Section: Pathology

Original Research Article

CLINICAL-PATHOLOGICAL STUDY OF PANCYTOPENIA WITH SPECIAL REFERENCE TO BONE MARROW ASPIRATION AND BIOPSY

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ABSTRACT

Background: Pancytopenia, a clinico-hematological condition characterized by simultaneous reduction in three major formed blood elements i.e. anaemia (Hb<12g/dL in female, Hb<13g/dL in male), leucopenia (TLC<4000/ml) and thrombocytopenia (Platelets<1.5 lacs/µl).

Aims: To study the clinical-hematological profile of the cases of pancytopenia and evaluate the role of bone-marrow aspirate (BMA) and biopsy (BMB) to diagnose and classify them according to Etiology.

Material and Methods: The Present study was a hospital based prospective study. A total of 150 cases of pancytopenia were studied between September 2020 to October 2022. Detailed clinical history and physical examination were taken along with Peripheral blood smear examination, Complete Blood Count and BMA. BMB were also performed wherever feasible.

Results: Most of the cases were in the age group of 11-20 years with Male: Female of 1.4:1 with age ranging of 2-75 years. BMA and BMB were done in 93 and 57 cases respectively. Most common cause of pancytopenia was Aplastic Anaemia (25.3%) followed by Megaloblastic Anaemia (16.7%). Aplastic anaemia showed concordance of BMA with BMB in only 27 cases out of 38, reflecting BMB is necessary procedure to be done for proper evaluation and diagnosis of Aplastic anemia. Most common cause diagnosed on BMA was megaloblastic anaemia (25) followed by Aplastic Anaemia (21).

Conclusion: BMA and BMB are important adjuncts to PBS examination for evaluation of pancytopenias. Along with proper clinical history, clinical examination, general blood picture studies, we need to do BMB procedures also with BMA for proper diagnosis and prognosis of a patient having Pancytopenia, specially in cases of dry tap.

Key words: Aplastic Anaemia, Bone marrow, Pancytopenia.

INTRODUCTION

Pancytopenia is a clinico-hematological condition developing due to bone marrow suppression. It is a condition characterized by simultaneous reduction in all the three major formed elements of blood, below their normal limit, leading to anaemia (Hb<12g/dL in female and Hb<13g/dL in male), leucopenia (TLC<4000/ml) and thrombocytopenia (Platelets<1.5 lacs/µl).[1,2]

Pancytopenia is a manifestation of various pathological condition affecting bone marrow either primarily or secondarily. It is not a disease entity, rather a laboratory finding that may be associated with bone marrow suppression caused by either inefficient production, inability of cells to mature,

fibrosis replacing normal bone marrow contents, peripheral destruction unrelated to bone marrow or drug induced pancytopenia associated with Chemotherapy. Depending upon the etio-pathogenesis of pancytopenia, duration and severity of illness, clinical manifestations like easy fatiguability, rise in body temperature, thrombotic phenomenon or serious significant ailments may occur. The etio-pathogenesis of pancytopenia differ in various communities depending on their age distribution, dietary preferences, environment and infectious agents.

MATERIALS AND METHODS

The present study was a hospital based prospective observational study. Bone marrow aspiration and biopsy samples were taken from Medicine and Pediatric department of Sir Sunderlal Hospital, Banaras Hindu University, Varanasi and the hematological work up (Complete blood count, General blood picture, BMA, BMB) was done in Department of Pathology, IMS, BHU from September 2020 to October 2022.

A detailed clinical history of the patients was taken along with physical examination. In blood investigations, we did Complete blood count (CBC) along with general blood picture examination, Renal function tests (RFT), Liver function tests (LFT), Iron studies and viral markers. Following this, we did Bone marrow aspirate procedure in ≥15 years old patient (under local anaesthesia) and in <15 years old patient (under general anaesthesia) from posterior superior iliac spine. Bone marrow biopsy were also performed wherever feasible along with bone marrow imprint and clot preparations.

Routine peripheral blood smears, bone marrow aspiration smears and bone marrow imprint preparations were stained with Leishman stain. Bone marrow cores were fixed in neutral bufferd formaline solution and decalcification was done using 10% formic acid solution for 2-3 hours followed by haematoxylin and eosin staining, Perl's staining was done for iron grading wherever necessitated. Special cytochemical stains (SUDAN BLACK B-SBB) were done in cases of leukemia presented with cytopenia.

Inclusion Criteria

Cases of pancytopenia coming to the department of Medicine and Paediatric for further evaluation.

Exclusion Criteria

Cases of pancytopenia due to chemotherapy and radiotherapy.

Ethical Consideration

Nature of study was explained to the participant after which, a written consent was obtained. Name and other identities were not disclosed anywhere in the study. The study protocol was approved by the institution ethics committee of IMS, BHU with respect to letter no. Dean/2022/EC/3550.

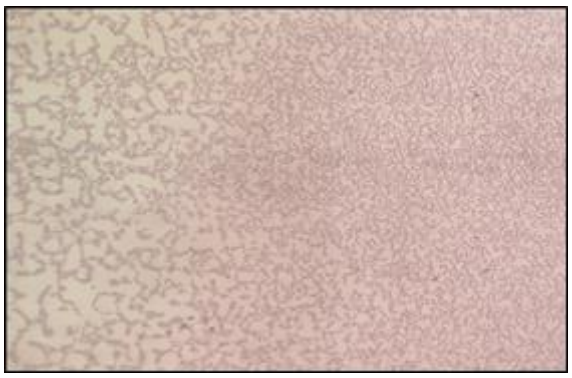

Figure 1: Peripheral blood smear of Aplastic anaemia showing pancytopenia (10x)

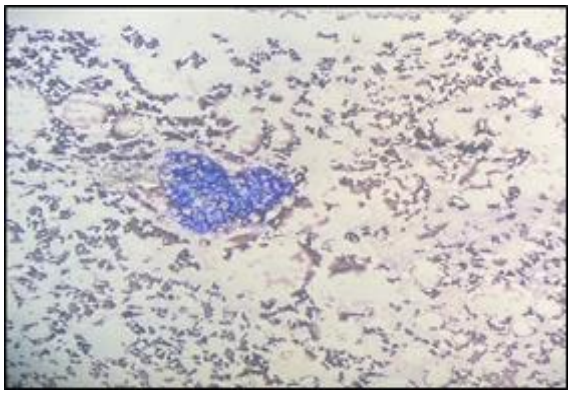

Figure 2: Bone marrow aspiration of Aplastic Anaemia showing hypocellular particle (4x)

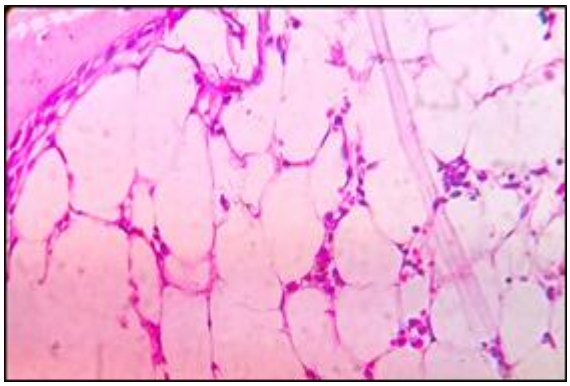

Figure 3: Bone marrow biopsy of patient of Aplastic anaemia showing hypocellularity (40x)

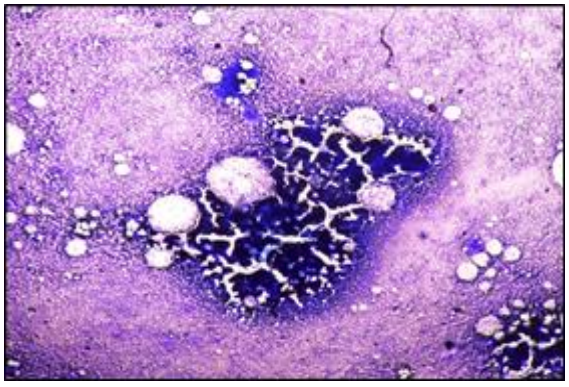

Figure 4: Bone marrow aspirate of Megaloblastic Anaemia showing hypercellular particle (10x)

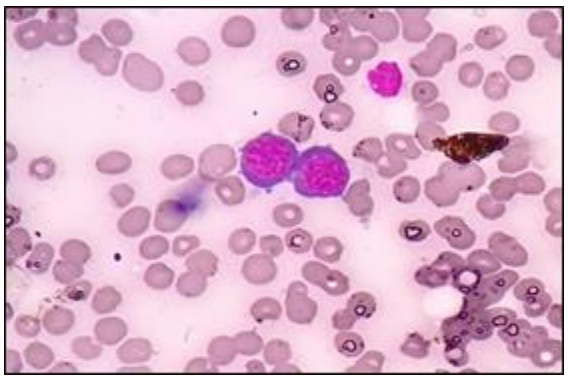

Figure 5: Bone marrow aspiration of Megaloblastic Anaemia showing Megaloblasts(40x)

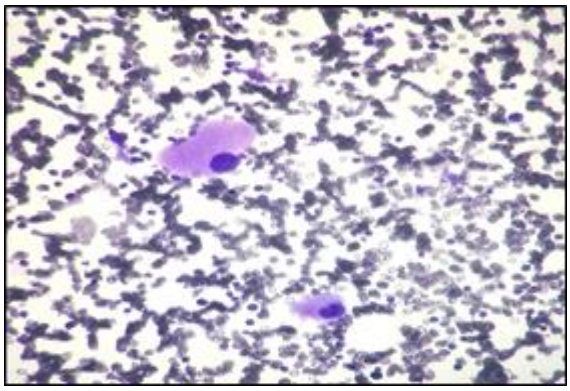

Figure 6: Bone marrow aspiration of MDS showing Hypolobated Megakaryocyte (40x)

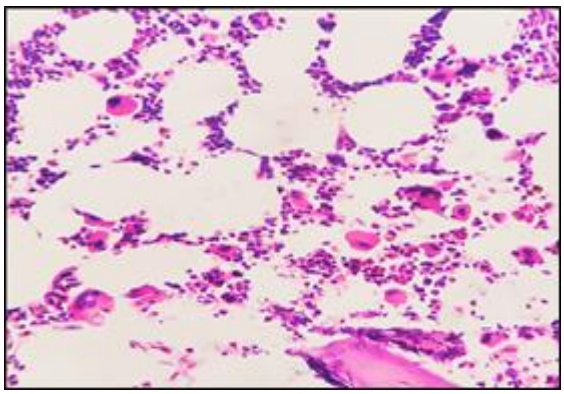

Figure 7: Bone marrow biopsy of MDS showing hypolobated forms of Megakaryocytes (40x)

Figure 8: Peripheral blood smear of Hypersplenism showing pancytopenia (4x)

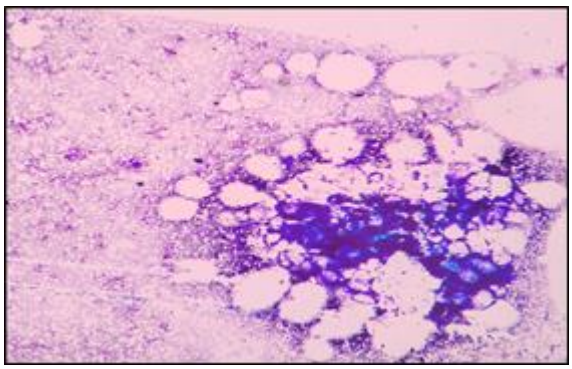

Figure 9: Bone marrow aspirate of Hypersplenism showing normocellular particle (10x)

RESULTS

We analysed total 150 cases of Pancytopenia between the study period of September 2020 to October 2022 with age range of 2-75 years. The mean age among pediatric cases of pancytopenia was 8.8 years and among adult age group was 39 years. Most of the cases were in the age group of 11-20 years (20.7%), followed by 21-30 years (18%) with mean age of total pancytopenia cases 35.4 years and M:F ratio 1.4:1. Total number of patients of pediatric age group were 21 and of adult age group were 129. Most common symptom in cases of pancytopenia was Generalised weakness. Splenomegaly was most commonly seen in Hypersplenism (7 cases), lymphadenopathy was most commonly seen in Reactive pathology (2 cases) and hepatomegaly was most commonly seen in Reactive pathology (5 cases). Total 34 cases had splenomegaly, 16 cases had hepatomegaly and 8 cases had lymphadenopathy.

According to demographical distribution, maximum number of patients were from Varanasi followed by Mau.

Comparison of different causes which were favoured on Bone marrow aspiration (BMA) were 76.7%, on bone marrow imprint (BMI) were 32.1%, Bone marrow clot (BMC) was 57.1% and Bone marrow biopsy (BMB) were 100%. Among all the causes, the most common cause of pancytopenia diagnosed on both BMA and BMB was Aplastic anaemia (25.3%). Total number of BMA was done in 93 cases and both BMA & BMB procedures was done in 57 cases. Most common cause diagnosed on BMA was Megaloblastic anaemia (25) followed by Aplastic anaemia/hypocellular marrow (21) and Hematological malignancies (17) including cases of Acute leukemia cases which were SBB-positive Acute leukemia, SBB-negative Acute leukemia, Acute myeloid leukemia (AML), Acute lymphoblastic leukemia (ALL), Acute promyelocytic leukemia (APML). All the cases (100%) of Megaloblastic Anaemia, Iron deficiency anaemia, Dimorphic anaemia, Anaemia of chronic disease, Reactive pathology and Plasma cell dyscrasia were diagnosed on BMA. Causes of pancytopenia diagnosed on BMB were 57 out of

150 cases. Most of the cases diagnosed was of Aplastic anaemia (27 cases) followed by hypersplenism (5 cases). (Table 1)

Most common cause of pancytopenia in present study was Aplastic anaemia which showed concordance of BMA with BMB in 27 cases out of 38 cases and disconcordance on BMA in 11 cases. Aplastic anemia patients may show hypocellularity and dry tap on bone marrow aspiration, due to which bone marrow biopsy is necessitated investigation for proper evaluation and diagnosis of cases of Aplastic Anaemia. 2nd most common cause of pancytopenia in our study was Megaloblastic anemia which showed concordance of BMA with BMB only in 2 cases out of 25 cases as only 2 cases required bone marrow biopsy to confirm the diagnosis and rest were diagnosed on bone marrow aspiration and no case of megaloblastic anemia showed disconcordance on BMA as it is usually diagnosed on BMA.

3rd most common cause of pancytopenia was hematological malignancies which showed concordance of BMA with BMB only in 4 cases out of 21 and 3 cases showed disconcordance on BMA, 81.8% cases of hematological malignancies were diagnosable on BMA but for rest cases, BMB was required for proper diagnosis. Most common benign and malignant causes which were diagnosed on BMA were Megaloblastic Anaemia and Hematological Malignancies respectively ,however, Most common benign and malignant causes which were diagnosed on both BMA & BMB was Aplastic anemia and Hematological Malignancies respectively. Maximum cases of dry tap on BMA were of Hematological malignancies (3) followed by Lympho-proliferative disease (2), Hypersplenism (1), Aplastic Anemia (1), Tuberculosis (1) and Reactive Pathology (1). (Table 2).

Table 1: Comparison of BMA, BMI, BMC and BMB favouring the diagnosis

Diagnosis	BMA	BMI	BMC	BMB
Aplastic Anaemia	21	4	15	27
Megaloblastic Anaemia	25	1	1	02
Hematological Malignancies	17	4	1	04
Reactive pathology	13	2	1	04
Dimorphic anaemia	11	1	0	01
Anaemia of chronic disease	09	1	0	02
Hypersplenism	03	2	4	05
Hemophagocytic lymphohistiocytosis	06	1	0	03
Iron deficiency anaemia	05	0	0	00
Myelodysplastic syndrome	03	0	1	01
Tuberculosis	0	1	0	03
Lympho-proliferative disorder	0	0	0	02
Plasma cell dyscrasia	02	0	0	0
Myelo-proliferative disorder	0	0	1	01
Paroxysmal nocturnal hemoglobinuria	0	0	0	01
Secondary sclerosis/Paget's disease	0	0	0	01
Total number of cases favoring diagnosis	115(76.7%)	17(32.1%)	24(57.1%)	57(100%)
Total cases considered	150	53	42	57

Table 2: Comparison of cases of pancytopenia diagnosed on BMA and BMB

Diagnosis	Total diagnosed cases(n)	Cases diagnosed on BMA n(%)	Disconcordance on BMA n(%)	Concordance of BMA with BMB (n=57)
Aplastic Anaemia	38	21 (55.3%)	11 (29%)	27
Megaloblastic Anaemia	25	25 (100%)	0	02
Hematological Malignancies	21	18 (81.8%)	03 (14.3%)	04
Reactive pathology	13	11 (84.6%)	02 (15.4%)	04
Dimorphic anaemia	11	11 (100%)	0	01
Anaemia of chronic disease	09	09 (100%)	0	02
Hypersplenism	08	03 (37.5%)	05 (62.5%)	05
Hemophagocytic lymphohistiocytosis	06	06 (100%)	0	03
Iron deficiency anaemia	05	05 (100%)	0	0
Myelodysplastic syndrome	04	03 (75.0%)	01 (25%)	01
Tuberculosis	03	0	03 (100%)	03
Lympho-proliferative disorder	02	0	02 (100%)	02
Plasma cell dyscrasia	02	02 (100%)	0	0
Myelo-proliferative disorder	01	0	01 (100%)	01
Paroxysmal nocturnal hemoglobinuria	01	0	01(100%)	01
Secondary sclerosis	01	0	01	01
Total Cases	150	115 (76.7%)	30	57

DISCUSSION

Patients presenting with Pancytopenia are very common in clinical practice and they have a wide spectrum of clinical features. For the evaluation of these cases, we should to go through the detailed clinical history and clinical examination of patients.

In laboratory workup we should look for the CBC, general blood picture, bone marrow examination (BMA and BMB), immunohistochemical and molecular studies.

Due to vast variety of causes of pancytopenia, most of the which are usually undiagnosed on general blood picture, bone marrow examination (BMA, BMI, BMC & BMB) plays a very crucial role. Bone marrow examination is also helpful in determining prognosis of the disease causing pancytopenia apart from diagnosis.

Table 3: Comparison of various studies of causes of pancytopenia

Authors	Year	No. of cases	Age distribution (Years)	Mean Age	Commonest cause
Khunger et al[3]	2002	200	2-70	Not provided	Megaloblastic anemia
Mohanty P et al [4]	2020	122	6-80	34.9	Aplastic anemia
Kumar R et al[5]	2001	166	Not provided	Not provided	Aplastic anemia
Jha et al [6]	2008	148	1-79	30	Hypoplastic marrow
Jain Naniwadekar [7]	2013	250	2m-95	Not provided	Hypersplenism
Chandan R.H et al[8]	2018	134	15-75	30.9	Megaloblastic anemia
Jyoti SK et al[9]	2019	166	14-80	Not provided	Hypersplenism
Deshpandey SV et al [10]	2019	101	18-80	48.5	Megaloblastic anemia
Kumari MK et al [11]	2021	56	Not provided	41.8	Megaloblastic anemia
Present study	**2022**	**150**	**2-75**	**35.4**	**Aplastic Anaemia**

In present study, most common diagnosis was Aplastic anemia. Also, the studies done by Mohanty P et al,[4] and Kumar R et al,[5] showed same result having Aplastic Anaemia as the most common cause of pancytopenia. Age distribution was ranging from 2 years to 75 years in present study, whereas in the studies done by Mohanty P et al,[4] and Jha et al,[6] age range were 6-80 years and 1-79 years respectively. In present study, the mean age was of 35.4 years in total pancytopenia cases whereas the mean age were 34.9 and 30 years in the studies done by Mohanty P et al,[4] and Jha et al,[6] respectively.

Bone marrow biopsy has an essential role in workup of aplastic anaemia. Also there was a significant number of cases of dry tap (9 cases, 6%) on BMA, diagnosis was only possible by BMB including 3 cases of hematological malignancies followed by lympho-proliferative disease (2), hypersplenism (1), aplastic anemia(1), tuberculosis(1) and reactive pathology (1). Cases of myelo-proliferative disorder and secondary sclerosis were diagnosed on BMB only, thus indicating the utility of supplementing bone marrow aspiration with biopsies in all the patients of pancytopenias. Most of these findings are consistent with other Indian studies.

In Study done by Metikurke et al,[12] males were more affected than female(M:F=3:2).

Focal lesion such as Tuberculosis and lympho-proliferative disorders showed 100% disconcordance on BMA along with Myeloproliferative disorder and Paraoxysmal nocturnal hemoglobinuria (PNH). Also Aplastic anaemia showed high disconcordance on BMA. These findings indicate that BMB is must do investigations along with BMA in patients having pancytopenia, specially in cases of Aplastic anaemia, tuberculosis and Lympho-proliferative diseases.

Concordance in cellularity between aspiration and biopsy showed 49.1% concordance in present study while Parajuli Set al,[13] study was showing 84% concordance

CONCLUSION

The present study concludes that detailed physical examination, primary hematological investigations along with bone marrow examination helps in diagnosis and ruling out the various causes of pancytopenia, also bone marrow aspiration cytology and trephine biopsy complements each other and should be performed simultaneously for complete bone marrow workup and evaluation. It is seen that bone marrow aspirate is superior for studying the morphology and is equally effective as biopsy in diagnosing anemias and leukemias, however, it is the histopathological study of trephine biopsy of bone marrow that gives well preserved marrow architecture with cellular and stromal components. A ‘dry’ or ‘blood tap’ is common in disorders causing pancytopenia. So, trephine biopsy becomes mandatory in the diagnosis of aplastic anemia, myelofibrosis and focal diseases like tuberculosis & chronic lympho-proliferative disorders. We also conclude that there is high prevalence of nutritional deficiency like megaloblastic anaemia among young population. Hence, this age range should be the primary target for education regarding proper dietary habits.

So, to conclude, along with detail clinical history, clinical examination, general blood picture studies, we need to do BMB procedures also, along with BMA for proper diagnosis and prognosis of a patient having Pancytopenia.

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