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DIAGNOSTIC UTILITY OF BONE MARROW IN PATIENTS OF PANCYTOPENIA

Pathology

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ABSTRACT

Introduction: Pancytopenia is not a disease entity but a triad of findings that may result from number of disease processes, primarily or secondarily involving bone marrow. [1, 2, 3] Presenting symptoms are attributable to anemia, leucopenia or thrombocytopenia. [1, 2, 4] Bone marrow aspiration and biopsy should be done simultaneously and is indicated in all cases of pancytopenia where underlying cause is not quite obvious. [5]

Aims And Objective:

1. To study various causes of pancytopenia in bone marrow examination.

2. To study the spectrum of clinical presentation in cases of pancytopenia.

3. To study the incidence of pancytopenia cases according to age and gender

Materials And Method: In this study, Bone marrow aspiration and biopsy examination were performed over 103 cases for different indication over a period of 2 years, out of which 37 cases fulfilled the criteria of pancytopenia. Patient's detail regarding name, age, gender, clinical history, complete blood count and peripheral blood smear examination findings were noted in pancytopenia cases. **Results:** Out of 37 cases of pancytopenia, the commonest cause of pancytopenia was Hypoplastic anaemia (27%) followed by Megaloblastic anaemia (24.3%). Most common age group of pancytopenia was 21-30 years (21.6%) and most common clinical presentation was generalized weakness and pallor (60%) followed by breathlessness (35%). **Conclusion:** Bone marrow aspiration coupled with trephine biopsy can diagnose majority of cases of pancytopenia. Hypoplastic anemia and megaloblastic anemia were the commonest cause of pancytopenia in the present study. Physical examination, primary haematological investigation along with bone marrow aspiration and biopsy in pancytopenia patient is helpful to diagnose or rule out cause of pancytopenia and determine further management and prognosis of patient. [1,6]

KEYWORDS

Pancytopenia, Megaloblastic anemia, Hypoplastic anemia

INTRODUCTION:

Sir William Harvey described blood as "the fountain of life and the primary seat of the soul. The marrow of our bones is the seed bed of our blood". [7]

Pancytopenia is a relatively common haematological identity. Pancytopenia is not a disease entity but a triad of findings that may result from number of disease processes,primarily or secondarily involving bone marrow. [1,2,3] It is the simultaneous presence of anemia, leucopenia and thrombocytopenia, therefore it exists where Haemoglobin is less than 13.5 gm/dl in males, 11.5 gm/dl in females, the W.B.C count is $<4x10^9$/L and platelet count is $<150x\ 10^9$/L. [1]

Presenting symptoms are attributable to anemia, leucopenia or thrombocytopenia. Leucopenia is uncommon at initial presentation of patient, but can become the most serious threat to life during subsequent course of disorder. [1,2,4]

Pancytopenia develops from variety of mechanisms such as decrease in hematopoietic cells production as a result of destruction of marrow by toxins or replacement by malignant cells or abnormal cells or suppression of normal marrow growth and differentiation. Other mechanisms are ineffective haematopoiesis with cell death in marrow, formation of defective cells which are rapidly removed from circulation, sequestration and/or destruction of cells by action of antibodies or trapping of normal cells in hypertrophied and overactive reticuloendothelial system. [8]

The marrow is generally hypocellular in cases of pancytopenia caused by a primary production defect. Cytopenia resulting from ineffective haematopoiesis, increased peripheral utilization or destruction of cells and bone marrow invasive processes are usually associated with a normocellular or hypercellular marrow. [4,5]

It is recommended that bone marrow aspiration and biopsy should be done simultaneously in cases of pancytopenia as aspiration smears are superior for morphological details while biopsy provides a more reliable index of cellularity and often reveals bone marrow infiltration, fibrosis and granulomas. [5]

AIMS AND OBJECTIVE:

1. To study various causes of pancytopenia in bone marrow examination.

2. To study the spectrum of clinical presentation in cases of pancytopenia.

3. To study the incidence of pancytopenia cases according to age and gender.

MATERIALS AND METHOD:

This is an retrospective study carried out in the Department of Pathology, Medical college, Vadodara from 4rth January 2022 to 31st December 2023. The patient's detail regarding name, age, gender, clinical history, complete blood count and peripheral smear examination were noted in pancytopenia cases. Cases of chemotherapy induced pancytopenia were excluded.

After taking informed consent, Bone marrow aspiration and biopsy were performed. Bone marrow aspiration slides were fixed with methanol and stained with Leishman/ Giemsa stain and Prussian blue stain. Bone marrow biopsy slides were stained with Hemotoxylin and Eosin stain and special stains like Reticulin, PAS Stain whenever required. Also Brilliant cresyl blue stain was done for reticulocyte count correlation.

The data was entered and analysed in Excel sheets. Descriptive analysis was done. Data was presented using frequency and proportions.

RESULT:

During the period of 2 years, Bone marrow examination was performed in 103 cases out of which 37 cases fulfilled the criteria of pancytopenia. The study was done in age range of 3 months to 76 years of age. Out of 37 cases, 14 (37.8%) were male and 23 (62.1%) were female with male to female ratio as 1:1.6.

Table 1: Age And Genderwise Distribution Of Cases Of Pancytopenia.

Age (years)	Male	Female	Total	Percentage
0-10	03	03	06	16.2
11-20	02	02	04	10.8
21-30	02	06	08	21.6
31-40	01	06	07	18.9

41-50	02	05	07	18.9
51-60	01	01	02	5.4
61-70	02	-	02	5.4
71-80	01	-	01	2.7
TOTAL	14 (37.8%)	23 (62.1%)	37	100

Maximum number of cases were in age range of 21-30 years (21.6%) followed by 31-40 years (18.9%) and 41-50 years (18.9%) as shown in **TABLE 1.**

The most common chief presentation were generalized weakness and pallor (60%) followed by breathlessness (35%), abdominal pain and distension (29.7%) and fever (27%). Most common physical findings were spleenomegaly (35%) followed by hepatomegaly (27%) as shown in **TABLE 2.**

Table 2: Clinical Presentation Of Cases Of Pancytopenia.

Clinical Presentation	Total Out Of 37 Cases	Percentage
GENERALIZED WEAKNESS AND PALLOR	22	60
BREATHLESSNESS	13	35
SPLEENOMEGALY	13	35
ABDOMINAL PAIN AND DISTENSION	11	29.7
FEVER	10	27
HEPATOMEGALY	10	27
GENERALIZED EDEMA AND PEDAL EDEMA	09	24.3
JAUNDICE	06	16.2
MENORRHAGIA	05	13.5
ANOREXIA AND WEIGHT LOSS	04	10.8
VOMITING	03	08

The most common causes of pancytopenia were hypoplastic anemia (27%) and megaloblastic anemia (24.3) followed by normocellular marrow (10.8%), acute leukemia (10.8%), myelodysplastic syndrome (8%), erythroid hyperplasia (8%), iron deficiency anemia (2.7%) and tuberculosis (2.7%). Two cases were inconclusive due to diluted bone marrow aspirate as shown in **TABLE 3**.

Table 3: Various Causes Of Pancytopenia In Bone Marrow Examination.

Causes	Total	Percentage
HYPOPLASTIC ANEMIA/ APLASTIC ANEMIA	10	27
MEGALOBLASTIC ANEMIA	09	24.3
NORMOCELLULAR MARROW	04	10.8
ACUTE LEUKEMIA	04	10.8
MYELODYSPLASTIC SYNDROME	03	08
ERYTHROID HYPERPLASIA	03	08
IRON DEFICIENCY ANEMIA	01	2.7
TUBERCULOSIS	01	2.7
INCONCLUSIVE	02	5.4
TOTAL	37	100

DISCUSSION:

Pancytopenia is one of the common haematological finding with variable clinical presentation. The present study was carried out in age range of 3 months to 76 years. Female patients outnumbered male patient with male to female ratio 1:1.6 which is similar to Aziz et al [9] (1:1.4) and Pathak R. et al [4] (1:1.04) but much different from other studies which showed male preponderance.

Variation in the frequency of various diagnostic entities causing pancytopenia has been attributed to difference in methodology and stringency of diagnostic criteria, geographic area, period of observation, genetic difference and varying exposure of myelotoxic agents etc. [1,5,10,11]

In the current study, most common presenting symptoms were generalized weakness and pallor (60%) followed by breathlessness (35%). Most common physical finding were spleenomegaly (35%) followed by hepatomegaly (27%). These findings were comparable with Javalgi et al [1], Desalpine et al [3], Mansuri et al [5], Sahay et al [6], Dagdia et al [7], Aziz et al [9], Chandra et al [12].

In the present study, Hypoplastic anemia (27%) was the most common cause of pancytopenia which was comparable with studies done by Desalpine et al [3] (26%), Jha et al [11] (29%), Pathak R. et al [4] (42%) as shown in **table 4**. This is in sharp contrast with various studies in Indian subcontinent where Megaloblastic anemia is the most common cause of pancytopenia. Aplastic anemia is a rare haemotopoietic stem cell disorder that results in pancytopenia and hypocellular marrow. Most cases are acquired and immune mediated but there are also inherited forms. Environmental triggers include drugs, viruses and toxins but most cases are idiopathic.[13] The incidence of Aplastic anemia is subjected to wide variation throughout the world, the reason apparently lying in environment rather than genetic factors, as people who move from east to west have same incidence as local population.[13] The use of various types of pesticides in the fields of agricultural industry is increasing day by day. Since Gujarat is an agricultural state, pesticides may have important role in high incidence of aplastic anemia / Hypoplastic anemia. A case of 18 year female had diluted marrow on bone marrow aspirate but was diagnosed hypoplastic anemia on bone marrow biopsy. **Figure 1.**

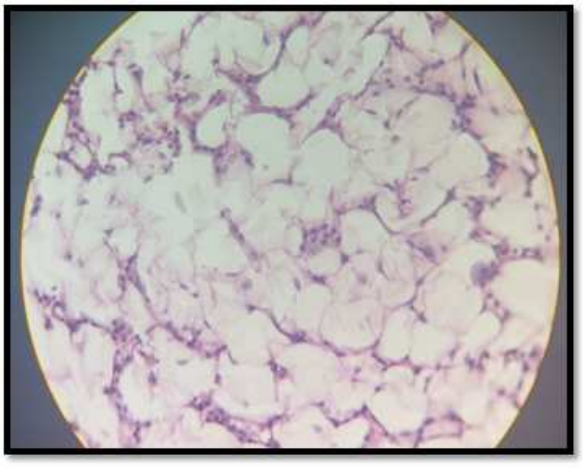

Figure 1: Bone Marrow Biopsy In Hypoplastic Anemia

Table 4: Comparison Of Various Causes Of Pancytopenia With Other Studies On Pancytopenia

NAME OF STUDY & YEAR OF STUDY	NUMBER OF CASES	MOST COMMON CAUSE	2ND MOST COMMON CAUSE	3RD MOST COMMON CAUSE
Gayathri BN et al [10](2011)	104	Megaloblastic anemia (74%)	Aplastic anemia (18.2%)	Subleukemic leukemia (3.8%)
Desalpine et al [3] (2014)	50	Aplastic anemia (26%)	Normoblastic erythroid hyperplasia (22%)	Megaloblastic anemia (16%)
Mansuri et al [5] (2017)	50	Megaloblastic anemia (58%)	Iron deficiency anemia (8%)	Aplastic anemia (8%)
Chandra et al [12] (2019)	68	Megaloblastic anemia (25%)	Hypoplastic anemia (19.11%) and Aleukemic leukemia (19.11%)	Leishmaniasis (11.76%)
Sahay et al [6] (2018)	85	Combined deficiency (51.8%)	Megaloblastic anemia (31.8%)	Myelodysplastic syndrome (8.2%)
Jha et al [11] (2008)	148	Hypoplastic anemia (29%)	Megaloblastic anemia (23.6%)	Hematological malignancies (21.6%)
Mohnish Patel et al[14] (2020)	80	Megaloblastic anemia (37.5%)	Nutritional anemia (16.2%)	Aplastic anemia (11.25%)
Pathal R. et al[4] (2012)	102	Hypoplastic anemia (42%)	Megaloblastic anemia (11.7%)	Acute leukemia (8.8%)

Dagdia et al [7] (2016)	75	Megaloblastic anemia (29%)	Aplastic anemia (18.6%)	Leukemia (17.2%)
Pinal Shah et al [2] (2017)	40	Megaloblastic anemia (35%)	Aplastic anemia (32.5%)	Acute lymphoblastic leukemia and Acute myeloblastic leukemia(4.5 %)
Javalgi et al[1] (2013)	106	Megaloblastic anemia (72%)	Iron deficiency anemia (12.2%)	Malaria (3.7%)
Present Study	37	Hypoplastic anemia (27%)	Megaloblastic anemia (24.3%)	Normocellular marrow (10.8%)

Megaloblastic anemia (24.3%) was the second commonest cause of pancytopenia which was comparable with studies done by Chandra et al [12] (25%), Sahay et al [6](31.8%), Dagdia et al [7] (29%), Jha et al [11] (23.6%). This may due to higher prevalence of nutritional anemia in Indian subcontinents leading to increased frequency of Megaloblastic anemia.[2,5,10] Three cases of megaloblastic anemia were diagnosed on bone marrow aspirate as bone marrow biopsy was not done. **FIGURE 2,3,4**

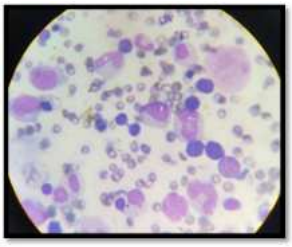

Figure 2: Bone Marrow Aspirate In Megaloblastic Anemia Showing Features Of Dyserythropoeisis And Giant Band Forms And Metamyelocytes.

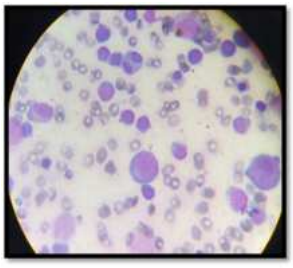

Figure 3: Bone Marrow Aspirate Showing Features Of Dyserthropooeisis And A Megaloblast .

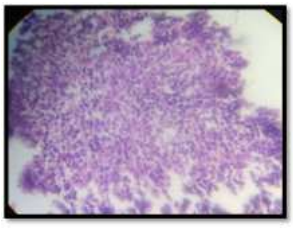

Figure 4: Bone Marrow Biopsy Showing Erythroid Hyperplasia

We also had cases of Normocellular marrow (10.28%). 4 Cases of Acute leukemia (10.8%) were found which was comparable to Desalpine et al[3] (14%), Aziz et al [9] (9.9%), Dagdia et al[7] (17%). 2 Cases of ALL were found in pediatric age group. Three cases of Myelodysplastic syndrome (8%) were found which was similar to studies done by Dagdia et al [7] (8%) and Pathak R. et al[4] (5.8%). One case of 50 year male of Myelodysplastic syndrome with excess blast was found on bone marrow aspirate, which was proven in bone marrow biopsy as " Leukemic transformation of probable Myelodysplastic disease".**FIGURE 6,7,8** Another case of 33 year female showed megaloblastic changes on bone marrow aspirate. On bone marrow biopsy, it showed the possibility of "Myelodysplastic syndrome without excess blast".

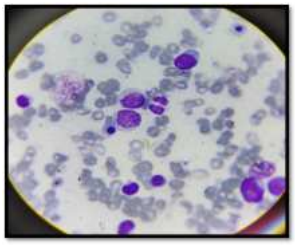

Figure 6: Bone Marrow Aspirate Of Patient With Myelodysplastic Syndrome With Excess Blast Showing Pseudopelger Huet Neutrophil And Blast Cells

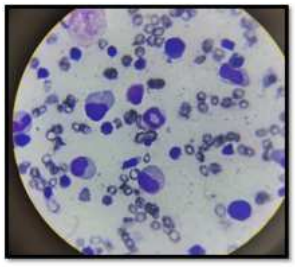

Figure 7: The Bone Marrow Biopsy Of Patient With Myelodysplastic Syndrome With Excess Blast Showing Features Of Dysmyelopoiesis.

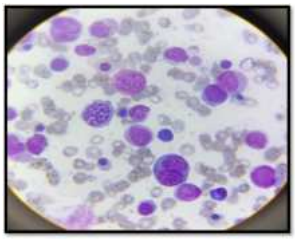

Figure 8: Bone Marrow Aspirate Of Patient With Myelodysplastic Syndrome With Excess Blast Showing Features Of Dyserythropoesis.

Three cases of erythroid hyperplasia (8%) were seen. Erythroid hyperplasia by itself is not the cause of pancytopenia. A possible hypersplenism needs to be ruled out in addition to different haemolytic anemias in cases of marrow showing erythroid hyperplasia.[2,4]

2 cases showed spleenomegaly and showed findings consistent with haemolytic anemia along with clinical features (Portal hypertension, cirrhosis of liver, hypersplenism). Also reticulocyte count ranged from 2.5% in given cases.

We had 1 case of iron deficiency anemia (2.7%). A case of disseminated tuberculosis was found (2.7%) which showed aggregates of epithelioid histiocytes along with histiocytic giant cells on bone marrow aspirate and chronic non specific inflammation on bone marrow biopsy. **FIGURE 9**

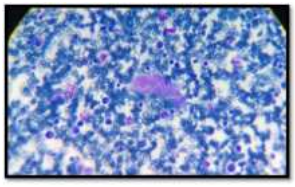

Figure 9: The Bone Aspirate In Case Of Disseminated Tuberculosis.

Limitation Of The Study:

The study had a small sample size and it was done at a single tertiary care centre in the region. Larger sample size and sampling from multiple centres in the region would have provided much clearer picture of the situation.

CONCLUSION:

Bone marrow aspiration coupled with trephine biopsy can diagnose majority of cases of pancytopenia. Hypoplastic anemia and megaloblastic anemia were the commonest cause of pancytopenia in the present study.

The present study concludes that physical examination, primary haematological investigation along with bone marrow aspirate coupled with biopsy in pancytopenia is helpful for understanding the disease process and to diagnose or to rule out causes of pancytopenia.[1,2,6] The severity of pancytopenia and the underlying pathology determines the management and prognosis of these patients.[1,6]

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