, repeated monthly. Evaluate at 3–6 months
- Cyclophosphamide (oral 1.5 mg/kg/day) it improves median survival and general health
- If the response to above standard treatment is not good, combination of vincristine, adriamycin, doxorubicin and dexamethasone is tried
- Thalidomide along with melphalan and prednisolone is the standard treatment for majority of patients especially in the elderly. Bortezomib added to melphalan and prednisolone is also very effective and is the treatment of choice
- Autologous peripheral stem cells transplantation is recommended as curative for patients less than 70 years of age with stable disease and stable renal, cardiac, pulmonary, hepatic functions
- Allogeneic BM transplantation for patients less than 30 years is an option in high risk or resistant cases, expected survival up to 5–10 years
- Bisphosphonates are very effective for bone lesions.
General Supportive Treatment

- Prompt treatment for infections. Pneumococcal, influenza vaccines are given to all patients.
- For prevention of renal complications of hyperuricemia, administer IV fluids, sodium bicarbonate and a small dose of furosemide to achieve 2 L/day output.
- Allopurinol for treatment of hyperuricemia.
- For hyperviscosity syndrome carry out plasmapheresis.
- Treatment for bone fractures, osteoporosis: ambulation, passive physiotherapy, analgesics, pamidronate or other bisphosphonates are recommended.
- Packed RBC for anemia.
- Erythropoietin in cases of renal failure to improve hemoglobin.
INTRODUCTION
There is extensive fibrosis of bone marrow causing compensatory myeloid metaplasia in liver and spleen resulting in massive hepatosplenomegaly.

SALIENT CLINICAL FEATURES
- Patients suffer from severe weakness, loss of weight, lethargy, pain over muscles, bones and massive hepatosplenomegaly
- The usual causes of death are bleeding, infections and thrombotic episodes.

INVESTIGATIONS
- Blood: Peripheral smear reveals microcytic anemia, tear drop erythroblasts, leukoblasts
- Bone marrow biopsy showing hypercellularity, megakaryocytic hyperplasia, myeloid hyperplasia and thickened hypertrophied bony trabeculae (Fig. 7.8)
- Hyperuricemia.

Principles of Management
- Blood transfusion
- Folic acid, corticosteroids, hydroxyurea, androgen therapy
- Splenectomy, spleen radiation and BM transplant.

VIVA VOCE
Q1. Describe conditions in which neutrophil alkaline phosphatase is increased.
- Polycythemia vera
- Essential thrombocythemia
- Myelosclerosis.

Q2. Describe conditions in which neutrophil alkaline phosphatase is decreased.
- Chronic myeloid leukemia
- Aplastic anemia.
MYELOPROLIFERATIVE DISORDERS

This term denotes that there is proliferation of all precursor cells of bone marrow—RBCs (polycythemia), WBCs (chronic myeloid leukemia) and platelets (primary thrombocythemia).

CASE 6: POLYCYTHEMIA VERA

SALIENT CLINICAL FEATURES

- There is an excessive increase in RBC cell mass (independent of erythropoietin), which results in clinical symptoms. The increased viscosity and vascular stasis leads to thrombotic accidents. Patient has plethoric and cyanotic hue color of the skin because of stagnation and deoxygenation of blood in peripheral blood vessels.
- Patient suffers from headache, giddiness, hypertension, angina, and cerebrovascular episodes. Abdominal symptoms such as melena, hematemesis, pain in left hypochondriac region (spleen area) due to splenic infraction or lumbar region (renal infarction). Splenomegaly is important and present in majority of patients.
- Late complications include failure of erythropoiesis, myelofibrosis, thrombocytosis and acute leukemia.

**Note: In polycythemia vera, patient has plethora of face with suffusion of conjunctiva.**

INVESTIGATIONS

- RBC count raised—7–10 million/μL
- Hb greater than 18 g/d
- PCV greater than 60%
- WBC count greater than 12000/μL
- Elevated neutrophil alkaline phosphatase
- Hyperuricemia
- Vitamin B₁₂ levels raised
- Iron store depleted
- Bone marrow hypercellular with panmyelosis (increase in erythropoiesis, granulopoiesis and megakaryopoiesis).

SECONDARY POLYCYTHEMIA

Basically 2 mechanisms result in secondary polycythemia

1. Hypoxia—Causes are:
   - High altitude
   - Congenital cyanotic heart disease
   - Chronic lung disease
   - Chronic smoking
   - Gross obesity, Pickwickian syndrome causing sleep apnea
   - Abnormal hemoglobins.
2. Inappropriate erythropoietin secretion by tumors of kidney (hypernephroma), liver (hepatoma), uterus (uterine fibroma) and pheochromocytoma.

MANAGEMENT

- Venesection (300–500 mL) of blood removed at one sitting. It is repeated every alternate days till hematocrit decreases to less than 45%. Later it can be repeated as and when necessary
- Hydroxyurea
- Interferon α-2b, if hydroxyurea fails
- Allopurinol to treat hyperuricemia which increases following chemotherapy
- Radioactive phosphorus (32 P).
INTRODUCTION
Platelet count is very high greater than 600,000/μL. Morphologically platelets are abnormal.

SALIENT CLINICAL FEATURES
- Approximately 35% patients are asymptomatic
- Presenting complaints are thrombotic episodes, hematemesis, melena, vascular headaches, paresthesias, burning feet, spleen enlargement but liver enlargement is rare.
- Life expectancy is normal.

INVESTIGATIONS
- Platelet count greater than or equal to 600,000/μL
- Hb%, PCV are normal
- Iron stores normal
- Philadelphia chromosome is absent.

MANAGEMENT
- In asymptomatic patients, aspirin (75 mg/day)
- For symptomatic patients, one may use following therapies
  - Busulfan or hydroxyurea [25 mg/kg/day (orally)]
  - Radioactive phosphorous (2.5–3 mci/m²) IV every 6 months for 2 years
  - In severe cases with very high platelet count, IFN-α in a dose of 2–4 MU/m² subcutaneously daily or on alternate days
  - Leukemic transformation is treated like acute myeloid leukemia.
LYMPHOMAS

Two types of lymphomas—Non-Hodgkin’s (70%) and Hodgkin’s lymphoma (30%).

CASE 8: NON-HODGKIN’S LYMPHOMA

INTRODUCTION

Here there is malignant monoclonal proliferation of mainly B lymphoid cells and few of T lymphoid cells.

SALIENT CLINICAL FEATURES

- Lymphadenopathy is the common presentation
- Patient may be asymptomatic
- Symptoms when they occur, can be similar to Hodgkin’s disease
- Larger the size of lymph nodes, more advanced is the disease
- In addition, one should investigate gastrointestinal tract and ENT system as lymphatic structures of these two systems may also be involved in addition to lymphadenopathy.

INVESTIGATIONS

- CT guided lymph node biopsy or in some cases laparoscopic lymph tissue biopsy from abdomen may be required
- Bone marrow biopsy
- HIV test should be done as HIV is usually associated with lymphadenopathy.

MANAGEMENT

- Chemotherapy: Invariably one gives single drug
- Radiotherapy.
INTRODUCTION

- It is a rare form of cancer (1% of all cancers)
- Seen in all age groups (peak occurrence in adolescents and elderly)
- Exact etiology is not clear. Possible etiological factor has been alluded to Epstein-Barr virus infection
- The hallmark of Hodgkin’s disease is Reed-Sternberg cells (large multinucleated giant cells having a mirror image nucleus)
- Lymph node structure on histopathology shows lymphocytes, histiocytes, plasma cells, eosinophils, fibroblasts and Reed-Sternberg cells (Fig. 7.9)
- Histopathologically Hodgkin’s disease is classified into four types:
  1. Lymphocyte depleted
  2. Lymphocyte predominant
  3. Mixed cellularity (common in developing countries)
  4. Nodular sclerosis most common in developed countries.

SALIENT CLINICAL FEATURES

- Insidious onset: Patient complains of painless lymph nodes enlargement commonly cervical glands. Glands (known as Virchow’s glands) have typical rubbery feel, nonmatted, nontender. There is pain in lymph glands after taking alcohol. Constitutional symptoms like fever, drenching night sweats, loss of appetite, loss of weight, itching are present.
- Fever which in some cases is typical (Pel-Ebstein type temperature) (Fig. 7.10), in which there are alternate afebrile and febrile periods. It may take 2–3 days to reach peak of fever, stay high for 2–3 days and remit over 2–3 days, followed by afebrile period of 7–8 days and then again fever comes on. With progress of the disease, liver and spleen get enlarged. Lymphadenopathy becomes generalized including mediastinal lymphadenopathy.

Clinical Staging (Ann Arbor Classification)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Salient Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of single lymph node region (I) or an extralymphatic site (E)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side above or below the diaphragm (II E)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of diaphragm with (II E) or without (III) localized extralymphatic involvement or involvement of the spleen (III S) or both (III SE)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse involvement of one or more extra lymphatic tissues, e.g. liver or bone marrow. The lymphatic structures include lymph node, spleen, thymus, Peyer’s patches, Waldeyer’s ring</td>
</tr>
</tbody>
</table>

Each stage is subdivided into A or B categories based on the absence or presence of systemic symptoms (fever, night sweats, weight loss).
INVESTIGATIONS

- **CBC**: Polymorphonuclear cells increased, lymphocytes reduced, eosinophilia, pancytopenia
- X-ray chest for mediastinal glands
- CT chest, PET scan of chest, abdomen and pelvis for lymph node enlargement
- Bone marrow biopsy
- Radioisotope bone scan
- When liver is enlarged, liver biopsy should be done
- Gallium scan.

DIFFERENTIAL DIAGNOSIS

- **Non-Hodgkin’s lymphoma**: These are heterogeneous group of cancers of lymphocytes. They are variable in their presentation and natural history, varying from a slow indolent course to a rapidly progressive course.
- Chronic tuberculous lymphadenitis
- Histoplasmosis.

PROGNOSIS

- Prognosis is good in lymphocytic predominant and poor in lymphocytic depleted. Mixed cellularity and nodular sclerosing have fair prognosis
- If untreated **Hodgkin’s disease** is fatal
- 5 years survival period in stage 1A is 90% and in stage 2A is 70% with therapy
- Autologous BMT is tried in patients with relapse, provided BM is free of disease.

MANAGEMENT

Treatment is either chemotherapy or radiotherapy.

**Radiotherapy is indicated in:**

- Stage IA and II A disease with three or less areas of involvement
- After chemotherapy, radiotherapy is targeted to areas of original bulk disease
- Lesions causing compression symptoms are targeted by radiotherapy.

**Chemotherapy is indicated in:**

- Stage III and stage IV disease
- All symptomatic patients
- Stage II with more than 3 areas of involvement.

**Combined therapy:**

- It is the treatment of choice
- Chemotherapeutic agents in combination like adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) are administered. This combination is given in bulk disease. After chemotherapy, radiotherapy is given to the original sites of bulk disease that has been reduced in size by chemotherapy.

**VIVA VOCE**

**Q1. Describe causes of neutropenia (<3000/μL).**

- **Protozoal infections**: Malaria, kala-azar
- **Viral infections**: Viral hepatitis, measles, influenza, HIV, infectious mononucleosis
- **Bacterial infection**: Typhoid, brucellosis, tuberculosis
- **Vitamin deficiency**: Vitamin B₁₂, folic acid deficiency
- **Side effects of drugs**: Antimalarials, anticonvulsants, antithyroid, antiarrhythmic and sulfonamides
- **Systemic rheumatic diseases**: SLE, Felty’s syndrome
- **Hypersplenism**.

**Q2. Describe causes of lymphocytopenia.**
- Viral infections (HIV, influenza, measles)
- Following chemotherapy or radiotherapy
- Immunosuppressive therapy, corticosteroids
- Thymus dysplasia
- Bone marrow failure
- Renal failure.

**Q3. What are the causes of eosinophilia?**
- Bronchial asthma, allergic disorders, hay fever
- Tropical eosinophilia
- **Loeffler’s syndrome**
- **Hematological disorders**: Eosinophilic leukemia, Hodgkin’s disease, myeloproliferative disorders
- Systemic rheumatic diseases (SLE, polyarteritis nodosa, rheumatoid arthritis)
- Skin diseases (eczema, psoriasis, urticaria, pemphigus)
- Parasitic infestations (ascariasis, filariasis, hookworm infestation, strongyloidiasis)
- Endocrine disorders (hypopituitarism, Addison’s disease)
- Postsplenectomy.

**Q4. What are the causes of thrombocytosis?**
- Polycythemia vera rubra
- Chronic myeloid leukemia
- Myelofibrosis
- Myeloproliferative disorders
- Idiopathic
- Acute infections
- Hemorrhage
- Splenectomy
- Chronic inflammatory disorders (Still’s disease, systemic vasculitis).

**Q5. What are the causes of thrombocytopenia?**

**Congenital (rare):**
- Wiskott-Aldrich syndrome
- Congenital aplastic anemia.

**Acquired:**
- Side effects of drugs (sulfonamides, NSAIDs, chemotherapeutic agents)
- Bacterial infections (typhoid fever)
- Parasitic infection (malaria)
- Viral infections (dengue)
- Aplastic anemia, megaloblastic anemia
- Autoimmune thrombocytopenia (AITP)
- Idiopathic thrombocytopenic purpura (ITP)
- Secondary autoimmune thrombocytopenia
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome.