

Review Article

Pancytopenia - A Physician's Perspective

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Abstract

Pancytopenia is a one of the challenging disorder to the treating physician due to its diverse etiologies. It may be due to bone marrow failure syndromes, malignancies, infections or side effect of drugs, and it is also noted in hypersplenism. These patients may present without any symptoms and diagnosed during routine blood investigations or may present with symptoms of thrombocytopenia, anemia and leucopenia. The workup for pancytopenia is often quite extensive and includes a detailed clinical history, meticulous physical examination, and appropriate laboratory investigations in relation to the clinical scenario. Bone marrow examination helps to find out the underlying condition causing pancytopenia. Treatment of the pancytopenia includes supportive care for infections, bleeding and symptomatic anemia until the patient receives definite and/or curative treatment which depends upon the etiology.

Key Words: Pancytopenia, Hypersplenism, Aplastic Anemia, Myelofibrosis

Introduction

Pancytopenia is one of the commonest hematological conditions encountered by the practitioners in their day to day practice. It is characterized by reduction in cell counts of all three lineages of the blood leading to anemia, leucopenia and thrombocytopenia^{1,2}.

The causes of pancytopenia being quite varied result in diagnostic dilemma. Cytotoxic therapies, including myeloablative radiation therapy and chemotherapy, are common and predictable causes of pancytopenia in patients being treated for malignancies; pancytopenia outside this setting, can be very challenging. Evaluation of patient begins with exhaustive history including but not limited to drug intake, exposure to toxins, family history and febrile illness; followed by meticulous physical examination and detailed investigations including bone marrow evaluation in most cases. All the cases of pancytopenia require a thorough approach to find out the cause.

There are no universally accepted guidelines for the management of pancytopenia. The treatment depends upon the underlying etiology. The main goal is to provide supportive care including broad spectrum antibiotics along with blood and blood components especially in patients with fever and bleeding till they receive treatment for the basic disease causing pancytopenia.

Definition

As pancytopenia is a not a disease by-itself, there is no clear cut definition that exists for it. However, this disorder can be defined by simultaneous presence of low counts of all three cell lines i.e. leukocytes, erythrocytes, and platelets in the peripheral blood as compared to age and sex adjusted normal range for healthy population. Therefore it is a combination of

anemia, leucopenia and thrombocytopenia. (Hemoglobin < 13.5gms in males or 11.5gms in females, WBC count < 4*10⁹/L and platelet count < 150*10⁹/L).

Severe pancytopenia is defined as absolute neutrophil count < 500/mm, platelet count < 20,000/mm, corrected reticulocyte count < 1%, which was initially proposed to assess the severity of severe aplastic anemia³.

Etiopathogenesis

As pancytopenia is a laboratory finding, and not a particular diagnosis, it has a broad differential diagnosis. On one hand it may be the only manifestation of an easily treatable disease like B12 deficiency but on the other hand it may be the striking feature of a life threatening condition like leukemia⁴.

The pathophysiological mechanisms to explain pancytopenia can be simplified by dividing the causes into two broader categories. Most often it is caused by decreased production of multiple cell lineages from primary dysfunction of marrow or the stem cells. Rarely it is caused by destruction or sequestration of cell lines in the periphery. Sometimes, the same disease produces pancytopenia by overlapping the mechanisms. Hypersplenism is the commonest cause for pancytopenia without primary deficits in the marrow or the stem cells. Causes and classification of pancytopenia is stated in Figure 1.

Bone marrow failure state is characterized by presence of pancytopenia or single lineage disorder resulting from defective hematopoiesis. The disorders which produce bone marrow failure syndromes with pancytopenia include aplastic anemia, myelodysplasia, and myelophthisis. These disorders have normocytic and normochromic anemia on peripheral smear with an inappropriately low reticulocyte count.

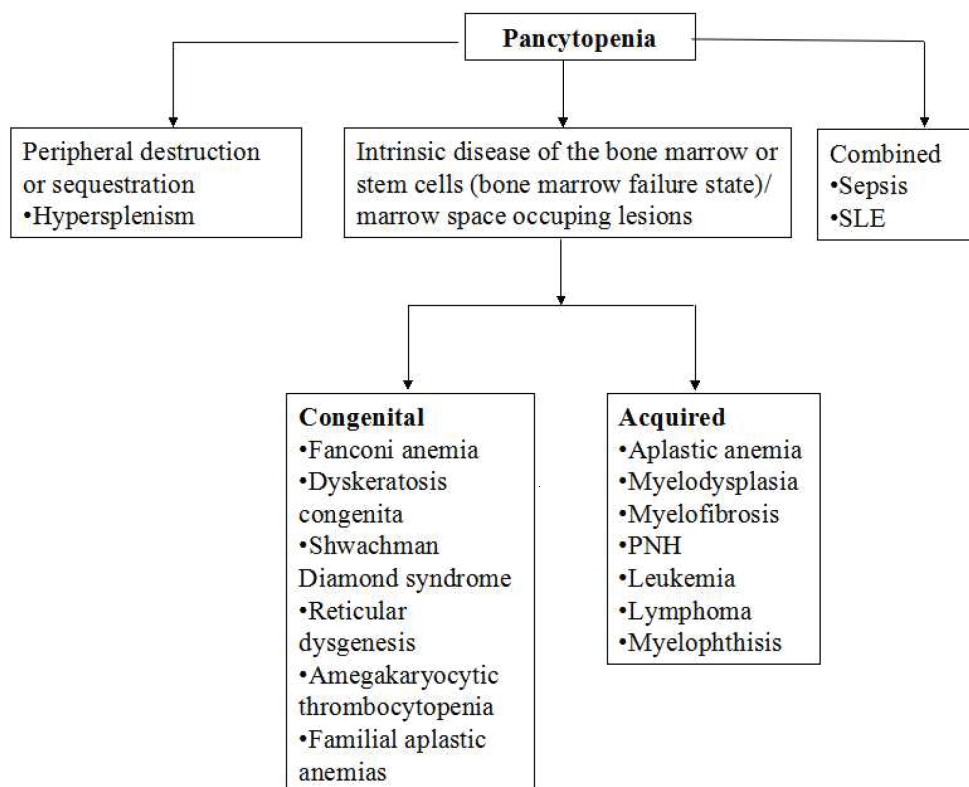


Fig 1 : Causes and classification of pancytopenia

Aplastic anemia is defined as pancytopenia with hypocellular marrow in the absence of abnormal infiltrate or increased fibrosis⁵. The disorder can result from both inherited and acquired causes or it may be iatrogenic⁶. The causes of acquired aplastic anemia is summarized in Table 1.

The most common congenital cause for pancytopenia is Fanconi's anemia. It is an autosomal recessive disorder which is characterized by congenital developmental anomaly, progressive pancytopenia, and an increased risk of malignancy. Dyskeratosis congenita is another inherited bone marrow failure disorder which is defined by triad of nail changes, oral leukoplakia, and a reticulated skin rash⁷.

Bone marrow failure with resultant pancytopenia may result from exposure to radiation or chemicals (benzene). Exposure to benzene is associated with aplastic anemia, acute leukemia, and blood and marrow abnormalities⁶.

The other causes of pancytopenia include acute leukemias (aleukemic leukemia), advanced stages of chronic leukemias. High grade lymphomas and myeloma can also produce pancytopenia. The mechanisms of marrow failure in these diseases can be related either due to active suppression of normal haematopoiesis or bone marrow infiltration by the abnormal cells.

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic and debilitating disorder which most frequently presents in early adulthood. It is a unique clinical syndrome which is characterized by the triad of hemolytic anemia, pancytopenia, and thrombosis⁸.

Myelodysplastic syndrome is a heterogeneous group of hematologic disorders characterized by cytopenias of any individual or all cell lines associated with abnormal appearing cellular marrow⁶. It is due to mutation in haematopoietic stem cells which results in defective differentiation and maturation of cells. It is more common in elderly population with increased risk (20-25%) of developing acute myeloid leukemia.

Myelofibrosis is characterized by replacement of the normal bone marrow by fibrous material. It can occur as a primary hematologic disease (myelofibrosis or myeloid metaplasia). Secondary myelofibrosis (myelophthisis) can occur as a response to invading tumor cells (usually an epithelial cancer of breast, lung, or prostate origin or neuroblastoma), infections (mycobacterium tuberculosis, mycobacterium avium, fungi, and HIV), and in sarcoidosis. It appears to be the final common pathway of chronically overstimulated marrow as occurs in essential thrombocytosis, polycythemia vera and chronic myeloid leukemia⁶.

Aplastic anemia was first diagnosed in a pregnant female. It can recur during successive pregnancies. It resolves after delivery or with spontaneous or induced abortion. Idiopathic aplastic anemia is a diagnosis of exclusion⁷.

Drugs are the commonest cause for many hematologic disorders, affecting white cells, red cells, platelets, and the coagulation system⁹, but less well recognized. They induce pancytopenia either by predictable (dose dependent manner) or by unpredictable manner (idiosyncratic). The drugs that are commonly implicated are listed in Table 2. They cause bone marrow suppression by three different mechanisms which

Secondary	
Radiation	
Drugs and chemicals	
Regular effects	
Idiosyncratic reactions	
Viruses	Epstein-Barr virus (infectious mononucleosis)
	Hepatotropic viruses
	Parvovirus B19 (transient aplastic crisis, PRCA)
	Human Immunodeficiency Virus
Immune diseases	Eosinophilic fascitis
	Hyperimmunoglobulinemia
	Large granular lymphocytosis (LGL)
	Thymoma/ Thymic carcinoma
	Graft versus host disease in immunodeficiency
Paroxysmal nocturnal hemoglobinurua (PNH)	
Pregnancy	
Idiopathic	

Table 1 - Causes of acquired aplastic anemia⁶

Cytotoxic drugs
Chloramphenicol
NSAIDs
Chloroquine
Colchicine
Anticonvulsants (hydantoins, carbamazepine)
Heavy metals (gold, arsenic, bismuth and mercury)
Antithyroid drugs (methimazole, methylthiouracil, propylthiouracil)
Carbonic anhydrase inhibitors (acetazolamide and methazolamide)
Sulfonamides
Antidiabetes drugs (tolbutamide, chlorpropamide),
Antihistamines (cimetidine, chlorpheniramine)
d-Penicillamine

Table 2 - Drugs implicated for pancytopenia

include direct toxicity, metabolite-driven toxicity, and immune-mediated¹⁰.

Several underlying mechanisms have been described for pancytopenia induced by infections^{11,12}. One of the commonest cause for infection related pancytopenia is

sepsis. Sepsis and the ensuing systemic inflammatory response, can cause cytopenias¹³. The postulated mechanisms include consumptive coagulopathy, hypersplenism, and release of inflammatory mediators which suppress the marrow. The second explanation for infection induced pancytopenia is due to the effect of viral infections. Any viral illness can be associated with transient bone marrow suppression due to direct damage of the haematopoietic precursor cells. But commonly implicated viral illness includes HIV, parvovirus B19, EBV, CMV, and hepatotropic viruses (A, B, and C)^{14,15}.

Abnormal immune response which follows some infections, can destroy the precursor cells in the marrow or blood cells in the periphery which results in pancytopenia

Infection can also lead to hemaphagocytic histiocytosis which is characterized by increased macrophage activity and phagocytosis of blood cells and precursors. Viral infections are most commonly involved (EBV, CMV, Measles, HHV-8, HIV), but virtually any other infectious agent can precipitate this syndrome like TB, brucella, salmonella, malaria, leishmaniasis and fungal infection^{16,17}.

Microorganisms that infect endothelial cells (e.g. rickettsia, babesia) may produce pancytopenia as part of a generalized vasculitis. Tropical infections like malaria, visceral leishmania can produce hypersplenism and resultant pancytopenia¹⁸. Finally infections may lead to pancytopenia by replacement of the marrow by infectious organisms such as mycobacterial infections and fungal infections like histoplasmosis^{19,20}.

In SLE, pancytopenia commonly results from an immune mediated bone marrow failure, myelofibrosis, vasculitis with bone marrow necrosis, excessive peripheral cells destruction and macrophage activation syndrome^{21,22}. Sometimes it may be secondary to drugs used for treatment of SLE or resulting from infections.

One of the commonest extra medullary cause for pancytopenia is hypersplenism. It is characterized by splenomegaly, cytopenia(s), normal or hyperplastic bone marrow, and a response to splenectomy. The cytopenias result from increased destruction of the blood cells secondary to reduced flow of blood through enlarged and congested cords (congestive splenomegaly) or to immune-mediated mechanisms²³. The size of the spleen does not correlate well with severity of cytopenias. The causes for hypersplenism include portal hypertension (cirrhosis of liver, extra hepatic portal obstruction), tropical splenomegaly (hyperreactive malarial splenomegaly and visceral leishmaniasis), lymphomas or rarely idiopathic²⁴.

Clinical manifestations

The clinical features depends upon both of the underlying disease process as well as relate to the blood cell lineages affected. Patients with mild pancytopenia are often asymptomatic and in most instances it goes unnoticed unless complete blood count is ordered for some other reason. Or the patients can present with life threatening infection or catastrophic bleeding manifes

tations. Symptomatic pancytopenia is more common in patients with primary dysfunction of the bone marrow or the stem cells.

The symptoms are attributable to anemia, leucopenia, and/or thrombocytopenia. As the platelets have shorter half life, symptoms of thrombocytopenia appears first. Mucocutaneous bleeding is the most common early symptom; a complaint of days to weeks of epistaxis, easy bruising, oozing from the gums, hematuria, menorrhagia, and sometimes petechiae will have been noticed. Massive hemorrhage is unusual with thrombocytopenia, but even small amounts of bleeding in the central nervous system can result in catastrophic intracranial or retinal hemorrhage.

Anemia develops slowly because red blood cells have longest half life compared to white blood cells and platelets. The symptoms depends on the rapidity of development of anemia and those include lassitude, weakness, shortness of breath, and a pounding sensation in the ears.

Infection is an unusual first symptom in pancytopenia due to bone marrow failure as compared to agranulocytosis. The features include pharyngitis, anorectal infection which respond poorly to antibiotics. Patients may develop overwhelming sepsis without any focal sign of infection, with malaise and fever being the only clinical features.

Evaluation

The need for detailed work-up should be based on the clinical scenario. Mild pancytopenia in patients with a recent viral illness or following drug exposure and who are clinically stable, less likely require further investiga-

tions. Similarly, pancytopenia in the midst of sepsis rarely need extensive evaluation unless the peripheral smear shows immature cells. But these patients need repeat blood counts to demonstrate resolution of cytopenias.

Initial evaluation of pancytopenia starts with proper history, followed by examination (Table 3) and then finally moving on to laboratory investigations (basic hematological, biochemical, radiological, and histopathological investigations as needed). A simplified approach to pancytopenia is given in Figure 2.

Clinical features	Clinical findings
Age	Petechiae and ecchymoses
Bone pain	Retinal hemorrhage
Fever	Blood in the stools and abnormal vaginal bleeding
Night sweats	Pallor
Malaise, weight loss	Fever
Bleeding from any site	Oral candidiasis, pharyngeal exudates (neutropenia)
Treatment history	Lymphadenopathy, organomegaly (hematological malignancy)
Alcohol Intake	
Dietary history	Bone tenderness (leukemia)
Occupational exposure	Gingival hypertrophy
Joint pain, rash, photosensitivity and recurrent fetal loss	Cafe au lait spots and short stature (Fanconi's anemia)
Family history	Peculiar nails, reticulated skin hyperpigmentation and leukoplakia (dyskeratosis congenita)
Early graying (telomerase defect)	

Table 3 - Initial evaluation of pancytopenia: clinical features and findings

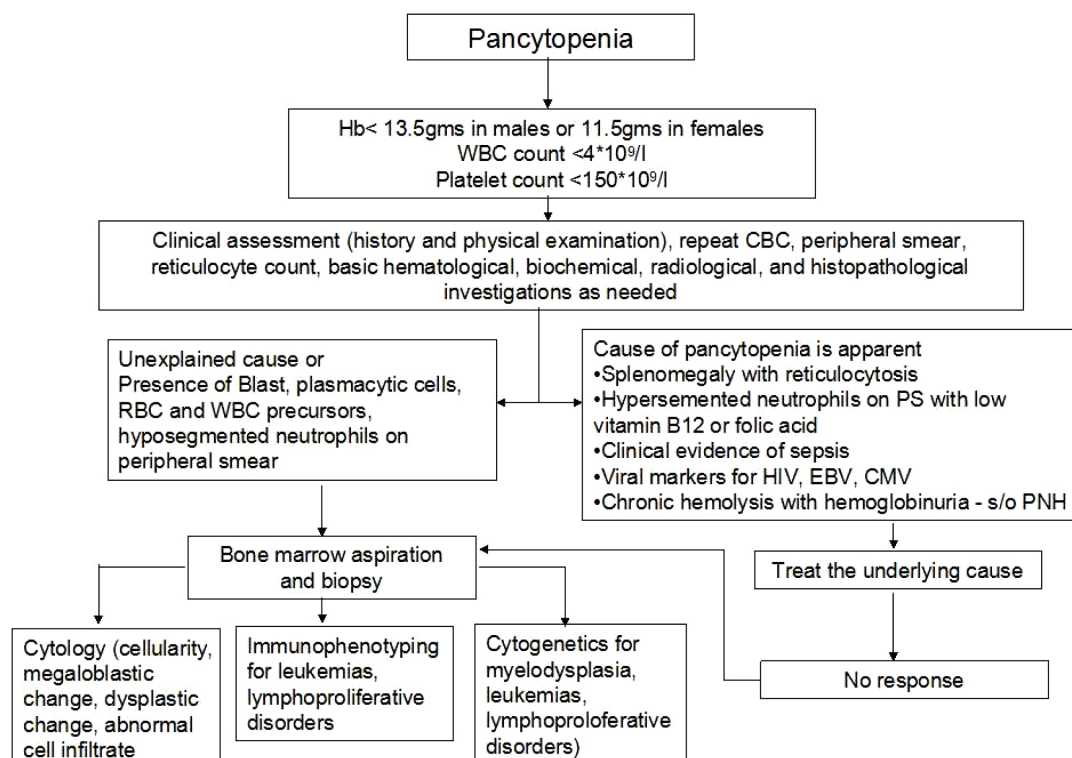


Fig 2 : Approach to Pancytopenia

All patients with pancytopenia have to be subjected to complete blood counts (CBC), reticulocyte count and a peripheral blood examination. CBC will show that all 3 cell lines are decreased. The reticulocyte counts will be decreased in bone marrow failure due to ineffective production of the cells by the marrow whereas it is more in cases when pancytopenia is secondary to the peripheral destruction of the cells. Peripheral smear may show anisopoikilocytosis (prominent in myelofibrosis), RBC and WBC precursors, Howel-Jolly bodies (megaloblastic anemia and myelodysplastic syndromes [MDS]), giant platelets (hypersplenism and MDS), toxic granules of the neutrophils (infections), hypogranulation of the neutrophils (MDS), hypersegmentation ((megaloblastic anemia) or hyposegmented (MDS) , blasts (acute leukemias, myelofibrosis, aleukemic leukemias) and plasmacytic cells (multiple myeloma). Increase in ESR is noted in infections and multiple myeloma.

In addition to basic hematological investigations most of the patients need liver function test, coagulation profile, fibrinogen, D-dimer, serum B12, folate levels, serum direct antiglobulin test, viral markers for hepatitis, serology for EBV, CMV and HIV, serum ferritin and triglycerides (elevated in hemophagocytic lymphohistiocytosis) and antinuclear antibodies (ANA).

In hypersplenism, increased reticulocyte production index reflects increased marrow production of red cells, although the value may be less due to increased sequestration of reticulocytes in the spleen. Blood and bone marrow culture for leishmaniasis, ELISA for leishmaniasis and serum titers of IgM malarial antibody shall be carried out in patients with suspected tropical splenomegaly.

Bone marrow examination (both aspiration and biopsy) is almost always indicated for evaluating the cases of pancytopenia unless the cause is otherwise apparent (e.g., hypersplenism, deficiency of vitamin B12 or

folate, sepsis or autoimmune diseases). Bone marrow examination permits to assess the cellularity (decreased-indicate decreased production of blood cells, normal or increased-indicate ineffective production or increased destruction or sequestration of blood cells). The classification pancytopenia based on bone marrow cellularity is shown in Table 4. This also helps to examine the cytology (megaloblastic change, dysplastic change, abnormal cell infiltrates, haemophagocytosis, and infection [e.g., Leishman-Donovan bodies, malarial parasites, tuberculosis and fungal infection]), immunophenotyping (leukemias, lymphoproliferative disorders) and cytogenetics (myelodysplasia, leukemias, lymphoproliferative disorders). It also permits examination of histology and evaluation for cellular infiltration, blasts, features of MDS (e.g., abnormal localization of immature precursors) and reticulin stain (fibrosis)^{25,26}.

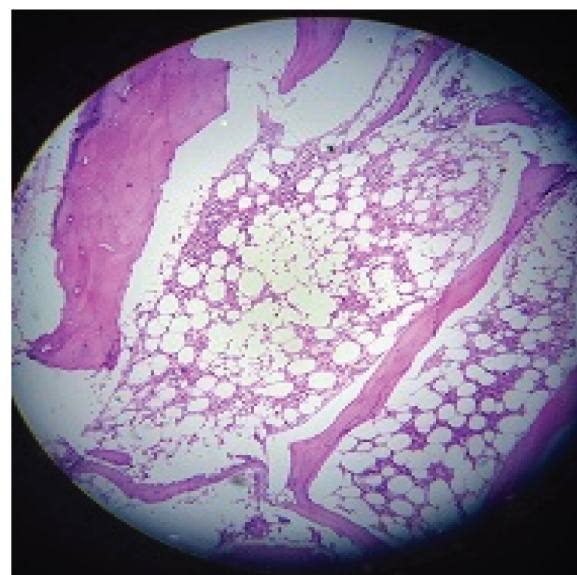


Fig 3 : Bone marrow showing aplastic anemia

Pancytopenia with hypocellular bone marrow	Pancytopenia with Cellular Bone Marrow	
	Primary bone marrow diseases	Secondary to systemic diseases
Acquired aplastic anemia	Myelodysplasia	Hypersplenism
Constitutional aplastic anemia (fanconi anemia, dyskeratosis congenita)	Paroxymal nocturnal hemoglobinuria (PNH)	B12 and folate deficiency
Some myelodysplasia	Myelofibrosis	Overwhelming infection
Rare aleukemic leukemia	Some aleukemic leukemia	Alcohol
Some acute lymphoid leukemia	Bone marrow lymphoma	Tuberculosis
Some lymphomas of the bone marrow	Hairy cell leukemia	Systemic lupus erythematosus
		Brucellosis
		Sarcoidosis
		Leishmaniasis

Table 4 - Classification of pancytopenia based on bone marrow cellularity⁶

In patients with splenomegaly, to find out the cause ultrasound abdomen or CT abdomen can be performed. X-ray chest may reveal evidence of tuberculosis, fungal infection, tumor masses. When metastatic bone infiltration is suspected, search shall be made for primary malignancy.

Management

The management includes identification and reversal of the underlying cause with appropriate and adequate supportive care until normal counts are restored. However, the treatment of underlying etiologies are not considered here owing to space constraints.

Life threatening infections, catastrophic bleeding and symptomatic anemia are much more common among patients with pancytopenia due to intrinsic diseases of the bone marrow or stem cells.

Supportive care⁶

First and the most important, is treatment of infections. Infection in the presence of severe neutropenia must be treated aggressively by early initiation of empirical broad-spectrum parenteral antibiotics, usually ceftazidime or a combination of an aminoglycoside, cephalosporin, and semisynthetic penicillin. Specific foci of infection should be sought by careful physical examination and by imaging studies. Vancomycin should be added in patients with indwelling catheter. Persistent fever spikes indicate fungal infection and warrants treatment with antifungal drugs. For overwhelming and refractory infection, granulocyte transfusions using G-CSF-mobilized peripheral blood can be tried. Growth factors or G-CSF analogues, such as filgrastim, may be used to boost WBC counts once a presumptive diagnosis is made. Use of nonabsorbable antibiotics for gut sterilization and total reverse isolation do not improve the outcome as compared to simple measures like hand washing.

Platelet transfusions are indicated for the treatment of bleeds caused by thrombocytopenia as well as prophylactically once or twice weekly to maintain the platelet count $>10,000/\mu\text{L}$ (bleeding from the gut increases precipitously at counts $<5000/\mu\text{L}$). Major problem related to platelet transfusions is the development of a refractory state caused by alloimmunisation. This can be minimized by use of single donors to reduce exposure and physical or chemical methods to diminish leukocytes. HLA matched platelet transfusions are quite effective in patients refractory to random donor products. Oral estrogens or nasal follicle-stimulating hormone/luteinizing hormone (FSH/LH) antagonists are given to suppress menstruation. The drugs which inhibit platelet function like aspirin should be avoided.

Anemia should be corrected with packed red blood cell transfusion to maintain hemoglobin value $>7\text{ gms/dl}$. If patients have underlying cardiac or respiratory disease, hemoglobin should be maintained above 9 gms/dl . For those patients who are likely to need repeated transfusion, use of leukoreduced products is recommended as it reduces febrile transfusion reactions, CMV transfer, and alloimmunization, as they are crucial in reducing complications of the further transfusions. Similarly, the

use of irradiated blood to destroy donor lymphocytes and prevent transfusion-associated graft versus host disease (GVHD) is recommended. In patients with bone marrow failure 2 units of blood is given every 2 weeks, which will replace normal losses. In patients with repeated transfusion, who have a reasonable expectation of survival iron chelators, deferoxamine and deferasirox should be given after every fiftieth transfusion.

Hematopoietic stem cell transplantation (HSCT) using allogeneic donor has been attempted successfully in some cases.

Conclusion

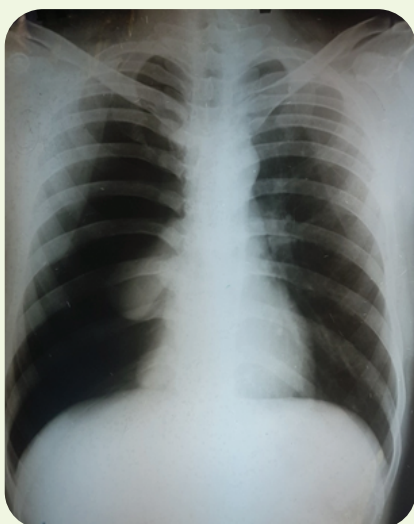
Pancytopenia is a laboratory finding which may indicate a constellation of underlying etiologies. Some of these are self limiting, while others may require exhaustive investigation and aggressive treatment. A systematic approach to pancytopenia will guide the treating physician towards appropriate therapy.

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Image Challenge - 2



Clue: 45 year old smoker with breathlessness and hemoptysis

- Answer in page : 93