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Original Research Article

Clinicohematological Study of Pancytopenia

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Abstract:

Pancytopenia is a very common laboratory abnormality observed in day to day clinical practice. It is a reduction in all three major formed elements of blood i.e. erythrocytes, leucocytes and platelets. In 1918, it was separated from Aplastic anemia. It has a very diverse etiology & is the only condition having highest geographic & genetic influences. Unawareness about this fact may create more heat than light when managing such cases.

Aims and objectives of the study: To find out the spectrum of conditions presenting as Pancytopenia. To correlate the clinical findings with hematological findings.

Materials and Methods: The current study was a prospective study, carried out in Dr VMGMC and CSMSR solapur from September 2005 to August 2007

Selection criteria: A case having Hb% <9 gm/dl b) TLC < 4000/cumm c) Platelet count < 1,50000/cumm

Total Number Of Cases: 60. In each case HB%, Blood Indices, TLC, DLC, Platelet count, P.B.S. examination were done. Bone marrow examination was done in all cases except 2 cases which was not possible due to low platelet count. Bone marrow biopsy was done where needed. Instrument used: Mythic 18 blood cell counter.

Results: Of the total 60 cases studied, the age distribution was 1 - 80 years with age 21-30 years most commonly affected, with male preponderance. Most common presenting symptom was weakness and easy fatiguability. Most common observation clinically was pallor.

Peripheral blood smear showed megaloblastic anaemia preponderance and bone marrow was hyper cellular showing megaloblastic picture in majority cases. The commonest cause for pancytopenia in our study was Megaloblastic anaemia (43.33%) followed by hypo plastic/aplastic anaemia(13.33%) and infections (10.83%).

Conclusion: Etiological Causes of Pancytopenia have geographic variation, due to differences in etiological factors from region to region Clinical findings, haematological workup along with bone barrow aspiration are crucial in the diagnosis of pancytopenia considering the varied aetiologies and presentations clinically.

Megaloblastic Anemia (43.33%) is the most common cause of pancytopenia in our geographic area followed by aplastic/ hypoplastic anemia& infection. Leukemia, Malaria can present as pancytopenia as against the general belief.

Keywords: Pancytopenia, Megaloblastic Anemia Care.

Introduction

Pancytopenia is defined as reduction in all three major formed blood elements: erythrocytes, leucocytes and platelets. It is the simultaneous presence of anaemia, leucopenia and thrombocytopenia that may result from a number of disease processes. [1,3].

Pancytopenia develops either due to decrease in the hematopoiesis in bone marrow as a result of destruction of marrow tissue by toxins (aplastic anemia / hypoplastic marrow), replacement by abnormal or malignant tissue or suppression of normal marrow growth or differentiation. In other cases, the marrow may be either normal or even hypocellular and no abnormal may be present. [2-8]

Pancytopenia in itself is not a disease but a striking feature of many underlying causes also including many life-threatening diseases [1,19]. The variation in the frequency of various diseases causing pancytopenia is attributed to differences in methodology, geographic distribution, diagnostic criteria, nutritional status, genetic differences in cases of malignancy as etiology, and environmental causes like exposure to toxic substances. [11-17]

Etiological data about Pancytopenia if available in India would help in planning of diagnostic and therapeutic approach of the patients. Keeping this in mind the present study was carried out with the twin aim of diagnosing patients of Pancytopenia and finding out the common disease entities responsible for it [6,9] along with comparison of the distribution of etiologies in current study region with available studies in other parts of India and the world. [20]

Aims and Objectives:

1. To study the frequency of pancytopenia in outpatient department and Patients admitted in Shri Chattrapati Shivaji Maharaj Sarvopachar Rugnalay, Solapur.
2. To study the probable etiology of pancytopenia.
3. To correlate the clinical findings, Hemograms, bone marrow aspirate or marrow biopsy (whenever needed)

Materials and Methods:

The present prospective study was carried out in Department of Pathology Dr VMGMC and Shri CSMSR, Solapur, for a period of 2 years from September 2005 to August 2007. Total of 60 cases were evaluated as follows.

All patients attending out patient department and admitted patients were screened for Pancytopenias per the defined criteria i.e.

Hemoglobin less than 9 gm/dl

Total leucocyte count less than 4000/cumm and

Platelet count less than 1,50,000 / cumm[1]

2 millilitres of EDTA blood was collected and processed through the Mythic semi-automated cell counter and all hematological parameters (Hb%, total leucocyte count, differential leucocyte count, platelet count, indices -mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) were assessed. Peripheral smear was stained using Leishman stain. Bone marrow aspiration was done in all cases and assessed for morphology, maturation of cells, megakaryocytes, presence of abnormal cells, parasites. Prussian blue stain was done on all marrow aspirates to assess marrow iron stores.

Bone marrow trephine biopsy was done using Jamshidi – Swaim needle no 11 G in adults and no 13G in children from posterior iliac spine in case of dry marrow aspirates.

Results:

A total of 60 cases of pancytopenia were studied, of which 29 were males and 31 were females indicating mild female preponderance. The male to female ratio was 1.13:1.

The age group ranged from 1 to 80 years with mean age group of presentation being 21-30 years (32%), followed by second decade (24%) then the fourth decade (18%). Thus the <40 years age group comprised of the chunk of the patients (83%). Etiology wise Megaloblastic anemia comprised majority of patients below 40 years of age while Aplastic/hypoplastic group was distributed in the age <20 years. As shown in Table 1.

Table 1: Age and sex distribution of Pancytopenia:

	Age (years)	Male	Female	Total cases	Percentage
1	<1	--	--	--	0
2	1-10	3	3	6	10
3	11-20	7	7	14	24
4	21-30	8	11	19	32
5	31-40	4	7	11	18
6	41-50	4	1	5	8
7	51-60	1	1	2	3
8	61-70	1	1	2	3
9	71-80	1	--	1	2
	total	29	31	60	100

Table 2: Presenting complaints and findings:

Clinical features	Megalo Blastic anemia	Aplasia/ Hypopl	Sub Leukemic Leukemia	MDS	Hyper splenism	Gaucher	Myelo fibrosis	ITP	SLE	Misc
Pallor	30	11	1	1	1	1	1	-	1	52
Weak/ Fatigue	15	3	1	-	-	-	-	-	-	25
Breath Lessness	16	6	1	1	-	-	1	-	-	34
Fever	7	6	2	-	-	-	-	-	-	21
Pedal	9	2	-	1	-	-	-	-	-	14

Edema										
Icterus	4	1	-	-	-	-	-	-	-	6
Bleeding	2	4	-	-	-	-	-	1	1	9
Spleno Megaly	6	1	-	-	2	1	1	-	-	13
Hepato Megaly	5	1	-	-	-	-	-	-	-	7

Most common presenting symptoms (Table 2) were weakness, fatiguability, and breathlessness. Bleeding manifestations like epistaxis, gum bleeding, per vaginal and per rectal bleeding, and petechial rash were common in the Aplastic / Hypoplastic group and Idiopathic thrombocytopenic purpura (ITP). Pallor was the most common finding followed by fever, pedal edema, hepatomegaly and splenomegaly (common in the Megaloblastic anemia group).

Considering the etiology wise distribution (Table 3) of cases, 50% cases belonged to the Megaloblastic anemia followed by Aplastic/Hypoplastic anemia and aleukemic leukemia. Miscellaneous causes comprised of 7% cases including SLE, typhoid fever and malaria presenting as pancytopenia. We encountered 1 case of Myelodysplastic syndrome, 2 cases of hypersplenism, 1 case each of storage disorder (Gaucher`s disease), Myelofibrosis, ITP.

Table 3: Etiology of pancytopenia in current study:

Causes	No of cases	%
Megaloblastic Anemia	30	50
Normoblastic Erythropoiesis	7	12
Aplastic/Hypoplastic anemia	6	10
Transient marrow suppression	5	8
Sub leukemic leukemia	2	3
Myelodysplastic syndrome	1	2
Hypersplenism	2	3
Gaucher`s disease	1	2
Myelofibrosis	1	2
ITP	1	2
Miscellaneous (SLE, Typhoid, Malaria, Hypersplenism)	4	7
Total	60	100

Out of the 30 cases of megaloblastic anemia, 53% (16 cases) showed pure megaloblastic picture of varying severity while 14 cases showed combination of megaloblastic anemia and Iron deficiency anemia (Table 4).

Table 4: Distribution of megaloblastic anemia

Causes	Cases	%
Megaloblastic Anemia	16	53
Combined Megaloblastic+Iron Deficiency anemia	14	47
Total	30	100

Of the 5 cases (Table 5) of Transient Aplastic/Hypoplastic anemia group, 3 belonged to pediatric age group (two were diagnosed with Viral fever and one was a case of mixed Typhoid-Malaria infection). Pancytopenia resolved after the control of infection. Rest of 2 cases belonged to adult age group had sepsis induced transient marrow hypoplasia.

Table 5: Distribution of Aplastic/Hypoplastic anemia

Causes	Cases	%
Hypoplastic anemia	3	27
Transient Marrow Hypoplasia	5	46
Aplastic Anemia	3	27
Total	11	100

Majority of the cases (43%) had severe anemia. Peripheral blood smear picture varied from Anisopoikilocytosis being the commonest morphological type, dimorphic picture in RBC. Hypersegmentation of neutrophils was the most common finding in WBC. Smear from myelofibrosis showed Tear drop cell. Immature myeloid cells were seen in acute leukemias, MDS, Myelofibrosis and 2 cases of septicemia.

Considering the 3 predominant causes of pancytopenia in our study, hematological parameters are as follows. (table 6)

Table 6:

Parameters	Megaloblastic anemia	Aplastic anemia	Sub-leukemic leukemia
Hb%	1.8 -7. 9	2.6 – 4.2	4.8 – 8
TLC	1000 – 3800	1000-3000	1800-2800
Platelet	16,000 – 1 lac	14,000 – 80,000	20,000 – 40,000

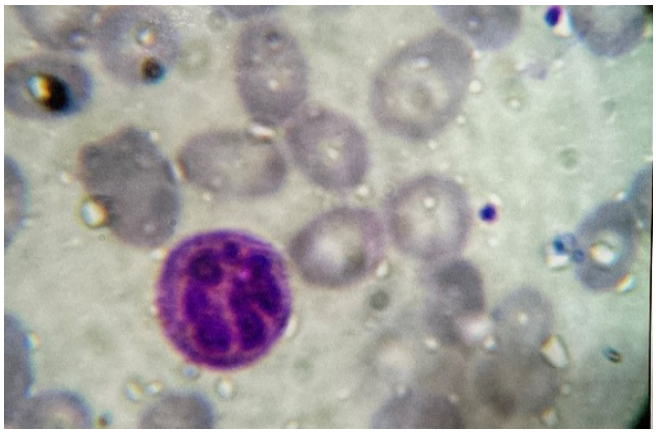

Figure 1: Peripheral blood smear showing features of Macrocytic anemia: Hypersegmented neutrophil (Leishman stain x1000)

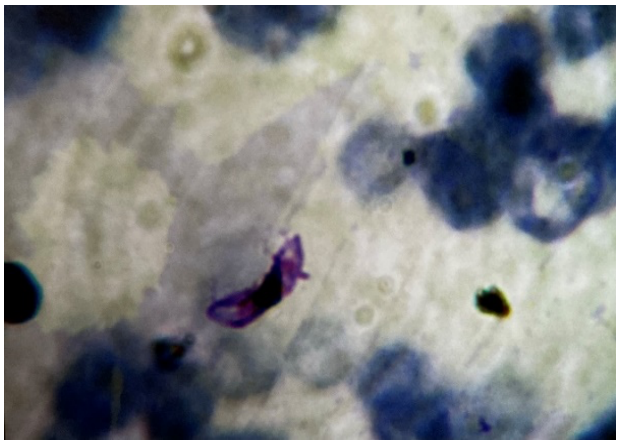

Figure 2: Smear showing Gametocyte of Plasmodium Falciparum in a case presenting as Pancytopenia

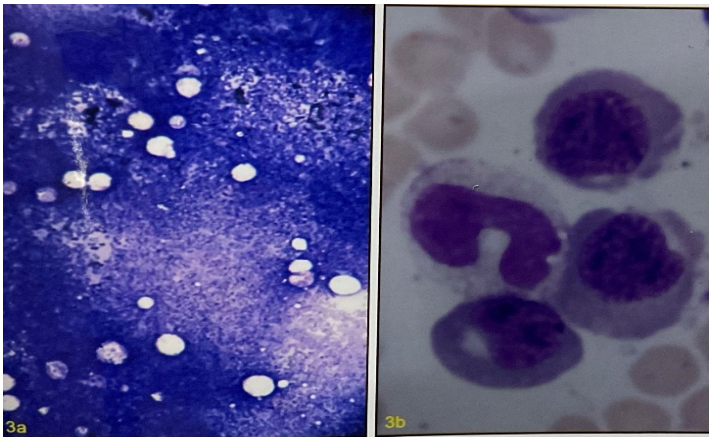

Figure 3: Bone marrow aspirate from Megaloblastic anemia :
3a: Hypercellular bone marrow aspirate
3b: Marrow in megaloblastic anemia showing giant Metamyelocyte, immature RBC.

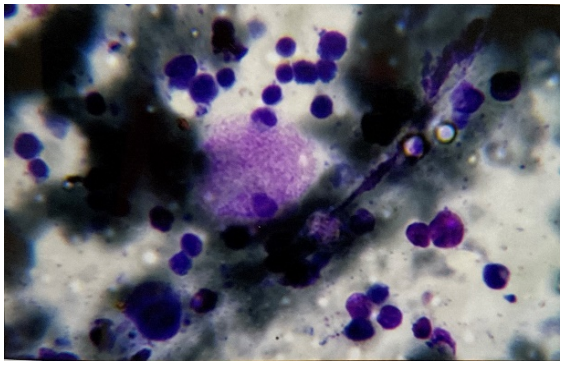

Figure 4: Bone marrow aspirate showing Gaucher cell

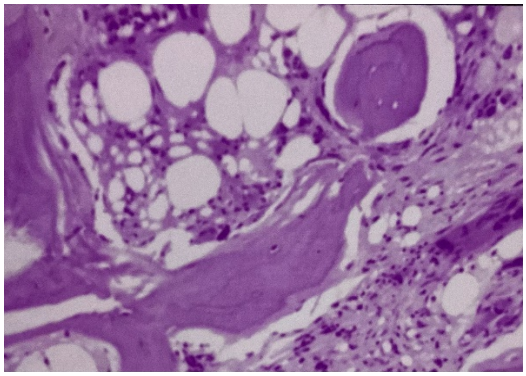

Figure 5: Bone marrow biopsy in Myelofibrosis, H&E stain showing replacement of marrow tissue with Adipose tissue

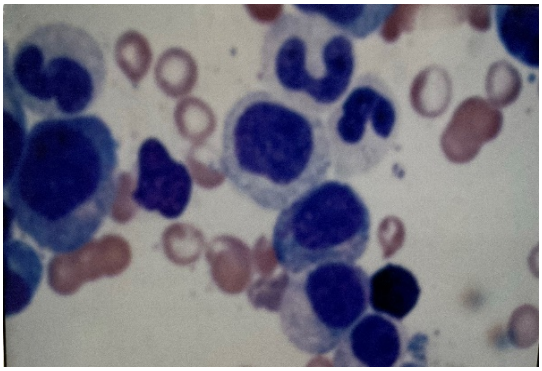

Figure 6: Bone marrow picture in Myelodysplastic syndrome

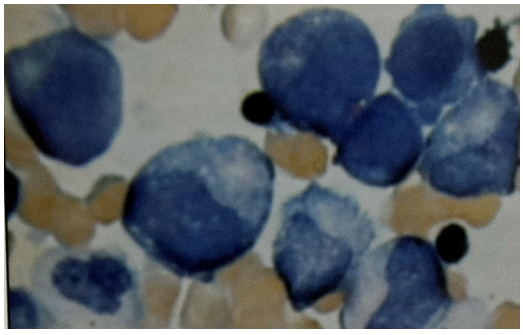

Figure 7: Peripheral smear in case of Acute Myeloid Leukemia presenting as pancytopenia

Discussion

A total of 60 cases of pancytopenia were studied. they were investigated for etiology, and analysis was done based on the clinical history and findings, hematological workup including hemogram, bone

marrow aspiration studies in all cases and bone marrow biopsies and other special tests as per the need of the case. These studies were then compared with various available studies as follows.(Table 7)

Table 7: Comparison of etiologies of pancytopenia with other studies

Authors	Tilak V,Jain R [4] (1999)	Khodke et al [6] (2001)	Kumar et al [9] (2001)	NiaziM,Fazl-I-Raziq [21] (2004)	Present study (2006)
Total cases	77	50	166	89	60
Common Causes	**Megaloblastic anemia (68%)**	**Megaloblastic Anemia (44%)**	**Aplastic Anemia (29.51%)**	**Aplastic Anemia (38.3%)**	**Megaloblastic anemia (50%)**
	Aplastic Anemia (7.70%)	Aplastic Anemia (14%)	Megaloblastic Anemia (22.28%)	Megaloblastic Anemia (24.7%)	Hypoplastic/ Aplastic anemia(18%)
	Malaria (3.8%)	Kala azar (14%)	Aleukemic Leukemia (12.04%)	Hypersplenism (16%)	Normoblastic Erythropoiesis (12%)
	Kala azar (2.5%)	Normoblastic Erythropoiesis (14%)	Hypersplenism (11.44%)	Acute leukemia (13.6%)	Hypersplenism &acute leukemia (3% each)

The commonest cause of pancytopenia in our study was Megaloblastic anemia which is consistent with those of Tilak V et al [4] and Khodke et al [6] in their study of 77 and 50 cases of pancytopenia respectively. This was followed by Aplastic anemia which is the commonest cause in study by Kumar et al [9] and Niazi et al [21] in contrary to our study. In aplastic anemia it is difficult to ascertain the cause as patient generally labelled as idiopathic [23], which formed 54.5% of our aplastic group and acquired comprised of 45.4%. Third commonest cause in our study group showed a normoblastic picture on smear and a normocellular marrow (cases attributed to alcoholic liver disease with splenomegaly where hypersplenism is the most likely explanation), 4 others had pancytopenia with normoblastic erythroid hyperplasia (may represent phase of evolution to hypoplasia or aplasia or just refractory anemias. Criteria for differentiation of this group remains unsatisfactory so patients should be kept under close follow up, similar to studies by Khodke et al [4] which also had normoblastic erythropoiesis with peripheral pancytopenia. Of the 2 cases of sub leukemic phase of acute leukemias, one each belonged to Acute myeloid and acute lymphoblastic leukemia. 2 cases of primary hypersplenism recovered after splenectomy, constituted 3% of cases contrary to 11.44% and 16% reported by Kumar et al [9] and Niazi et al [21] respectively. Available literature [1,3,2] shows normal hemogram except low platelets but our case had leucopenia and mild anemia.1 case each of Myelofibrosis, Gaucher disease (PAS positive Gaucher cell in marrow), SLE were seen. 2 cases of Malaria, one with cerebral malaria and other with mixed typhoid-malaria infection (infection related or drug induced not ascertained) were noted, similar to Kumar et al [9] and Tilak et al [6].

Age of presentation and sex distribution: the age range in our study was 1-80 years with female preponderance. Commonest age of presentation was between 21-30 years comparable with Niazi et al21, with slight variation in other studies, Tilak et al4 study shows majority cases under 20 years of age. Our study had female preponderance 0.9 :1 contrary to other studies by Tilak et al [4], Khodke et al [6] who had ratio of 1.3:1.

In the Aplastic / Hypoplastic group 64% cases belonged to age <20 years contrary to study by Young et al [22] where peak incidence was in 21-30 age group. Tilak et al[6] reported 50% cases in first two decades and the rest in 6th and 7th decade while in our cases only one patient belonged to the 60-70 age group.[24]

Clinical features and presentation (Table 9)

Breathlessness (35%), Weakness and fatiguability (25%) and fever (21%) was commonest presenting symptom. Pallor was the most common finding, less common presentations being bleeding, hepatomegaly, splenomegaly and pedal edema.

Table 9: Clinical features compared:

Authors	Commonest Presentation	2nd common presentation	3rd common presentation	4th common Presentation
Khodke et al., (2001)[6]	Pallor	Fever	Weakness	Splenomegaly
Niazi M, Fazl-I-Raziq(2004)[21]	Pallor	Weakness	Fever	Bleeding tendencies
Present Study	Pallor	Breathlessness	Weakness	Fever

Table 10: Peripheral Blood smear findings:

PBS findings / Authors	Anisocytosis	Hypersegmented neutrophils	Immature cells (Myeloid and erythroid)	Relative lymphocytosis
Tilak et al., (1999) [4]	64%	45%	1.29%	14.28%
Khodke et al., (2001) [6]	60%	40%	12%	10%
Present study	78%	30%	12%	12%

Anisocytosis of varying severity was commonest morphological finding comparable with other studies, followed by immature cells (myeloid/erythroid). Of the 60 cases, 26 cases (43%) had hemoglobin levels between 3-5 gm%, Total leucocyte counts fell in the range of 3000-4000/cu mm and platelets ranged from 50,000-1 lac /mm^3. Relative lymphocytosis was noted in 12% of our cases comparable with studies by Tilak et al., (14.28%) [4] and Khodke et al., (10%) [6].

Table 11: Marrow findings: Distribution of Megaloblastic anemia

	Total cases	Pure Megaloblastic anemia	Megaloblastic + Iron deficiency anemia
Sen et al., [20]	111	75(67.5%)	36(22.5)
Present study	30	16(53%)	14(47%)

Table 12: Idiopathic vs Acquired Marrow aplasia/Hypoplasia.

	Total cases	Idiopathic	Acquired
Kumar et al.,[9]	49	36(73%)	13(26.5%)
Present study	11	6(54.5%)	5(45.4%)

In our study marrow could not be done in 1 case of SLE due to very low platelet count. 2 patients succumbed to the disease while rest other patients had a good outcome.

Conclusion

After analysing the data from our study, we feel that the symptoms of pancytopenia are related to the anemia or thrombocytopenia and rarely due to leucopenia which however may become more serious threat in due course of disease adding to the morbidity and mortality as suggested by deGruchy[1]. Megaloblastic anemia should always be considered in evaluation of pancytopenia in Indian patients and is also the most treatable causes of pancytopenia. However, detail workup should be done in every case, so we don't miss the less frequent but life threatening conditions also.

In our study, majority had treatable etiology of pancytopenia. Early treatment canbe planned depending on the cause and severity of Pancytopenia. Bone marrow examination has a definite role in ascertaining the etiology of pancytopenia.

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