Review Article

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Pancytopenia: A Challenging Problem for treating Physician

Chowdhury MRK[1], Begum A[2], Rashid MH[3], Hasan MK[4]

Abstract

Pancytopenia is an important clinico-haematological entity and striking feature of many serious and life-threatening illnesses. Many haematological and non-haematological diseases involve the bone marrow primarily or secondarily and cause pancytopenia. Decrease in haemopoietic cell production, ineffective haemopoiesis and peripheral sequestration or destruction of the cells are the main pathophysiology of pancytopenia. The cause of pancytopenia thus may be lying in the bone marrow or in the periphery or both. Careful history, physical examination, simple blood work, review of the peripheral blood smear, sometimes bone marrow examination and trephine biopsy are required for diagnosis. Treatment and prognosis depend on the severity of pancytopenia and underlying pathology.

Key words: pancytopenia, ICUS, reticulocyte, supportive care.

Introduction

Pancytopenia is a common haematological problem with an extensive differential diagnosis and a challenging problem to the treating physician. It is not a disease but a triad of anaemia, leucopenia and thrombocytopenia. Various pathophysiological mechanisms are related to development of pancytopenia and this includes reduced or ineffective haematopoiesis and increased destruction by either sequestration or destruction by antibodies.[1] The cause of pancytopenia may thus lie in the bone marrow, periphery or both. Various factors encompassing geographic distribution and genetic disturbances may cause variation in the incidence of disorders causing pancytopenia.[2-4] The presenting symptoms are often attributed to anaemia/ thrombocytopenia. Leucopenia is an uncommon cause of initial presentation but can become the most serious threat to life during the course of the disorder.[5] A detailed history, physical examination and complete blood counts with reticulocyte count and peripheral blood smear remain essential for diagnosis. Bone marrow examination is essential to determine the cause of pancytopenia, as it plays a major role in haematological malignancies, unexplained cytopenia and storage disorders.[6] Trephine biopsy is mainly undertaken when hypoplasia or aplasia of bone marrow is suspected on aspiration.[7] The severity of pancytopenia and the underlying pathology determine the management and prognosis of these patients.[8]

Authors

1. Md. Rezaul Karim Chowdhury, MBBS, MD, D-Card, Associate Professor, Department of Haematology, EMCH.email: rkchow71@gmail.com
2. Amina Begum, Medical officer, Department of physiology, BSMMU.
3. Md. Haroon Ur Rashid, MBBS, MD, Associate Professor, Department of Pulmonology, EMCH.
4. Md. Kamrul Hasan, Assistant Professor of Haematology, Colonel Malek Medical College, Manikganj.

* for correspondence

Definition

All cellular blood components are derived from haematopoietic stem cells.[9] In a healthy adult person, approximately 10^{11}-10^{12} new blood cells are produced daily in order to maintain steady state levels in the peripheral circulation (Semester 4 Medical Lectures by Leif Jansson at Uppsala University, 2008).[10,11] The normal adult marrow produces about 1.7 x 10^{11} RBC, 1.0 x 10^{11} neutrophils, and 2 x 10^{11} platelets each day and thus it has a tremendous capacity to substantially increase the output of these cells when necessary with the help of growth factors and other cytokines.[12] The circumstances that lead to pancytopenia due to bone marrow failure include both defects in the stem cells (seed) or defects in the stromal cells or micro-environment (soil). However, quite obviously majority of the defects are in the stem cells.[13]

Cytopenia is a reduction in the number of each type of peripheral blood cell. A low level of red blood cells is referred to as anaemia. A low level of white blood cells is referred to as leucopenia. A low level of platelets is referred to as thrombocytopenia. Bicytopenia means reduction in any of the two cell lines of blood (anaemia plus thrombocytopenia, anaemia plus leucopenia, or thrombocytopenia plus leucopenia). Pancytopenia is a combination of anaemia, leucopenia and thrombocytopenia in the peripheral blood as compared to age and sex adjusted normal range for healthy population. Severe pancytopenia is defined as: i) absolute neutrophil count $<0.5x10^9$/L, ii) Platelet count $<20x10^9$/L, and iii) Corrected reticulocyte count <1%.[14]

Aetiology

Simple treatable disease to serious life-threatening condition can cause pancytopenia. Aetiology of pancytopenia differs in different population, different methodology and diagnostic criteria, genetic difference, nutritional status, prevalence of infection and exposure to toxic drugs. Basically, four main etiological factors are related to pancytopenia i.e. bone marrow failure, marrow space occupying lesions, ineffective production by marrow or peripheral destruction of haematopoietic cells. So, we can divide the pancytopenia as pancytopenia with hypocellular marrow and pancytopenia with cellular marrow (table 1 & 2).

Table 1: Cause of pancytopenia with hypocellular marrow

Inherited	Acquired
Fanconi anaemia	Acquired aplastic anaemia
Shwachman-Diamond syndrome	Myelodysplasia
Dyskeratosis congenital	Leukaemia
Amegakaryocytic thrombocytopenia	Lymphomas of the bone marrow

Table 2: Cause of pancytopenia with cellular marrow

Primary bone marrow diseases	Secondary to systemic diseases
Leukaemia	Megaloblastic anaemia(vit-B12 and folic acid deficiency)
Myelodysplasia	Hypersplenism
Myelofibrosis	Alcoholism
Bone marrow lymphoma	Systemic lupus erythematosis, Sarcoidosis
Hairy cell leukaemia	Sepsis, enteric fever
Paroxysmal nocturnal haemoglobinuria	HIV infection, hepatitis B, hepatitis C, ebstein-barr virus, cytomegalovirus.
	Malaria, leishmaniasis, filariasis.

Pathophysiology

Pancytopenia is a laboratory finding and related to many disease processes. So, the pathophysiology of pancytopenia relates to the underlying aetiology. Most common mechanism causing pancytopenia are failure of production of stem cells in bone marrow, infiltration of bone marrow by malignant cells or fibrosis, immune mediated bone marrow suppression, ineffective erythropoiesis and dysplasia, peripheral sequestration of blood cells by overactive reticuloendothelial system, and immune or non-immune mediated increased destruction of blood cells.

Fanconi anaemia (FA) is an autosomal recessive disease and considered the most common inherited cause of bone marrow failure. Patients are presented with congenital abnormalities, defective haemopoiesis, and a high risk of developing both haematological and solid tumours (including leukaemia, carcinomas, and liver tumours). Many genes can be responsible for this disease; however, all these genes have one thing in common: they do not allow the DNA repair mechanisms work properly.[15-17]

Dyskeratosis congenita (DC) is a multisystem inherited syndrome, characterized by mucocutaneous abnormalities, BM failure, and a predisposition to cancer. Mutations in at least ten telomere- and telomerase-associated genes have been linked to DC, although the genetic basis of the disease is still undetectable in approximately 30%-40% of cases. Principally DC is a disease of defective telomere maintenance and patients usually have very short telomeres, subsequent replicative senescence, leading to premature stem cell exhaustion and tissue failure.[18,19]

Aplastic anaemia is a rare haemopoietic stem-cell disorder that results in pancytopenia and hypocellular bone marrow. Although most cases are acquired, there are unusual inherited forms. The pathophysiology of acquired aplastic anaemia is immune mediated in most cases; autoreactive lymphocytes mediate the destruction of haemopoietic stem cells. Environmental exposures, such as to drugs, viruses, and toxins, are thought to trigger the aberrant immune response in some patients, but most cases are classified as idiopathic.[20]

Most concerning causes of pancytopenia are haematological and non-haematological malignancies. The mechanism of pancytopenia in haematological neoplasm like acute and chronic leukaemia is unclear but probably due to active suppression of normal haemopoiesis and bone marrow infiltration by the abnormal cells. High-grade lymphomas and plasma cell myeloma also commonly replace the bone marrow and cause pancytopenia. Myelodysplastic syndromes are a cluster of conditions where mutations in stem cell lines cause ineffective haematopoiesis and cytopenia of any individual or all cell lines. In case of primary and secondary myelofibrosis normal marrow is replaced by fibrous material and causes pancytopenia.

Non-haematological malignancies like solid tumour can cause pancytopenia by marrow replacement and myelophthisis occur late in the disease course as the burden of disease increases.

In Paroxysmal nocturnal haemoglobinuria (PNH) cells lack of phosphatidylinositol glycoproteins (PGI) transmembrane anchors caused by mutation in X-linked PGI-A gene. The mechanism of pancytopenia in PNH is possibly due to stem cells destruction by complement, but the cause or causes are still poorly understood.

Haematological abnormalities have been frequently observed in patients with infection. Sepsis, viral infection and infiltration of infectious organism in marrow are related to development of cytopenia. Sepsis and systemic inflammatory response cause mild to moderate cytopenia through disseminated intravascular coagulation, hypersplenism and bone marrow suppression. Any viral illness can be associated with transient bone marrow suppression due to direct damage of the haematopoietic precursor cells. Commonly implicated viral illness is HIV, parvovirus B19, EBV, CMV, and hepatotropic viruses.[21, 22] Infections may lead to pancytopenia by replacement of the marrow by infectious organisms such as mycobacterial infections and fungal infections like histoplasmosis.[19,20] Some infections alter immune response which can destroy the precursor cells in the marrow or blood cell in the periphery leads to pancytopenia. Microorganism sometime causes generalized vasculitis and pancytopenia by infecting endothelial cells.

Infection can also lead to haemophagocytic syndrome. The manifestation of haemophagocytic syndrome is thought to be mediated by hypersecretion of proinflammatory cytokines such as INF-γ, TNF-α, IL-6, IL-10 and macrophage colony-stimulating factor (M-CSF). Such excess of proinflammatory cytokines results in tissue infiltration by lymphocytes and macrophages, leading to haemophagocytosis and the characteristic laboratory abnormalities including cytopenia, coagulopathies and hypertriglyceridaemia.[23]

In systemic lupus erythematosus (SLE) most common haematological abnormalities include anaemia, leucopenia and thrombocytopenia. They commonly result from an immune mediated bone marrow failure, excessive peripheral cell destruction or certain drugs and infections.[24]

The most common drug-induced haematological disorders include aplastic anaemia, agranulocytosis, megaloblastic anaemia, haemolytic anaemia, and thrombocytopenia. The mechanisms of drug-induced haematological disorders can be the result of either direct drug or its metabolite toxicity or an immune reaction.[25]

Hypersplenism include splenomegaly, a peripheral blood picture of anaemia, neutropenia, and thrombocytopenia (either singly or in combination), a cellular bone marrow, and significant improvement in peripheral blood picture following splenectomy. In hypersplenism increased numbers of cells are consumed and sequestered and/or destroyed in the spleen. The causes of hypersplenism include portal hypertension, tropical splenomegaly, lymphomas or rarely idiopathic.[26]

Idiopathic Cytopenia of Uncertain Significance (ICUS)

The term 'idiopathic cytopenia(s) of undetermined significance' has been proposed for patients who have one or more blood cytopenia (usually anaemia) that remain unexplained despite appropriate evaluation, including marrow examination.[27]

Diagnostic criteria for ICUS include: i) persistent cytopenia for 6 months (Hb <11g/dL, neutrophil $<1.5x10^9$/L, and platelets $<100x10^9$/L); ii) no morphologic feature of myelodysplasia; iii) normal chromosome analysis; and iv) absence of other secondary causes of cytopenia excluded by detailed clinical history and investigations.

The suggested workup includes: (a) a complete history including occupational, chemical and infectious exposures; (b) a complete listing of all medications; (c) a complete physical examination with assessment of splenic size; (d) peripheral blood smear examination; (e) bone marrow examination; (f) an evaluation for HCV, HIV, CMV, EBV and other viral pathogens; (g) chromosome analysis by FISH; (h) flow cytometry on peripheral blood and bone marrow; and (i) additional molecular studies as indicated.[28]

These patients need regular follow up at regular intervals to see that the condition progresses, persists or resolves. ICUS may take one of several courses over time: 1) reactive non-clonal conditions may prove to be self-limited and eventually resolve without specific cytopenia-directed therapy; 2) some individuals with ICUS will ultimately be found to have MDS or another myeloid neoplasm that is not diagnosable at the time of initial presentation using World Health Organization (WHO) diagnostic criteria; 3) occult non-myeloid neoplasms or non-neoplastic disorders may become overt with time; and 4) some patients have persistent unexplained cytopenia that last for years.

Diagnostic Approach

Pancytopenia is not a diagnosis of a disease but it has broad differential diagnoses. The clinical presentation is related to underlying disease process, blood cell lineages affected and the degree of cytopenia. Mild pancytopenia is often symptomless and detected incidentally when complete blood count is ordered for some other reason.

The symptoms related to pancytopenia are attributable to anaemia, leucopenia and/or thrombocytopenia. Thrombocytopenic features appear first because platelets have shorter half-life. Bleeding with minimal trauma may occur when platelets count is between 10 to 30×10^9/L and count less than 10×10^9/L increases the risk of spontaneous bleeding, petechiae, and bruising. Spontaneous bleeding (i.e. mucosal, intracranial, gastrointestinal, and genitourinary bleeding) is more likely to occur in patients with platelet counts less than 5×10^9/L and is considered a haematologic emergency.[29] With platelet count >30x10^9/L, bleeding is unlikely except when there is concomitant presence of primary or acquired platelet dysfunction. Compared to white blood cells and platelets, red blood cells have longest half-life; therefore, symptoms related to anaemia develop later. Lassitude, weakness, shortness of breath, palpitations, and a pounding sensation in the ears are common presenting symptoms observed in anaemia. Severity of these symptoms is related to the degree of anaemia, rapidity of its onset and co-morbidity such as cardiac failure. Sore throat or chest or soft tissue infections is the early manifestation of neutropenia, usually occur with commensal organisms of the skin or gastrointestinal tract. Pancytopenic patients sometimes develop overwhelming septicaemia without any focal sign of infection; the only clinical features being malaise and fever.

Evaluations

Proper history and meticulous physical examination are essential for evaluation of pancytopenia. If done properly with a systematic manner it will lead very near to the diagnosis.

Patient with mild pancytopenia who are clinically stable, without other abnormalities, less likely require further investigations. It may be due to recent viral infections or following drug exposure. But repeat blood count is needed to demonstrate the resolution of cytopenia.

The history should include the age (in children inherited causes of bone marrow failure, Evan's syndrome), sex (autoimmune disease like SLE more common in female), duration of symptoms (tells about the severity), bone pains (acute leukaemia, myeloma), fever (infections, acute leukaemia), night sweats (lymphoproliferative disorder), malaise, weight loss (tuberculosis, malignancy), loss of height (myeloma), bleeding from any site (magnitude of thrombocytopenia), jaundice (hepatitis viruses), recurrent oral ulcers and chronic diarrhoea (HIV infection), joint pain, rash, photosensitivity (lupus), repeated early foetal loss, any radiation exposure, exposure to potentially toxic chemicals, treatment history including herbals and drug intake, blood transfusions, dietary history (megaloblastic anaemia, anorexia nervosa), alcohol intake, occupational exposure history (benzene), early greying (telomerase defect).

A thorough physical examination including vitals, anthropometry, general physical examination and systemic examination is required for diagnosis of the causes of pancytopenia. Eye examination includes retinal haemorrhage (thrombocytopenia), leukaemic infiltrates (acute leukaemia), jaundiced sclera (paroxysmal nocturnal haemoglobinuria, hepatitis, cirrhosis) and epiphora (dyskeratosis congenita). Oral examinationincludes oral petechiae or haemorrhage (thrombocytopenia), stomatitis or cheilosis (neutropenia, vitamin B_{12} deficiency), gingival hyperplasia (leukaemia), oral candidiasis or pharyngeal exudate (neutropenia, herpes family virus infections). Cardiovascular examination includes tachycardia, oedema, congestive cardiac failure (all signs of symptomatic anaemia), evidence of prior cardiac surgery (cardiac disease associated with congenital syndromes). Respiratory examination includes clubbing (lung cancer), tachypnoea (sign of symptomatic anaemia). Abdominal examination includes right upper quadrant tenderness (hepatitis), lymphadenopathy (infection, lymphoproliferative disorder, HIV disease), signs of chronic liver disease, splenomegaly (infection, myeloproliferative and lymphoproliferative disorders). Skin examination includes malar rash (SLE), purpura/bruising (thrombocytopenia), reticular pigmentation, dysplastic nails (dyskeratosis congenita), hypopigmented areas, hyperpigmentation, café au lait (Fanconi anaemia). Musculoskeletal examination includes short stature (Fanconi anaemia, other congenital syndromes), swelling/synovitis (SLE), abnormal thumbs (Fanconi anaemia). Signs associated with HIV disease include morbilliform rash early, Kaposi sarcoma, ulcerating nodules later. Neurological examination includes degradation of joint position sense and a positive Romberg in the setting of macrocytic anaemia may well suggest B_{12} deficiency. Generalized peripheral neuropathy may suggest a paraprotein-elaborating malignancy such as myeloma.

Laboratory Evaluation

The key investigations of pancytopenia are complete blood counts with RBC indices, reticulocyte count and a peripheral blood examination. These three investigations guide clinician to further investigations.

Macrocytosis is common in liver disease, congenital and acquired bone marrow failure disorders for example, aplastic anaemia, paroxysmal nocturnal haemoglobinuria (PNH), MDS (round macrocyte) and B_{12} deficiency and/or folate deficiency (oval macrocyte). Nucleated red cells in the peripheral smear suggest a myelophthisic process, myelofibrosis, or other infiltrating marrow disorder. Tear drop cells are found in myelofibrosis, metastatic marrow infiltration and MDS. Target cells indicate liver disease. Basophilic stippling is seen in megaloblastic anaemia and MDS. Howell-Jolly bodies are found in dyserythropoietic states. Toxic granules are found in infections whereas hypogranulation of the neutrophils is a characteristic of myelodysplastic syndromes. The neutrophils can have hypersegmented (megaloblastic anaemia) or hyposegmented (MDS, chronic leukaemia) nuclei. The presence of large granular lymphocytes should lead to the suspicion of a viral illness or LGL leukaemia, blasts (acute leukaemia, myelofibrosis, subleukaemic leukaemia) or plasmacytic cells (multiple myeloma). Giant platelets can be seen in myelofibrosis and MDS. Normal sized platelets are found in aplastic anaemia. The immature platelet fraction (IPF) is a measure of platelet production, is low in primary bone marrow failure disorders and elevated in the setting of peripheral destruction. Marked rouleaux formation are found in multiple myeloma and kala-azar.

By absolute reticulocyte count (ARC) physician can differentiate the hypoproliferative and hyperproliferative state of bone marrow. Normal range of absolute reticulocyte count is 50-100x10^9/L. All cases of pancytopenia with very low ARC (<25x10^9/L) or high ARC (>100x10^9/L) should be examined by bone marrow aspiration unless there is a history suggestive of sepsis or malaria. Pancytopenia with ARC 25-50x10^9/L should initially be evaluated with serum B_{12}, folate and ferritin assays and if any one of these is found to be low, bone marrow aspiration is not needed.

Before bone marrow examination sometime other tests including serum LFTs and hepatic serology, serum coagulation profile, bleeding time, fibrinogen, and d-dimer, serum direct antiglobulin test, serum B_{12} and folate, serum HIV and nucleic acid testing are needed.

Bone marrow examination (aspiration and biopsy) is essential for haematological disorder and for any cases of unexplained, persistent, or severe cytopenia except the cause is otherwise apparent (e.g. megaloblastic anaemia, autoimmune diseases, established liver disease with portal hypertension, hypersplenism or sepsis). In bone marrow aspiration, first we assess the cytology (blast, megaloblastic change, dysplastic change, abnormal cell infiltrates, haemophagocytosis, and infection e.g. Leishman-Donovan bodies, malarial parasites, tuberculosis and fungal infection) then immunophenotyping (lymphoproliferative disorders, acute and chronic leukaemia) and cytogenetics (leukaemia, myelodysplasia, lymphoproliferative disorders).

By bone marrow trephine biopsy, we assess the marrow cellularity. Low cellularity (excessive amount of fat cells) indicate decreased production of blood cells, normal (50%-70% haematopoietic cells with 30%-50% fat) or increased (80%-100% cells with little fat) cellularity indicate ineffective production or increased destruction or sequestration of blood cells. We also evaluate cellular infiltration, features of myelodysplasia (e.g., abnormal localization of immature precursors), reticulin stain (fibrosis) with trephine biopsy.

Some special test like peripheral blood immunophenotyping for deficiency of phosphatidylinositol-glycan-linked molecules on peripheral blood cells (e.g., CD16, CD55, CD59) for paroxysmal nocturnal haemoglobinuria, serum IgM and IgG for CMV infection, serum monospot, viral capsid antigen (VCA), and Epstein-Barr nuclear antibody (EBNA) for Epstein-Barr virus, immunophenotyping, cytogenetics, lymph node biopsy for lymphoproliferative disorders, immune-electrophoresis for multiple myeloma, diepoxy butane (DEB) test for chromosomal breakage in peripheral blood lymphocytes for Fanconi anaemia, blood and bone marrow culture, serum ELISA for Leishmaniasis and other rare infections, serum PSA in suspected cases of prostatic malignancy, leukocyte glucocerebrosides for rare genetic and metabolic disease, and radiological survey are sometimes needed.

Management

The basic components of management for pancytopenic patients are supportive care and management of underlying cause. Bleeding and infection due to cytopenia is a medical emergency. So, supportive care is the most important aspect of management of pancytopenia.

Decision of platelet transfusion depends on active bleeding or risk of bleeding. Active bleeding should be promptly managed with either random donors or single donor platelet concentrates transfusion until bleeding resolves. When platelet count $<5x10^9$/Lor $<10x10^9$/L and patient with fever or platelet count $<20x10^9$/L and patients receiving heparin, $<50x10^9$/L and patient who will undergo invasive procedure within the next 4 hours or neurosurgical patients with platelet count $<100x10^9$/L needs prophylactic platelet transfusion.[30] The development of a refractory state caused by allo-immunisation is the major problem of platelet transfusion which can be minimized by use of single donors to reduce exposure and physical or chemical methods to diminish leucocytes. HLA-matched single donor platelets are useful for patients who are refractory to platelet transfusions because of anti- HLA antibodies. Oral oestrogens or nasal follicle stimulating hormone / luteinizing hormone (FSH/LH) antagonists are given to suppress menstruation. Avoid aspirin, NSAIDs, intramuscular injections (unless platelets> $50x10^9$/L), tight clothing such as girdles and tight undergarments or pants, contact sports, strain for bowel movements. Do not use tampons, any rectal suppositories or enemas.

Any infection in a neutropenic patient is a life-threatening event, with or without the presence of pyrexia. Any sudden deterioration in a patient who is neutropenic is almost always due to infection unless prove otherwise. Prompt hospitalisation and initiation of broad-spectrum antibiotic therapy should be instigated without any delay. Front-line therapy is typically with a broad-spectrum beta-lactam with activity against a broad range of gram-negative organisms, including pseudomonas. Cefepime, ceftazidime, piperacillin-tazobactam, or carbapenems are currently recommended first-line therapy for neutropenic fever. Vancomycin should be added in patients with indwelling catheter or mouth sores or any signs of irritation around peripheral lines or other signs of skin infection. Persistent fever despite broad-spectrum antibacterial coverage indicate fungal infection and warrants treatment with antifungal drugs. Use of growth factors or G-CSF analogues, such as filgrastim may be used for boosting WBC counts which depends on the underlying clinical situation. For prevention of infection reverse barrier isolation is one of the important managements of neutropenia. Neutropenic patients should avoid raw or undercooked meats, soft cheeses and fruits/vegetables. Hand wash before eating, after going to the bathroom, and before handling a central line is very important. Careful maintenance of skin hygiene, good dental care, and rectal hygiene is absolutely essential. There is general agreement that when haemoglobin (Hb) levels of >10 g/dL RBC transfusion is typically not indicated. When the Hb level is <7 g/dL and stable, non-bleeding medical and surgical inpatients are considered for RBC transfusion. Patients with acute coronary syndromes and Hb level <8 g/dL RBC transfusion should be considered. Adult critical care medical and surgical inpatients being treated for sepsis during the first 6 hours of resuscitation may be transfused with an Hb level < 10 g/dL. Non-bleeding inpatients should be transfused single unit RBC. If additional unit is indicated based on Hb level, post-transfusion Hb must be obtained before ordering[30]. If repeated transfusions are needed, use of leuco-reduced products is recommended as it reduces febrile transfusion reactions, CMV transfer, and allo-immunization, as they are crucial in reducing complications of the further transfusions. For prevention of transfusion associated graft versus host disease (GVHD), use of irradiated blood (to destroy donor lymphocytes) is recommended.

Conclusion

Pancytopenia is an important laboratory finding with an extensive differential diagnosis. Sometime it is difficult to find out the cause. A proper history, physical examination and complete blood counts with reticulocyte count and peripheral blood smear are essential tools for diagnosis. Bone marrow aspiration and trephine biopsy are needed for evaluating the aetiology of pancytopenia. Management and prognosis of pancytopenia depends on the severity of cytopenia and underlying pathology.

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