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EVALUATION OF CAUSES OF PANCYTOPENIA WITH ITS CLINICAL CORRELATION IN TERTIARY CARE HOSPITAL

Pathology

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ABSTRACT

Pancytopenia is an important clinico-hematological entity encountered in our day-to-day clinical practice1. The causes of pancytopenia vary in different populations depending on age, gender, nutrition, geographic location, standard of living, and exposure to certain infections and drugs. The severity of pancytopenia and its underlying pathology will determine the management and prognosis. Therefore, diagnosis of the correct cause will help in implementing appropriate therapy2,3,4. **Aims & Objectives:** 1. To study and identify the underlying etiopathology of pancytopenia. 2. To study the clinical presentations in pancytopenia due to various causes. 3. To evaluate hematologoical parameters in pancytopenia. **Methods** :The study included 70 patients over a period of two years with patient age ranging from 11-80 yrs. Routine hematological investigations and Bone marrow examinations(aspiration and biopsy)were done. **Results:** Nutritional anaemia was predominant clinical diagnosis among patients accounting for 13 cases (19.1%) followed by acute febrile illness and retroviral disease (18%). After thorough investigations including bone marrow, Megaloblastic anaemia (41.3%) was the commonest cause of pancytopenia followed by Iron Deficiency anaemia(26%), Dimorphic anaemia(10%) and Hypersplenism (7.3%). **Conclusion** : Megaloblastic anaemia and iron deficiency anaemia being the commonest and second common cause of pancytopenia, generally show improvement by iron and vitamin B 12 therapy.

KEYWORDS

INTRODUCTION :

Pancytopenia is a triad of findings characterized by presence of anaemia, leukopenia and thrombocytopenia resulting in reduction of all the three major formed elements of blood i.e., erythrocytes, leucocytes and platelets respectively below their reference values. Pancytopenia usually is insidious in onset and is attributable to anaemia and thrombocytopenia. However, rarely leukopenia can poses serious threat. The essential investigations for diagnosing pancytopenia are routine hematological parameters and bone marrow examination. Bone marrow biopsy plays a significant role in understanding the etiology and selected cases require radiological, microbiological, and biochemical investigations. Pancytopenia is not a disease entity, but a triad of findings, resulting from a number of disease processes - primarily or secondarily involving the bone marrow. There are varying trends in its clinical pattern, treatment modalities and outcomes. Therefore, diagnosis of the correct cause will help in implementing appropriate therapy[2,3,4].

MATERIALS AND METHODS :

The study was prospective cross-sectional study from June 2017 to June 2019 in the Department of Pathology in a tertiary care hospital. The study included 70 patients of pancytopenia ranging from 11-80 years. M:F-1.7:1. Inclusion criteria was Hb <10g/dl, TLC < 4000/cumm and Platelet count < 1.5lakh /cumm. Patients whose peripheral smear showed malarial parasite were excluded.

OBSERVATION AND RESULTS :

In our present study, a detailed routine hematological investigations were done including CBC, MCV, MCH, MCHC, Peripheral smear and Retic count in all 70 cases while Bone marrow examination were done only in 59 cases. Study shows maximum number of cases (17 cases) in third decade(24.3%)followed by fourth decade (18.6%) as shown in Table1.

Table 1 :Age wise distribution of cases of pancytopenia (n-70)

Sr. No	Age Range (In Year)	No. Of Cases (n)	Percentage
1	11-20	9	12.8 %
2	21-30	16	22.8 %
3	31-40	17	24.3 %
4	41-50	13	18.6 %
5	51-60	8	11.5 %
6	61-70	6	8.57 %
7	71-80	1	1.43 %
	Total	70	100 %

A detailed clinical history was noted in all cases. Majority of patients complaints was generalised weakness in 46 cases (65.71%) followed by fever in 32 cases (45.17%) as in Table 2. Pallor was a universal finding in our study followed by splenomegaly, hepatomegaly, icterus, ascites, edema, lymphadenopathy, bone pain and few patient show purpura (Table 3). Bone marrow study showed 28 patients(47.45%) had hypercellular marrow,16patients (27.13%) had normocellular marrow followed by 14 patients(24.2%) hypocellular marrow and only one patient (2%) had diluted marrow(Table 4).

Table 2: Clinical presentation in of cases of pancytopenia (n-70)

Sr. No	Presenting Complaints	No. of Cases(n)	Percentage(%)
1	Generalized Weakness	46	65.71%
2	Fever	32	45.17%
3	Breathlessness	28	40%
4	Pain in abdomen	18	25.71%
5	Bleeding	16	22.8%
6	Weight Loss	13	18.57%
7	Loose stool	11	15.71%
8	Generalized body ache	1	1.42%

Table 3: Clinical findings in cases of pancytopenia.(n-70)

Sr. No	Clinical Findings	No. of cases	Percentage(%)
1	Pallor	70	100%
2	Splenomegaly	33	47.14%
3	Hepatomegaly	27	38.57%
4	Icterus	15	21.42%
5	Ascites	5	7.14%

6	Edema	4	5.71%
7	Lymphadenopathy	3	4.3%
8	Bone Pain	3	4.3%
9	Purpura	1	1.42%

Table 4: Bone marrow cellularity in case of pancytopenia.

Sr. No	Bone marrow cellularity	No. of cases	Percentage(%)
1	Normocellular	16	27.13%
2	Hypocellular	14	24.2%
3	Hypercellular	28	47.45%
4	Diluted	1	2%
	Total	59	100%

Table 5: Clinical Diagnosis, Peripheral smear diagnosis and Bone marrow diagnosis in cases of pancytopenia.

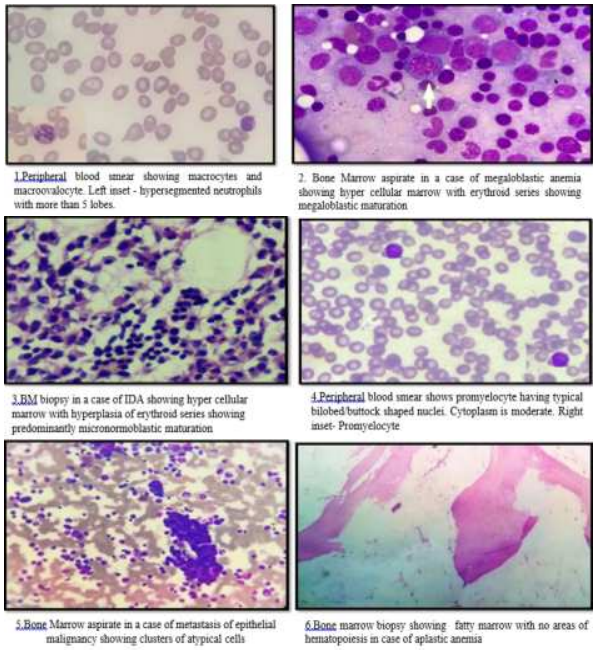
Sr. No.	Clinical Diagnosis	Peripheral smear diagnosis	Bone marrow aspirate and biopsy diagnosis
1.	Nutritional Anaemia(14)	Pancytopenia (11)	Aplastic anaemia(1), MA(8), IDA(2)
		Megaloblastic Anaemia (2)	Bone marrow investigations not done(2)
		Subleukaemic leukaemia (1)	Acute promyelocytic leukemia(APML)(1)
2.	Retroviral disease (13)	Pancytopenia(11)	IDA(5), MA(4), Malignancy(1), plasmacytosis(1)
		Megaloblastic anaemia(1)	Megaloblastic anaemia (1)
		Dimorphic anaemia (1)	Bone marrow investigations not done
3.	Acute febrile illness (11)	Pancytopenia(4)	IDA(1), MA(3)
		Megaloblastic anaemia(3)	Bonemarrow investigations not done
		Dimorphic anaemia (4)	Bonemarrow investigations not done
4.	Retroviral disease associated with Tuberculosis (8)	Pancytopenia(8)	IDA(3)
			Megaloblastic anaemia (2)
			Tuberculosis (3)
5.	Alcoholic liver disease (7)	Pancytopenia(5)	IDA(2), MA(1)
		Dimorphic anaemia (2)	Hypersplenism (1)
			Bonemarrow investigations not done
6.	Hypersplenism(6)	Pancytopenia(6)	Hypersplenism (4)
			IDA(1),
			MA(1)
7.	Acute gastroenteritis (4)	Pancytopenia(3)	IDA(1), MA(1), MDS(1)
		Dimorphic anaemia (1)	Bonemarrow investigations not done
8.	Tuberculosis (2)	Pancytopenia(2)	IDA(1), MA(1)
9.	Cardiovascular disease (2)	Pancytopenia(1)	MA(1)
		Megaloblastic anaemia(1)	Bonemarrow investigations not done
10.	SLE(1)	Dimorphic anaemia (1)	Bonemarrow investigations not done
11.	Fracture (1)	Pancytopenia(1)	Aplastic Anaemia(1)
12.	Pyelonephritis (1)	Pancytopenia(1)	IDA (1)

In our present study, most common clinical diagnosis was nutritional anaemia (14 cases), retroviral disease (13 cases), acute febrile illness (11cases), retroviral disease with tuberculosis (8 cases), acute gastroenteritis(4 cases), alcoholic liver disease(3 cases) and 2 cases each of Tuberculosis and cardiovascular disease which on peripheral smear diagnosed as pancytopenia in 53 cases, followed by dimorphic anaemia in 9 cases, megaloblastic anaemia in 7 cases and subleukaemic leukaemia in only one case. Out of all 70 cases, Bone marrow examination were done only in 59 cases. On bone marrow examination, of these 53 cases of pancytopenia, majority cases were diagnosed as megaloblastic anaemia in 22 cases, followed by Iron deficiency anaemia in 17cases, hypersplenism in 5 cases, Tuberculosis in 3 cases, Myelodysplastic syndrome and Aplastic anaemia in 2 cases each, malignancy and Plasmacytosis one case each. Out of 9 cases of Dimorphic anaemia on peripheral smear, bone marrow investigation was done only in one case which show Iron deficiency anaemia. While in 7 cases of megaloblastic anaemia diagnosed on peripheral smear, bone marrow investigations done only in one case which confirmed the diagnosis of megaloblastic anaemia and in rest 6 cases, medical treatment were given after hematological and biochemical investigations and patient showed improvement. And only one case of subleukaemic leukaemia on peripheral smear, bone marrow show Acute promyelocytic leukaemia. shown in (table 4) below.

Table 6: Final diagnosis of pancytopenia cases :

Sr. No	Final diagnosis	Number of cases	Percentage(%)
1	Megaloblastic anaemia	29	41.3%
2	Iron deficiency anaemia	18	26%
3	Hypersplenism	5	7.3%
4	Tuberculosis	3	4.2%
5	Aplastic anaemia	2	2.8%
6	Myelodysplastic Syndrome	2	2.8%
7	Myelofibrosis	1	1.4%
8	Malignancy	1	1.4%
9	Plasmacytosis	1	1.4%
10	Acute promyelocytic leukemia	1	1.4%
11	Dimorphic anaemia	7	10%
	Total	70	100%

After thorough evaluation, in present study, Megaloblastic anaemia 29 cases(41.3%) and Iron deficiency anaemia 18 cases (26%) were the major causes of pancytopenia followed by hypersplenism as shown in above Table 6.



1.Peripheral blood smear showing macrocytes and macroovalocyte. Left inset - hypersegmented neutrophils with more than 5 lobes.

2. Bone Marrow aspirate in a case of megaloblastic anemia showing hyper cellular marrow with erythroid series showing megaloblastic maturation

3.BM biopsy in a case of IDA showing hyper cellular marrow with hyperplasia of erythroid series showing predominantly micronormoblastic maturation

4.Peripheral blood smear shows promyelocyte having typical biloded/buttock shaped nuclei. Cytoplasm is moderate. Right inset- Promyelocyte

5.Bone Marrow aspirate in a case of metastasis of epithelial malignancy showing clusters of atypical cells

6.Bone marrow biopsy showing fatty marrow with no areas of hematopoiesis in case of aplastic anemia

DISCUSSION :

In our present study, 70 patients of pancytopenia were evaluated to analyse the age pattern, gender distribution, their clinical findings, incidence of various causes of pancytopenia along with hematological and bone marrow examination. In our present study, 70 cases of pancytopenia age ranged from 11-80 years as shown in Table 1. Majority of them were in age group of 31-40 years which was similar with study done by **Mir et al**[5] (31-40 years). There was male preponderance and the male to female ratio was 1.7:1in our study which was similar to study by **V Unnikrishnan et al**[7] (M:F ratio-1.8:1), **Manzoor et al**[6] (M:F ratio-1.6:1) and **Gayathri et al**[4](M:F 1.2:1). But, in study by **Vandana Raphael et al** (M:F ratio- 1:1.2) and **Kulkarni Naveen S et al** [8](M:F ratio - 0.9:1) there was female preponderance.

Pallor (100%) was the most common presentation followed by generalized weakness (65.71%) seen in 45 cases as shown in Table 3. Studies done by **Thakkar BB et al**[11] , **Mir et al**[5], **V. Unnikrishnan et al**[7], **Vandana Raphael et al** and **Kulkarni Naveen S et al**[8] also revealed pallor(100%) as the commonest clinical presentation. However, study done by **Khodke et al** showed fever (40%) as the most common clinical presentation followed by weakness (30%) and bleeding manifestation (20%). In another study by **Niazi and Raziqet al**[9] revealed weakness (68.2%) as the most common clinical presentation followed by fever (47.7%) and bleeding manifestations (33.7%).

Splenomegaly in our study was seen in 33 patients (47.17%) followed by hepatomegaly in 27 of cases (38.57%) and least common was lymphadenopathy in 3 cases (4.3%) as shown in Table 3.**Vandana Raphael et al** and **Thakkar BB et al**[11] show similar findings where splenomegaly was common followed by hepatomegaly.

In the present study Megaloblastic anaemia (41.3%) was the commonest cause of pancytopenia, followed by Iron deficiency anaemia(26%), Dimorphic anaemia (10%), Hypersplenism(7.3%), Tuberculosis (4.2%), Aplastic anaemia (2.8%), Myelodysplastic syndrome(2.8%), Myelofibrosis(1.4%), Malignancy(1.4%), Plasmacytosis(1.4%) and Acute promyelocytic leukaemia(1.4%) as shown in Table 6. Megaloblastic anaemia as the commonest cause of pancytopenia in our study corresponds with the study of **Tilak et al**[13]**, Kishor Khodke et al**[2], **Mir et al**[5], **Mansoor F**, **Anita P et al**[10] , **Khunger et al and Gayathri et al**[4]. However, Aplastic anaemia was the commonest cause in **Santra et al** [12] and Dimorphic anaemia in **Kulkarni Naveen S et al**[8].

In cases of Megaloblastic anaemia, in our study, Haemoglobin is in range of 6.1-9 gm/dl, TLC count range from 3000-4000 cells/cumm and platelet count range from 31000-60000 cells/cumm. Peripheral smear findings showed findings of pancytopenia (Macro ovalocyte, cabot ring, basophilic stippling and hypersegmented neutrophils). Bone marrow study(aspirate and biopsy) show hypercellularity with altered M:E ratio, megaloblastic erythroid hyperplasia.

Megaloblasts had the characteristic feature of sieved nuclear chromatin, asynchronous nuclear maturation and bluish cytoplasm. Giant metamyelocytes and band forms were predominant in granulocyte series and unremarkable megakaryocyte series. Our study matched with study done by **Gayathri et al** (2011)[4]in which megaloblastic anaemia patients found that Hb in range of 1.8-9.2 gm/dl, TLC in range of 500- 3900cells/cumm and platelet in range of 12,000-95,000cells/cumm. Highest MCV -123fl and lowest vitamin B12 level- 67 ng/dl was recorded in megaloblastic anaemia . Lowest MCV -67.7 fl was recorded in iron deficiency anaemia.

Iron Deficiency Anaemia (26%) in present study was seen as second common cause similar to **Anita et al**[10] as against study done by **Kumar and Raghupathi et al and Kulkarni Naveen S et al**[8] where Megaloblastic Anaemia was the second common cause as shown in Table 7. This shows that there is higher prevalence nutritional anaemia in Indian population and subcontinent which is mainly attributed due to low socioeconomic condition, poverty, dietary habits and environmental factors[2,13] .Table 7 is given below.

Sr. No.	Study Name	Commonest cause	Second common cause	Third common cause
1.	Gayathri BN et al(2011)	Megaloblastic Anaemia (74.04%)	Aplastic Anaemia (18.26%)	Subleukemic leukaemia (3.86%)
2.	Anita et al (2013)	Megaloblastic Anaemia (73.6%)	Iron Deficiency Anaemia (12.2%)	Malaria (3.7%)
3.	Mansoor F et al (2014)	Megaloblastic Anaemia (56%)	Aplastic Anaemia (14%)	Hypersplenism (8%)
4.	Mir et al (2015)	Megaloblastic Anaemia (72.37%)	Acute leukaemia (6.81%)	Multiple myeloma (5.3%)
5.	Kulkarni Naveen S et al (2017)	Dimorphic Anaemia (36.23%)	Megaloblastic Anaemia (34.78%)	Vivax Malaria (4.34%)
6.	Present study (2018)	Megaloblastic Anaemia (41.1%)	Iron Deficiency Anaemia (26%)	Hypersplenism (7.3%)

CONCLUSION:

Pancytopenia is caused by various conditions like Aplastic anaemia, Myelofibrosis, Hypersplenism, Myelodysplastic syndrome etc. amongst which Nutritional anaemia is the most common cause. People in India and other developing nations continue to suffer from iron and vitamin deficiencies, which cause anemia and pancytopenia. Hence, there is higher prevalence of nutritional anemia in subcontinent and Indian population and this is also reflected in our study where Megaloblastic anemia is the commonest and IDA as the second common cause of Pancytopenia.The variation of incidence of megaloblastic anaemia depends on the nutrition, socioeconomic condition of that particular region of the study.

In developing countries like India, there should be high suspicion for megaloblastic anaemia and careful evaluation of peripheral blood smear should be done. Presence of oval macrocytes, hyper-segmented neutrophils, Cabot ring, Howell-Jolly bodies and basophilic stippling favour the diagnosis of megaloblastic anaemia in peripheral smear. The diagnosis of Megaloblastic anaemia should be supplemented by biochemical investigations like Iron studies, vitamin B12 and folic acid level. These cases generally show improvement with vitamin B12 and folic acid therapy . Hence it is necessary to treat such cases initially with iron and/or vitamin B12 and then to repeat hemogram after few weeks. Invasive procedures like bone marrow examination can be avoided and becomes necessary only if there is no clinical improvement or signs suggesting severe diseases like leukemia, Myelodysplastic syndrome (MDS) etc. Bone marrow biopsy becomes essential when bone marrow aspiration is unsuccessful and yield dry tap, as in aplastic anaemia and myelofibrosis.

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