PANCYTOPENIA- CLINICO-HAEMATOLOGICAL STUDIES OF BONE MARROW EXAMINATION

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BACKGROUND: Pancytopenia is an important clinicohematological entity having varying presentations and underlying cause ranging from megaloblastic anemia to fatal bone marrow aplasia and leukemias. Underlying pathology determines the treatment and prognosis.In majority of cases it is megaloblastic anemia which is readily treatable. **OBJECTIVE**: In our country causes of pancytopenia are not very well defined especially in Central India, so the present study has been undertaken to evaluate various causes and to correlate the peripheral blood finding with bone marrow. **MATERIAL AND METHOD:** It was a retrospective study of 155 cases presented with pancytopenia and evaluated clinically with hematological parameters and bone marrow aspiration in Department of Pathology, Gandhi Medical College, Bhopal during the period 2009-2012**. RESULTS:** Among 155 cases studied, age ranged from 2-80 years with mean age of 28 years with preponderance in male under 14 years age and female in 20-40 years age group. Generalised weakness and pallor were noted in all cases. Other common presentations were fever followed by bleeding manifestations. Splenomegaly was more common followed by hepatomegaly. Majority of patients had severe anemia, haemoglobin<5 gm%, platelet count<50,0000/cumm. Bone marrow examination concluded most common cause was megaloblasticanemia(43.2%) followed by hypoplastic anemia(12.9%). **CONCLUSION:** The present study concludes that detailed hematological investigations along with bone marrow examination in pancytopenic patients is helpful to diagnose or rule out the causes of pancytopenia and further planning of investigation and management**.**
KEYWORDS: Pancytopenia, Bone marrow, Megaloblastic anemia.

INTRODUCTION: Pancytopenia is an important clinico-haematological entity worldwide but with varying patterns in clinical presentations & underlying causes, therefore the management and outcome of the patients varies(1). Pancytopenia is characterized by decrease in all three major formed elements of blood i.e. red blood cells, white blood cells and platelets (2). It may result from a number of disease processes –primarily or secondarily involving the bone marrow(3). The causes of pancytopenia are not very well defined for inhabitants of India especially in central region, so the present study was undertaken to evaluate the various causes, clinical presentations and to correlate the peripheral blood findings with bone marrow aspirates(4, 5).The findings of the study would definitely help in planning the diagnostic and therapeutic approach in cases of pancytopenia.

MATERIAL AND METHOD: In our study we reviewed all cases of pancytopenia diagnosed from January 2009 to December 2012 at Department of Pathology, Gandhi Medical College. The study included all cases of pancytopenia i.e. hemoglobin less than 9 gm/dl, total leucocyte count less than

4, 000 cells/ cumm, platelet count less than 1, 00, 000 per cu mm, who underwent bone marrow examination.

Patients who had received chemotherapy or immunosuppressive drugs and those who had dual pathology were excluded. Recording of clinical details was done from the medical records. Hematological parameters were reviewed, leishman stained peripheral and bone marrow aspiration smears were examined in detail.

RESULT: A total of 155 patients who presented with pancytopenia were studied. The study group consisted of 82 males and 73 females with a male to female ratio of 1.12:1.

The age of patients ranged from 2 to 80 years (Mean age 28 years). Out of 155 cases, 36 cases were in paediatric age group (0-14years) which consisted of 23 males and 13 females. Maximum cases - 60 were observed in the age group of 20 to 40 years of which 26 were male &34 females. In the age group 40-60, only 21 cases were reported with 11 male and 10 females. Thus male preponderance was observed in pediatric age group whereas female preponderance was seen in 20-40 year age group. There was no significant difference in sex distribution in 40-60 years age group.

S. no.	Disease	Total cases	Male	Female	Most common age group
1	Megaloblastic anemia	67	43	24	20-40
2	Hypoplastic anemia	20	9	11	00-14
3	Dimorphic anemia	13	6	7	20-40
4	ALL	9	6	3	00-14
5.	AML	8	3	5	20-40
6	Bone marrow reactive to infection	8	3	5	20-40

Table 1: Common causes of pancytopenia with age and sex distribution in the study

The most common cause of pancytopenia among the 155 cases was found to be megaloblastic anemia which was present in 67 (43.22%), with maximum number of cases in 20-40 years age group, male: female ratio was 1.79:1(43:24), the second most common cause of pancytopenia was hypoplastic anemia 20/155 (12.90%) followed by Dimorphic anemia 13/155 (8.38%) with maximum frequency of cases in females both under 14 and 20-40 years age group, male :female ratio being 0.81:1 and 0.85:1 respectively.

Other causes of pancytopenia found in our study were hypersplenism (3.22%), aplastic anemia(2.58%), ITP (1.93%), MDS (1.29%), one each of Myeloproliferative disorder, Chediak Higashi syndrome, Congenital dyserythropoietic anaemia, Pure red cell aplasia, erythroid hyperplasia and gaucher's disease. No definitive diagnosis was established in 10 cases due to laboratory constraints.

Generalised weakness & pallor was noted clinically in all patients of pancytopenia.

The following table presents the distribution of cases according to presenting complaints and physical findings:

Sl. No.	Symptoms	Number of cases	Most common cause	2nd most common cause
1	Fever	45	Megaloblastic anemia (27/67)	Hypoplastic anemia (11/20)
2	Epistaxis	17	Megaloblastic anemia (5/67)	ITP (2/3)
3	Gum bleed	8	Hypoplastic anemia (3)	ITP(1/3)
4	Petechiae	3	Hypoplastic anemia (3/20)	-
5	Rash	9	Hypoplastic anemia (5/20)	ITP (Megaloblastic anemia (2/67)
6	Haemetemesis	5	Hypersplenism (2/5)	MDS (1/1), Megaloblastic anemia
7	Hematuria	5	Megaloblastic anemia (3/67)	Aplastic anemia(1/4), ALL (1/9)
8	Malena	7	Megaloblastic anemia (2/67), Hypersplenism (2/5)	MDS(1/1). ALL(1/9), Hypoplastic anemia(1/20)
9	Bleeding Per rectum	3	Megaloblastic anemia (2/67)	Dimorphic anemia (1/13)
10	Pedal edema	14	Megaloblastic anemia (9/67)	Dimorphic anemia(1/13), BM reactive to infection(1/8)
11	Facial edema	4	Megaloblastic anemia (1/67), dimorphic anemia (1/20)	–
12	Icterus	7	Megaloblastic anemia (5/67)	Hypoplastic anemia (1/20)
13	Jaundice	9	Megaloblastic anemia (5/67)	BM reactive to infection (2/8)
14	Hepatomegaly	26	Megaloblastic anemia (12/67)	Hypoplastic anemia (3/20)
15	Splenomegaly	47	Megaloblastic anemia (20/67)	Hypersplenism(5/5), Dimorphic anemia (5/13)
16	Lymphadenopathy	17	Megaloblastic anemia (6/67)	ALL (3/6)

Table 2: Distribution of cases-presenting complaints and physical findings.

For bleeding manifestations -epistaxis, hematuria, malena and bleeding per rectum, most common cause was found to be megaloblastic anemia while hypoplastic anemia was common cause for gum bleed, petechiae and rash. Haematological parameters in 3 subgroups of pancytopenia observed were as follows:

Severe anemia (Hemoglobin less than 5 gm %) was found in more than 50% cases in megaloblastic anemia, hypoplastic anemia, dimorphic anemia and bone marrow reactive to chronic infection. Most common cause for this was hypoplastic anemia(13/20 or 65 % cases).

Moderate (Hemoglobin-5-8 gm %) and mild (Hemoglobin -8-9 gm %) anemia were found most commonly in megaloblastic anemia in 55.22% (37/67 cases) and 8.9 % (6/67 cases) respectively.

Platelet count less than 50, 000 /cumm were found in 85%, 69.2% and 66% cases of hypoplastic anemia, dimorphic anemia and megaloblastic anemia respectively.

We encountered 17 patients of sub leukemic leukemia (9 ALL and 8 AML), their age ranged from 16 to 60 years.

ALL had higher number of cases under 14 years of age with a total of 9 (5.80%) cases having male: female ratio 2:1, while, AML cases were 8(5.16%), which were more common in 20-40 years age group with male female ratio of 1:1.66.

We also observed one case of storage disorder i.e gaucher's disease, a 8 years old boy who presented with fever, weakness and splenomegaly. Also one case of Chediak hegashi syndrome, 4 year old boy who presented with hypo pigmented macule on trunk, pedal edema, oculo-cutaneous albinism and hepatosplenomegaly.

DISCUSSION: Reviewed retrospectively all 155 cases of pancytopenia who have undergone bone marrow aspiration in a time span of four years. Clinical details - age, sex distribution, presenting symptoms and signs were noted from medical records, hematological parameters, findings of leishman stained peripheral blood picture and bone marrow aspiration smears were reviewed. The underlying cause of pancytopenia was studied in all cases and observations were compared to other studies published in literature.

The age of patients ranged from 2 to 80 years with mean age of 28 years pancytopenia were observed more in males (52.9%), with male to female(M:F) ratio of 1.12:1.

Age and sex distribution was compared with other studies

S, no	Authors	No. of cases	Age range(y)	M:F
1	Khunger JM et al (2002)[7]	200	2-70	1.2:1
2	Kumar R et al (2001)[5]	166	12-73	2.1:1
3	Khodke K et (2001)[8]	50	3-69	1.3:1
4	Tilak V et al (1999)[4]	77	5-70	1.14:1
5	B N Gayatri et al (2011)[14]	104	2-80	1.2:1
6	Present study	155	2-80	1.12:1

Table 3: Age, sex distribution compared to those in other studies of pancytopenia

The most common presenting complaints in our study were generalized weakness and easy fatigability(100%), followed by fever (29%).The most common physical findings were pallor (100%) followed by splenomegaly(30.3%) and hepatomegaly (16.7%).

The symptoms were mostly attributed to anemia and thrombocytopenia.

Variations in the frequency of the various diagnostic entities causing pancytopenia have been attributed to difference in methodology and stringency of diagnostic criteria, geographic area, period of observation, genetic differences and varying exposure to myelotoxic agents, etc.[4]

The commonest cause of pancytopenia reported in various studies throughout the world has been aplastic anemia.[4].This is sharp contrast with results of our and other studies conducted in India where the commonest cause was found to be megaloblastic anemia[5, 7, 8].This seems to reflect the higher prevalence of nutritional anemia in Indian subjects.

Megaloblastic anemia constituted 43.2% cases in our study as compared to 72% reported by Khunger JM et.al ;and 68% by Tilak V et al. both of the studies have stressed the importance of megaloblastic anemia being major cause of pancytopenia.It is a rapidly correctable disorder and should be promptly notified.[4, 7].Although bone marrow aspiration studies are uncommon in suspected cases of megaloblastic anemia. But, if the diagnosis does not appear clear and hematological assays are not available, bone marrow aspiration is indicated. As facilities of folic acid and vitamin B 12 levels are not routinely available in most centres in India.[5]

Prevalence of aplastic anemia varies from10%to52% among pancytopenic patients.[8]the incidence of hypoplastic in our study was 12.9 % (20/155 cases)which correlated with the corresponding figures in study done by Khodke K et al. and the Khunger JM et al., both observed an incidence of 14 %[7, 8].A higher incidence viz 29.5% was reported by Kumar R et al[5]

We encounterd 10.9 % incidence of subleukemic leukemia, compared to 5 % reported by khunger JM et al. Kumar et al reported 12 % incidence of aleukemic leukemia. Pancytopenia was the common feature in our study: this correlated with corresponding finding in the studies by Kumar R et al and Khunger JM et al [5, 7]. The diagnosis of Acute Leukemia was based on bone marrow aspiration studies morphologically and we reported 8 cases of AML and 9 cases of ALL. Kumar et al reported 5 cases of ALL, 13 cases of AML, 2 cases of Hairy cell leukemia out of 166 cases of pancytopenia, over a 6 year period.[5]

Study	Country	Year	no. of cases	Commonest cause	2nd Most Commonest Cause
International agranulocytosis anemia study group[11]	Israel & Europe	1987	319	Hypoplastic anemia (52.7%)	MDS (4.5%)
Keisu & Ost[12]	Isreal& Europe	1990	100	Neoplastic disease radiation (32%)	Hypoplastic anemia (19%)
Hossain et al[13]	Bangladesh	1992	50	Hypoplastic anemia	Chronic malaria & chronic kalaazar
Verma & Dash[9]	India	1992	202	Hypoplastic anemia (40.6%)	Megaloblastic anemia (23.26%)
Tilak & Jain[4]	India	1999	77	Megaloblastic anemia (68%)	Hypoplastic anemia (7.7%)
Kumar et al [5]	India	1999	166	Hypoplastic anemia (29.51%)	Megaloblastic anemia (22.3%)
Khodke et al [8]	India	2000	50	Megaloblastic anemia (44%)	Hypoplastic anemia (14%)

Bajracharyarya et al[11]	Nepal	2005	10	Hypoplastic anemia	Megaloblastic anemia
B N Gayathri et al[10]	India	2007	104	Megaloblastic anemia (74.04%)	Hypoplastic anemia (19%)
Present study	India	2012	155	Megaloblastic anemia (43.2%)	Hypoplastic anemia (12.9%)

Table 4: A comparison of the first and second most common causes of pancytopenia in different studies

We came across 8 cases of chronic infection in our study, 3 of them were tubercular constituting 5 % of total cases. In our study no cases of malaria was found whereas Khunger J.M et al reported malaria 1%, Tilak V et al 3.9% and Kumar et al of 3 % of total cases[4, 5, 7].

Reported incidence of Multiple Myeloma in pancytopenia patients was 4% by Khodke K et et al, 1.3 % by Tilak V et al and 1 % by Khunger JM et al.[4, 7, 8] while we have not found any case of multiple myeloma having pancytopenia.

We found a single case of Gauchers disease in our study.Kumar R et al, Khunger JM et al and Khodke et al have not reported any case of storage disorder as a cause of pancytopenia In their studies [5, 7, 8].

CONCLUSION: Pancytopenia is not an uncommon hematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever, tendency to bleed, lymphadenopathy and hepatosplenomegaly. No specific symptoms are related with any specific diagnosis.

In our country main cause of pancytopenia being fortunately megaloblastic anaemia which responds very well to treatment if diagnosed correctly in time.The present study concludes that detailed haematological investigations along with bone marrow examination in cytopenic patients are not only helpful in understanding the disease process but also to diagnose or to rule out the causes of pancytopenia and planning further investigations and management of these patients.

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