Original Research Article

Diagnostic utility of bone marrow aspiration in pancytopenia

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Abstract

Back ground: Pancytopenia is a common haematological finding in clinical practice. It is a striking feature of many serious and life-threatening illnesses, ranging from simple drug-induced bone marrow hypoplasia, megaloblastic anaemia to fatal bone marrow aplasias and leukaemia. The severity of Pancytopenia and the underlying pathology determine the management and prognosis. Thus, identification of the correct cause will help in implementing appropriate therapy .Pancytopenia is a common haematological finding for which bone marrow aspiration is conducted.
Aim: To study the bone marrow aspiration smears in Pancytopenia cases and correlating with peripheral smear and clinical findings to arrive at a diagnosis.
Materials and methods: This was a study conducted at Department of Pathology, Gandhi Medical College on 148 cases of Pancytopenia presenting over a period of 2 years. Clinical findings, complete blood counts and peripheral smear findings were recorded and Bone marrow aspiration was done. Smears were stained with Leishman stain. Perls' stain was done in all cases. Special stains like MPO, PAS, Reticulin staining was done if needed.
Results: Out of 148 cases of Pancytopenia 67 cases were males and 81 were females. Most of the cases were in the age group of 10-20 followed by 20-30. Megaloblastic Anaemia was found to be the most common cause of Pancytopenia followed by hypoplastic marrow.
Conclusion: A thorough Evaluation of bone marrow smears can diagnose underlying pathology in most cases of Pancytopenia. Correlating bone marrow features with clinical and haematological findings aid in diagnosing and management of most cases of Pancytopenia.

Key words

Bone marrow, Megaloblastic Anemia, Pancytopenia.

Introduction

Pancytopenia is a clinicopathological entity in which all the three formed elements of blood that is Red blood cells, White blood cells and Platelets are decreased. Pancytopenia may be due to decrease in the production or increase in the destruction of the hemopoietic elements. The causative mechanisms include bone marrow failure, ineffective marrow production, marrow space occupying lesions, autoimmune disorders or infections. The frequency of underlying pathology causing Pancytopenia depends on various factors including geographic distribution. Patients usually present with complaints of unexplained weakness, fatigue, shortness of breath, pallor, prolonged fever and tendency to bleed. They may have associated findings like jaundice hepatomegaly, splenomegaly and lymphadenopathy.

The severity of Pancytopenia and underlying pathology determine the management and prognosis of patients. Bone marrow examination is the frequently requested investigation to determine the cause of Pancytopenia. Bone marrow aspiration is a reliable and rapid method of marrow evaluation. The indications for bone marrow aspiration include further workup of hematological abnormalities observed in peripheral blood smear, evaluating primary and metastatic bone marrow tumors, fever of unknown origin and storage disorders [1].

Clinical history, physical examination, primary hematologic investigations coupled with bone marrow aspiration is helpful in diagnosing underlying pathology in most of the patients with Pancytopenia. Bone marrow trephine biopsy provides overall cellularity, detection of focal lesion and infiltration. Flow cytometry may be needed in typing of leukemia.

Aim

- To study the bone marrow aspiration smears in Pancytopenia cases and correlating with peripheral smear and clinical findings to arrive at a diagnosis
- To estimate frequency of different diseases producing Pancytopenia.

Materials and methods

The present study was conducted in the Department of Pathology, Gandhi Hospital for a period of 2 years from May 2016 to April 2018. Patients of all age groups and both sexes were included in the study. Cases with hemoglobin less than 10 gm/dl, total leukocyte count less than 4000/cu.mm and platelet count less than 1.5 lakhs/cu.mm were included in the study. Cases of chemotherapy induced Pancytopenia were excluded from study. During 2 years study period a total of 290 bone marrow aspirations were performed out of which 148 were done in patients with Pancytopenia.

Bone marrow aspiration was done under aseptic conditions after infiltrating the sight of aspiration with xylocaine. Common sites of aspiration were posterior iliac crest and sternum. Bone marrow aspiration was done from tibial tuberosity in infants and young children. Sterilised Salah's needle and 10cc syringe were used for aspiration. Aspirated material was expressed on to clean glass slides and smears prepared. Simultaneously complete blood count was done and peripheral blood smear was prepared. Bone marrow aspiration smears and peripheral blood smears were stained with leishman stain. Marrow smears were examined for cellularity, megakaryocytes, erythroid myeloid ratio, erythropoiesis, myelopoiesis, other cells such as plasma cells, lymphocytes, blasts and parasites. Perl's stain was done in all cases for iron stores. When required special stains, periodic acid-Schiff stain and myelo peroxidase stain were used. Reticulin stain was done in suspected myelofibrosis cases. Trephine biopsy was done in 18 cases for further

evaluation of bone marrow. Trephine biopsy specimens were fixed in formalin processed and the sections were stained with haematoxylin and eosin. Flow cytometry was advised in some cases of leukaemia for typing.

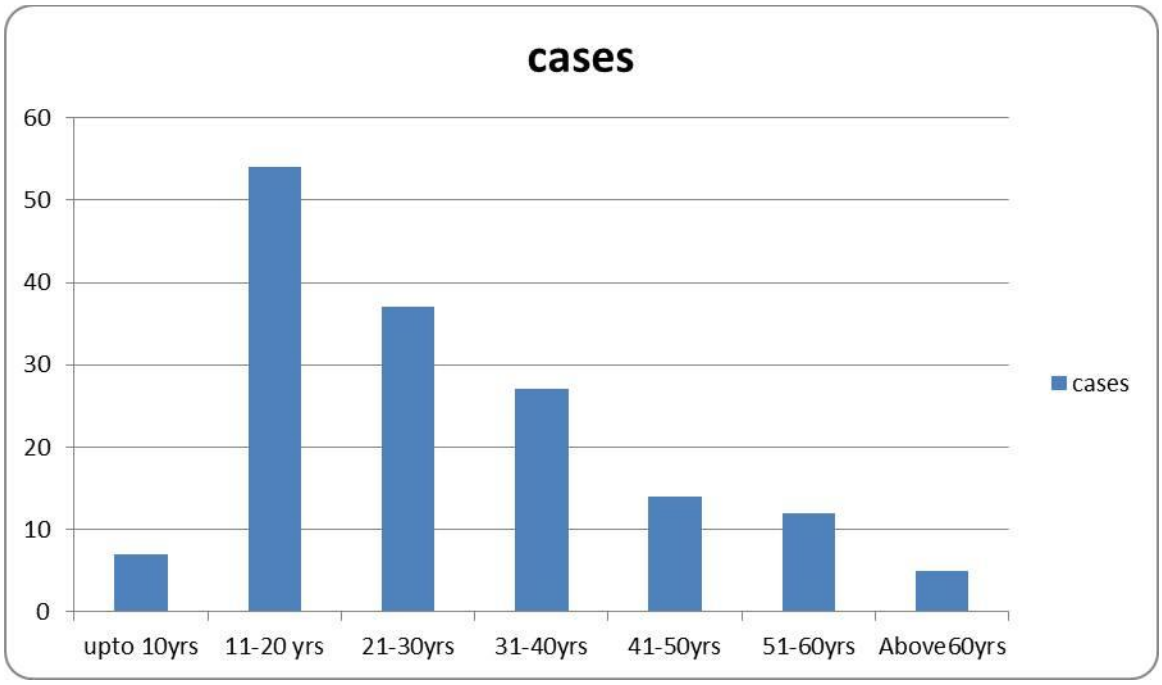
Results

A total of 148 cases of Pancytopenia were studied out of which 67(45%) were males and 81(55%) were females. The age of the patients ranged from 3 months to 72 years. Maximum number of cases were seen in the age group of 11-20 (36%) followed by 21-30 (25%) age group. Least number of cases was seen in the patients above 60 years (**Figure – 1**).

Patients with Pancytopenia presented with a variety of different clinical features, but some common features were identified. Commonest presenting complaint was fever in 60% of cases followed by weakness (45%). Other presenting complaints were fatigue, shortness of breath, icterus. Progressive pallor was the most common clinical feature and it was found in almost every case. Icterus was seen in 12% cases. Bleeding manifestations like epistaxis, gum bleeding and petechial rashes were seen in 32% cases. Splenomegaly was seen in 26% cases and hepatomegaly in 14% cases (**Table – 1**).

The predominant blood picture was dimorphic anemia (49%), followed by macrocytic anemia (23%). Peripheral smear showed macro-ovalocytes with hyper segmented neutrophils in 42% cases. Normocytic normochromic anaemia constituted 12% of the cases; and normocytic hypochromic anaemia in 16% cases. Leukopenia and thrombocytopenia were seen in all cases. Atypical cells were seen in 3% cases.

Figure – 1: Age wise distribution of Pancytopenia cases.



The commonest cause of Pancytopenia was megaloblastic anaemia and was seen in 101(68%) cases followed by hypoplastic marrow 21 (14%). The other causes of Pancytopenia were acute leukaemia, storage disorders, gelatinous transformation, multiple myeloma, myelofibrosis and viral pyrexia. Bone marrow was hypercellular in 98 (66%) cases, hypocellular in 32(22%) cases and normocellular in 18 (12%) cases (**Table – 2**). In the present study, out of 21 cases of bone marrow hypoplasia, cause was not known in 9 cases and was grouped under idiopathic bone marrow hypoplasia. 8 patients had history of herbal

medication. 2 patients gave history of HIV on anti-retroviral treatment and one patient with carbamazepine treatment for epilepsy. 60 (40%) cases had concurrent iron deficiency along with megaloblastic anemia. Bone marrow aspiration showed megaloblastic erythroid hyperplasia along with micronormoblasts. Megaloblasts had the characteristic feature of sieved nuclear chromatin, asynchronous nuclear maturation and bluish cytoplasm with cytoplasmic blebs. Giant metamyelocytes and band forms were predominant in granulocyte series. 7 cases were of AML (acute myeloblastic leukemia) and 5 cases were ALL (acute lymphoblastic leukaemia). Bone marrow was hypercellular in all cases. Erythroid and megakaryocytic series were reduced. In AML Majority of cells were myeloblasts and in ALL lymphoblasts constituting more than 40% in marrow. Multiple myeloma was diagnosed in 2 cases who presented with weakness and bony tenderness. Bone marrow showed increased number of plasma cells, including binucleate and trinucleate forms. 2 cases of storage disorder were diagnosed. A 13-year-old male presented with pallor, splenomegaly. Bone marrow showed large cells with eccentrically placed nucleus and abundant cytoplasm which was PAS (periodic acid Schiff) positive. Hence diagnosis of Gaucher's disease was considered. Another case was a 3 months old child who presented with anaemia and splenomegaly. Bone marrow revealed features of Gaucher's disease. In both the cases enzyme studies were advised for confirmation of diagnosis. One case with history of herbal medication was diagnosed as Myelofibrosis which showed increased reticulin staining (reticulin fibrosis). A 51 year old male patient with chronic liver disease with portal hypertension showed Gelatinous transformation of bone marrow. Out of 148 cases of Pancytopenia 12 cases had dry tap/blood tap on aspiration. Bone marrow biopsies in these cases revealed hypoplastic marrow in 7 cases Leukemia in 4 cases and normocellular marrow in one case. Dry tap may be due to faulty technique in this case of normocellular marrow.

Table – 1: Clinical findings in Pancytopenia cases.

Clinical findings	No of cases
Pallor	148(100%)
Fever	89(60%)
Weakness	67(45%)
Bleeding	47(32%)
Dyspnea	40(27%)
Icterus	18(12%)
Splenomegaly	38(26%)
Hepatomegaly	21(14%)

Table – 2: Bone marrow findings in 148 cases of Pancytopenia.

Diagnosis	No of cases	%
Megaloblastic anemia	101	68%
Hypoplastic marrow	21	14%
Acute myeloid leukemia	7	4.7%
Acute lymphoid leukemia	5	3.4%
Normal marrow	7	4.7%
Storage disorder	2	1.4%
Multiple myeloma	2	1.4%
Myelofibrosis	1	0.7%
Myelodyslastic syndrome	1	0.7%
Gelatinous transformation	1	0.7%

Discussion

Pancytopenia can be due to reduction in hematopoietic cell production in the bone marrow as in aplastic anemia or due to infections, toxins, alcohol, chemotherapy, radiotherapy, malignant cells infiltration and parasitic infestation or due to increased cell destruction either in bone marrow itself or in spleen as in hypersplenism, autoimmune disorders, infection etc.

In the present study, most of the cases were in the age group 10-30 (61%) which is similar to studies of Khodke, et al. [2] with 40% cases in the age group of 12-30 and Pathak, et al. [6] with 30% of cases in the age group of 15-30 years. In this study, females outnumbered male with male to female ratio of 1:1.2 similar to the studies of Pathak, et al. (1:1.1) [6] and Aziz, et al. (1:1.2) [7] whereas in the studies conducted by Khodke,

et al. [2] and Shah, et al. [4] males were more than females.

Pallor was seen in almost all cases. In the present study fever and generalized weakness were other clinical findings which were seen in 60% and 45% cases respectively. Poonam, et al. [11] found fever (56%) as the most common symptom followed by generalized weakness (46%). In a study by Tilak, et al. [3] generalised weakness (51%) was the commonest symptom followed by fever (27%).

The commonest cause of Pancytopenia, reported in various studies throughout the world has been aplastic anemia. The commonest cause of Pancytopenia in the present study is megaloblastic anaemia (68%) followed by hypoplastic marrow (14%).This is similar to study done by B N Gayathri and Kadam [9] where in most common cause for Pancytopenia is megaloblastic anemia (74.04%) followed by aplastic anemia (18.26%). Incidence of megaloblastic anemia was 72% and 68% in the studies done by Khunger, et al. [10] and Tilak, et al. [3] respectively. All the above studies have been done in India, and they stress the importance of megaloblastic anaemia being the major cause of Pancytopenia. It is a rapidly correctable disorder and should be promptly notified. Although bone marrow aspiration studies are not indicated in suspected cases of megaloblastic anaemia, if the diagnosis does not appear straight forward or if the patient requires urgent treatment and haematological assays are not available, bone marrow aspiration is indicated. As facilities for estimating folic acid and vitamin B_{12} levels are not routinely available in most centres in India, the exact deficiency is usually not identified.

The only dietary sources of Vitamin B_{12} are foods of animal protein origin such as kidney, liver, meat, fish, eggs, cheese and milk. In contrast to folate, vegetables contain practically no Vitamin B_{12}. Vitamin B_{12} is synthesized in the human large bowel by microorganisms but is not absorbed from this site and thus, the humans are entirely dependent upon dietary sources. Vegetarians are more prone for megaloblastic anaemia as compared to that of non-vegetarians.

In India poor eating habits, poverty, poor quality of foods, and lack of education and self-avoidance of necessary foods may be the cause of nutritional deficiency leading to megaloblastic anaemia. Megaloblastic anaemia can be prevented by improving the nutritional status of our population. The incidence of hypoplastic anaemia in our study was 14%, which correlated with the studies of Gayathri and Kadam (19%) [9]; Khodke, et al. (14%) [2]. A higher incidence (29.5%) was reported by Kumar, et al. [5]. Aplastic anaemia may be due to environmental factors or exposure to pesticides/ drugs/ toxic chemicals, infections. In the present study of 21 cases of hypoplastic marrow, 14 cases were diagnosed in bone marrow aspiration. And when correlated with bone marrow biopsy it increased to 21.

This study provides a very important message that in all the cases of Pancytopenia both bone marrow aspiration and bone marrow biopsy must be performed.

Acute leukemia was found to be third most common in our study that is 8% of total cases of Pancytopenia. This correlated with the study done by Shah, et al. (7.5%) [4] and Aziz, et al. (10%) [7]. The other causes of Pancytopenia were storage disorder, gelatinous transformation, multiple myeloma, myelofibrosis and viral pyrexia.

Difference in the frequency of disorders causing Pancytopenia has been due to variation in study design, diagnostic criteria, geographic area, and duration of observation, genetic differences and varying exposure to cytotoxic/chemical agents.

Conclusion

Pancytopenia is a common hematological problem encountered in clinical practice and should be evaluated thoroughly. Bone marrow

aspiration is an important diagnostic tool in haematology which helps to evaluate various cases of Pancytopenia. In the present study, Megaloblastic anaemia is the most common cause of Pancytopenia. Although bone marrow aspiration studies are not indicated in suspected cases of megaloblastic anemia, if the diagnosis does not appear straight forward or if the patient requires urgent treatment and haematological assays are not available, bone marrow aspiration is indicated.

The present study concluded that detailed physical examination; primary hematological investigations along with bone marrow aspiration coupled with biopsy in Pancytopenic patients are helpful for understanding disease process and to diagnose or to rule out the causes of Pancytopenia. These are also helpful in planning further investigations and management.

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