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Approach to Pancytopenia

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Abstract

Pancytopenia is reduction in all the three cellular components of the blood, namely Red blood cells (RBCs), leucocytes (WBCs) and platelets. It is a common entity which is encountered by practitioners. The presentation is in the form of cytopenias leading to infections, anemia or bleeding manifestations. All the cases of pancytopenia need a through approach to reach to the cause of the same so that it can be it can be managed in the best possible manner. This paper will mainly concentrate on the approach to a case of pancytopenia.

Keywords: Pancytopenia, Anemia, Leucopenia, Thrombocytopenia.

Introduction

Cytopenias are reduction in any of the three cellular components of the blood i.e. RBCs, WBCs or platelets. It can be reduction in two cellular components (bicytopenia) or a reduction in all the three cellular components (pancytopenia). In bicytopenia, the most common combination to be seen is anemia and thrombocytopenia, whereas the least common is leucopenia with thrombocytopenia.[1] For practical purposes, it should have haemoglobin <10g%, absolute neutrophil count < 1,500/cumm and platelets <1,00,000/ cumm. It is labelled as severe when the three values are <7g%, <500/cu mm and <20,000/cu mm respectively.[2]

Pancytopenia basically arises secondarily to four main etiologies i.e. bone marrow failure, marrow space occupying lesions, effective production by marrow or peripheral destruction of hematopoietic cells.[3] The causes can be both congenital and acquired. The inherited causes of bone marrow and their salient features are summarized in Table 1.

Table 1: Inherited causes of bone marrow failure

Disease	Defect	Features
Fanconi anemia	Defect in DNA repair leads to increased chromosomal breakage with cross linking agents)	Skeletal anomalies (skeletal, thumb), short stature, urogenital anomalies
Dyskeratosis congenita	Shortened telomeres	Triad (leukoplakia, nail dystrophy, lacy skin pigmentation), pulmonary fibrosis
Shwachman Diamond syndrome	Mutation in SBDS gene	Exocrine pancreatic insufficiency
Congenital amegakaryocytic thrombocytopenia	Myeloproliferative Leukemia Virus Oncogene	Severe thrombocytopenia with its sequele
Hemophagocytic Lymphohistiocytosis	Multiple genes PFR1, UNC13D	Fever, splenomegaly, hepatitis, rash

The acquired causes of pancytopenia include non-inherited aplastic anemia, megaloblastic anemia, malignant marrow infiltrative disorders (acute leukemias, myelodysplastic syndromes, solid tumors), non-malignant infiltrative disorders (storage disorders, osteopetriosis), infections(HIV, tuberculosis, hepatitis viruses, EBV, CMV), immune disorders (lupus, Evan's syndrome, thymoma), acquired clonal bone marrow failure disorder (PNH), metabolic (anorexia nervosa) and peripheral destruction of blood cells i.e. hypersplenism.[4]

Pancytopenia is always to be approached in a systematic manner through proper history, examination first and then moving on to laboratory investigations as the first two parts if done properly and a systematic manner will lead very near to the diagnosis. The history should include the salient points viz age (inherited causes of bone marrow failure), sex, duration of symptoms (tells about the severity), bone pains (acute leukemias), fever (infections, acute leukemias), night sweats (Hodgkin's disease), malaise, weight loss (tuberculosis, malignancy), bleeding from any site (magnitude of thrombocutopenia), jaundice (hepatitis viruses), joint pain, rash, photosensitivity (lupus), any radiation exposure, exposure to potentially toxic chemicals, treatment history including herbals and drug

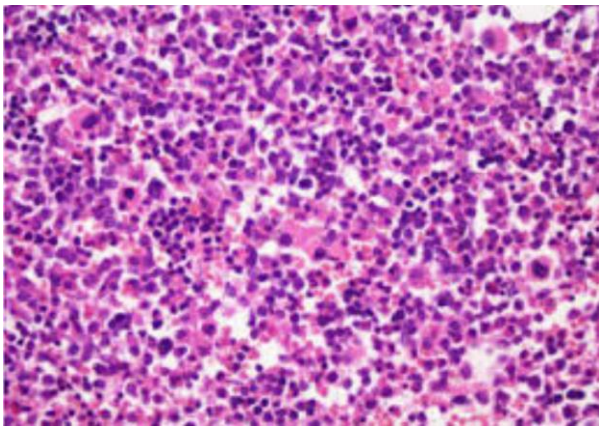
intake, blood transfusions, dietary history (megaloblastic anemia, anorexia nervosa), ooccupational exposure history (benzene).

A thorough examination should be done including vitals, anthropometry, general physical examination and systemic examination. Some salient features in examination will point towards particular etiologies like: anthropometry including stature (short stature in Fanconi anemia) dysmorphic features 9Fanconi anemia), pallor (severity of anemia), icterus (hepatitis viruses), lymphadenopathy (leukemias), edema, sings of CHF, stomatitis, cheilitis (neutropenia, neutrational deficiency), triad of nail dystrophy, leukoplakia, skin pigmentation (dyskeratosis congenita), oral candidiatis, pharyngeal exudates (neutropenia), petechie, purpura, hyperpigmentation, sternal tenderness(acute leukemias), gum hypertrophy (Acute myeloid leukemia), hepatosplenomegaly, joint swelling, sinuvitis (lupus).

Moving on to the laboratory investigations of pancytopenia, it requires complete blood counts with RBC indices, reticulocyte count and a peripheral blood examination. Bone marrow examination: aspiration and biopsy (to know the cellularity of the marrow) and specific investigations to find the causes leading to pancytopenia are needed. Complete blood counts will show that all the 3 cell lines are decreased. In bone marrow failure where there is ineffective production of the cells by the marrow, the reticulocyte counts will be decreased, whereas it will be higher in cases where pancytopenia is secondary to the peripheral destruction of the cellular components of the blood. Aniso-poikiliocytosis i.e. variation in the sizes of RBCs along with the change in their shapes is very prominent in myelofibrosis whereas it is invariably absent in acute leukemias. Peripheral smears can show blasts (acute leukemias, myelofibrosis, subleukemic leukemias) or plasmacytic cells (multiple myeloma). RBC and WBC precursors in the peripheral blood are not typical of aplastic anemia, so their presence in pancytopenia suggests diagnosis other than aplastic anemia. Howel-Jolly bodies (basophilic nuclear remnants) can be found in the peripheral smear of megaloblastic anemia or myelodysplastic syndrome. Hypersplenism and myelodysplastic syndrome peripheral smear can show giant platelets whereas normal sized platelets are found in aplasic anemia. The granulations of the neutrophils are to be taken into account; toxic granules are found in infections whereas hypogranulation of the neutrophils is a characteristic of myelodysplastic syndromes. The neutrophils can have hypersegmentaion (megaloblastic anemia) or hyposegmented (myelodysplastic syndromes, chronic leukemias). Multiple myeloma and cases of infections on the other hand will show an increase in ESR (erythrocyte sedimentation rates).

Bone marrow examination is almost always indicated in cases of pancytopenia unless cause is very apparent. Both aspiration and biopsy of the bone marrow are needed. Bone marrow aspirate permits examination of cytology (megaloblastic change, dysplastic change, abnormal cell infiltrate), immunophenotyping (leukemias, lymphoproliferative disorders) and cytogenetics (myelodysplasia, leukemias, lymphoproloferative disorders).

The differentials of pancytopenia are based on the cellularity of the marrow as normocellular (50-70% hematopoietic cells with 30-50% fat), hypocellular (excessive amounts of fat cells) or hypercellular (80-100% cells with little fat); Fig. A:



Hypercellular

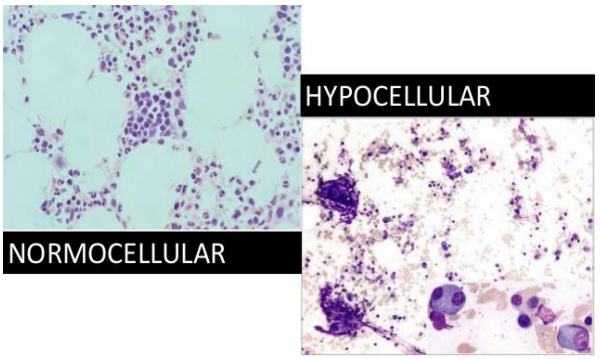


Fig. A: Depicting the cellularity of the bone marrow

The bone marrow examination findings are summarised below in Table 2.

Table 2: Bone marrow findings in different cases of pancytopenia

Bone Marrow Findings	Conditions
Cellularity	Hypercellular: Megaloblastic anemia, Hyperslenism Dry Tap: Myelofibrosis Hypoplastic: Myelodysplastic syndromes
Erythropoisis	Dysplastic: MDS, some AML Increased: Hemolysis
Myelopoisis	Dysplastic: Myelodysplastic syndrome Mophologically normal:

	Myeloproliferating disorders
Blasts	Myelodysplastic disorders, Acute Leukemias
Megakaryopoisis	Dysplastic: Myelodysplastic disorder
Other cells	Reedsternberg cell: Hodgkin cell Bacteria, Fungus, Parasite, Viruses, LD bodies

Specific investigations are required to reach to the final diagnosis in different causes of pancytopenia. Vitamin B12 and folic acid levels are needed for megaloblastic anemia whereas blood cultures are needed in cases of sepsis induced pancytopenia. X-rays of the bones will guide in multiple myeloma and metastasis. Liver and kidney function assays will point towards the etiology confining to these organs. Rare tests like chromosomal breakage studies are required for diagnosing congenital bone marrow failure syndrome- Fanconi anemia. Anti- nuclear antibody assay will point towards lupus.

Hence, a proper and systematic workup is needed in pancytopenic patients as elimination of the cause is needed to treat the condition.

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