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Etiology of Pancytopenia in Adult Population by Bone Marrow Examination - A Description Study

Dr. Simi Sidharthan[1], Dr. Shameem Ummer Ali[2], Dr. Prabhalakshmi[3]

[1]Assistant Professor Pathology , Govt Medical College Calicut, India

[2]Additional Professor Pathology, Govt Medical college Allapuzha

[3]Additional Professor Pathology, Govt Medical College Thrissur

Abstract: ***Pancytopenia is defined as reduction of all three formed elements of blood below the normal reference ranges. It is the manifestation of a number of disease processes affecting the bone marrow. Aim to identify the various causes of pancytopenia in adult population by bone marrow examination ,then the most common cause of pancytopenia and to find the frequency of pancytopenia in relation to age and sex. This is two years description study. Peripheral smears, buffy coat smears, marrow aspiration smears and trephine biopsies of thirty six cases were studied. Special stain done for suspicious cases of leukemia and lymphoma. Relevant clinical history and investigations were collected. Megaloblastic anaemia was the most common cause of Pancytopenia followed by Aplastic anaemia. Most common age group between 51 to 60 years followed by 61-70 years. Female predominate with 21 cases and male 15 cases Hence Pancytopenia is basically a laboratory diagnosis. Bone marrow aspiration and trephine biopsy are mandatory for the diagnosis of the various causes of pancytopenia. Comprehensive clinical and haematological study on pancytopenia cases is needed to identify the cause with certainty.***

Keywords: Pancytopenia, peripheral smear, bone marrow aspirate, bone marrow biopsy

1. Introduction

Normal haematopoiesis occurs in bone marrow within a specialised microenvironment. Haematopoiesis will increase to increased demands. Mature blood cells derived from pleuripotent stem cells are then increasingly released into peripheral circulation. When all the three formed elements, namely the red blood cells, white blood cells and platelets are found reduced in circulation; this condition is known as pancytopenia.

Pancytopenia is defined as reduction of all the three formed elements of blood below the normal reference ranges[1] Pancytopenia is not a disease entity but a manifestation resulting from a number of disease processes affecting the bone marrow either primarily or secondarily[2]The presenting symptoms of pancytopenia are most often attributable to anemia or thrombocytopenia.

Pancytopenia is a serious hematological problem, the underlying cause of which is diagnosed by bone marrow aspiration and biopsy. Bone marrow examination is extremely helpful in evaluation of Pancytopenia[3,4,5]Since underlying pathology determines the management and prognosis of patients with pancytopenia it becomes vital to study the etiology and underlying mechanism of this condition. Our study focus on this aspect of pancytopenia and attempts to find out any relevant underlying factors causing pancytopenia by bone marrow smear and biopsy study in adults.

Aims and objectives of the study

a) To identify the various causes of pancytopenia in adult population attending Government Medical college and to correlate the causes of pancytopenia with the bone marrow picture.
b) To identify the most common cause of pancytopenia in such patients .
c) To determine the frequency of pancytopenia in relation to age and gender.

2. Materials and method

Settings: Clinical Pathology laboratory in Pathology Department, Government Medical College.

Materials: Peripheral smears, bone marrow aspirates and bone marrow trephine biopsies of all cases of pancytopenia during the year August 2009 to August 2011 were studied.

Case selection: All cases who has Hemoglobin < 10gm%, Total WBC Count <4000cells/cumm and Platelet Count <1,00,000cells/cumm were included in this study. Paediatric cases, pancytopenic patients on chemotherapy and cases without bone marrow study were excluded in the study.

Method

Clinical details of the selected cases were documented. Peripheral smears and buffy coat smears were stained with Leishman stain and studied. Bone marrow study was advised in these cases for further evaluation of pancytopenia. Bone marrow aspiration and Trephine biopsies were done by clinicians. Bone marrow aspirate smears and Imprint smears were stained with Leishman stain. Special stains like MPO and Sudan black were done in suspicious cases of Leukemia /Lymphoma. Bone marrow trephine biopsies were fixed in Bouin's fluid, decalcification was done in 5% nitric acid and processed in the Histokinette. Trephine biopsies were stained in Haematoxylin and Eosin. Bone marrow study was not done in the cases of macrocytic anaemia where vitamin B12 assay was available. Total 36 cases of pancytopenia whose

peripheral smears, bone marrow aspirate smears and trephine biopsies were available and those cases were studied.

Stastistical analysis: Datas were entered in Excel 8.Analysis is done in Epi Info software 2008

3. Observation

During the period of two years, thirty six cases of pancytopenia were studied.

Table 1: Distribution of cases according to age

Age	*Cases*	*Precentage*
11-20	2	5.6%
21-30	2	5.6%
31-40	5	13.9%
41-50	6	16.7%
51-60	10	27.8%
61-70	8	22.2%
71-80	3	8.3%

Table 2: Distribution of cases according to gender

Sex	*Cases*	*Percentage*
Female	21	58.3%
Male	15	41.7%

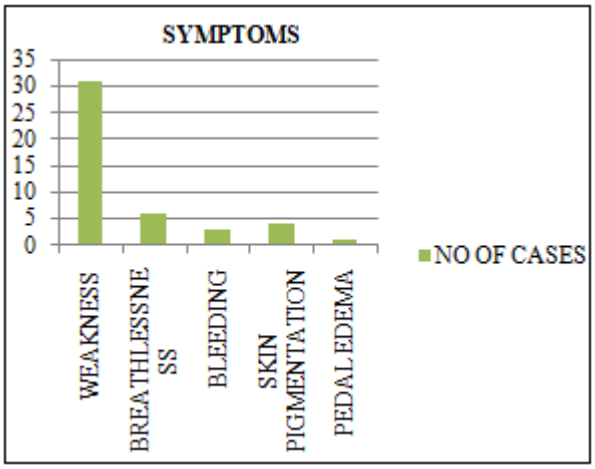

Figure 1: Distribution of cases according to presenting symptoms

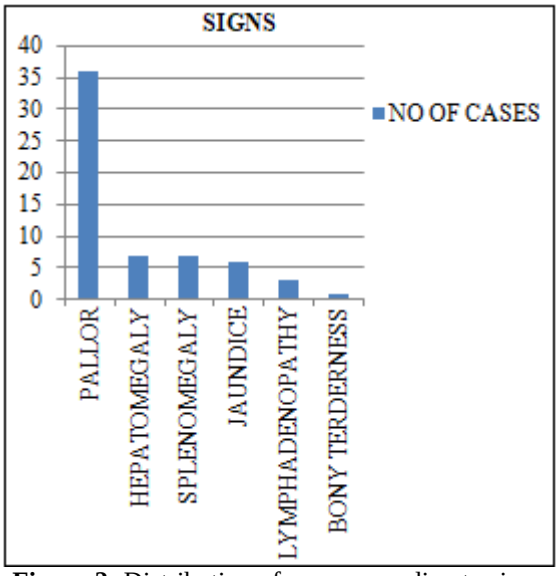

Figure 2: Distribution of cases according to signs

Most of the patients had Haemoglobin values between5.1 gm% to 9 gm% (38.9%) and no cases had Haemoglobin value more than 9gm%. Majority of cases leucocyte count were in the range of 1001 to 3000/cumm (55.6%) followed by 3001 to 4000/cumm (36.1%). Predominant cases platelet count were in the range 20000 to 50000 (38.9%)

Table 3: Peripheral smear findings observed in pancytopenia

Peripheral Smear Findings	*Present*	*Absent*
Anisocytosis	28(77.8%)	8(22.2%)
Poikilocytosis	22(61.1%)	14(38.9%)
Macrocytes	30(83.3%)	6(16.7%)
Macro ovalocytes	15(41.7%)	21(58.3%)
NRBC/100WBC's	9(25%)	27(75%)
Hypersegmented neutrophils	10(27.8%)	26(72.2%)
Blast cells	3(8.30%)	33(91.70%)

Table 4: Erythroid hyperplasia observed in bone marrow

Erythroid Hyperplasia	*No Of Cases*	*Percentage*
Present	19	52.8%
Absent	17	47.22%

Table 5: Distribution of cases in erythroid hyperplasia

Disease groups	No of cases (19/36 cases)
Megaloblastic anaemia	18
Myelodysplastic syndrome	1
Total	19

Table 6: Bone marrow trephine cellularity

Cellularity	No of cases	Percentage
Hypercellularity	25	69.44%
Normocellularity	2	5.56%
Hypocellularity	9	25%

Table 7: Distribution of cases in hypercellular marrow

Disease groups	No of cases
Megaloblastic anaemia	17
Acute myeloid leukemia	4
Multiple myeloma	2
Non Hodgkin Lymphoma	1
Myelodysplastic syndrome	1
Total	25

Table 8: Distribution of cases in Hypocellular marrow

Disease groups	No of cases
Aplastic anaemia	6
Hypoplastic MDS	1
Viseral Leishmaniasis	1
Total	8

Table 9: Distribution of cases in normocellular marrow

Disease groups	No of cases
Megaloblastic anaemia	2
Lymphoma	1
Total	3

Table 10: Etiology of pancytopenia

Etiology	Cases	Percentage
Megaloblastic anaemia	19	52.8%
Aplastic anaemia	6	16.7%
Leukemia	4	11.1%
Lymphoma	2	5.6%
Multiple myeloma	2	5.6%
Myelodysplastic syndrome	2	5.6%
Kala azar	1	2.8%

Table 11: Various bone marrow study of pancytopenia

S NO	STUDY	AGE IN YEARS	YEAR OF STUDY	DURATION OF STUDY	NO OF CASES	1st COMMON CAUSE	2nd COMMON CAUSE
1	Santra et al KOLKATA	13 -65 yrs	2010	1 YR	111	Aplastic anaemia	Hypersplenis
2	Tariq et al PAKISTHAN	> 14 yrs	2008	10 months	50	Aplastic anaemia	Megaloblasti anaemia
3	Gayathri et al KARNATAKA	2 -80 yrs	2005 -2007	2 years	104	Megaloblastic anaemia	Aplastic anaemia
4	Osama et al RAWALPINDI	12 – 82 yrs	2001	1 year	100	Megaloblastic anaemia	Aplastic anaemia
5	Khodke et al NEW DELHI	3 -69 yrs	1999	6 months	50	Megaloblastic anaemia	Aplastic anaemia
6	Present study	18- 80 yrs	2009 -2011	2 years	36	Megaloblastic anaemia	Aplastic anaemia

4. Discussion

Pancytopenia is an important clinicohematological entity seen in our day to day clinical practice. There are varying trends in clinical pattern, treatment modalities, and outcome. A total of thirty six cases of pancytopenia were studied in a period of two years. Age, gender, presenting complaints, peripheral blood picture, bone marrow aspirate smears and bone marrow trephine biopsy smears were studied in all cases and observations were compared with those in studies published in the literature.

In the present study, pancytopenia was due to the following causes Megaloblastic anemia (52.8%) was the commonest cause of Pancytopenia (Table 11) is comparable with other studies like Kishore Khodke et al [6]with 44%,Gayathri et al [7] with 39%, and Osama Ishtiaq et al[8] with74.04% The commonest cause of Pancytopenia reported from various studies throughout the world has been aplastic anaemia.This is in sharp contrast with the results of present study where the commonest cause of pancytopenia was megaloblastic anemia. This seems to reflect the higher prevalence of nutritional anemia in Indian subjects as well as in developing countries.

Present study 27.8% of patients were in the age group of 51 to 60 years followed by 22.2% in the age group of 61 to 70 years. [Table1] This is in contrast to the study by Santra et al[9] in which 37% of patients were within the range of 31 to 45.This may be because in present study only the adult population were included and patients on chemotherapy were excluded.

Megaloblastic anaemia more common in the age group of 60 to 70 yr (26.3%) in the study which is comparable to Caucasian and Chinese population where Megaloblastic anaemia is reported to occur more in older age groups[10]

Current study showed male to female sex ratio of 1:1.4[Table 2] and was in contrast to Gayathri et al and Santra et al in their study had male preponderance with male to female ratio of 1.2:1 and 1.47:1 respectively. Megaloblastic anaemia was commonest and with female preponderance similar to a study done by Uma khanduri and Archana Sharma[11] where 175 cases of Megaloblastic anaemia were studied in which 71% were female patients. Present study shows Megoblastic anaemia as the commonest cause with 19 cases among which 17 were females. In the present study, neoplastic disease as a cause of pancytopenia was found to be more common in male patients.

The most common presenting symptom was weakness (86%) followed by breathless (16.67%) [Figure 1].This is similar to the study by Kishore Khodke et al in which 40% of cases showed weakness, another study by Mussarat et al[2] in which 68.2% of cases and Gayathri et al in which 100% of cases showed weakness The most common sign pallor (100%) followed by hepatomegaly and splenomegaly [Figure 2]which was in comparable to the study by Kishore Khodke et al[6] Mussarat et al[2] Gayathri et al[7] and Santra et al[9]

Leukocyte count the range was comparable to the study by Santra et al (34). Megaloblastic anaemia shows anisocytosis (100%) with the 'p' value of 0.008 (significant) which was in comparable to the study by Osama Ishtiaq et al[8] Macrocytes were seen in all cases of Megaloblastic anaemia in the present study with the 'p' value 0.006% (significant) Macro ovalocytes were noted in 15 cases of pancytopenia (41.7%) and among them 14 patients (73.68%) had Megaloblastic anaemia with 'p' value 0.000285(significant), these observations were comparable to Osama Ishtiaq et al [9]

Hypersegmented neutrophils[Table 3] were noted in 27.8% of the total number of cases of pancytopenia and among which 22.22% of cases were contributed by Megaloblastic anaemia with,'p' value 0.046 (significant) and was comparable to the study by Gayathri et al and Tilak et al [14] Nucleated RBC's were noted in 9 cases (25%) in the present study of which 5 cases were diagnosed as Megaloblastic anaemia, 3 as leukemia and 1case as MDS.

Erythroid hyperplasia [Table 4]was noted in 19/36 cases in this study, Megaloblastic anaemia shared 18 cases (94%) and one case was MDS. Bone marrow aspiration showed megaloblastic erythroid maturation with characteristic feature of sieved nuclear chromatin, asynchronous nuclear and cytoplasmic maturation, giant metamyeloctes and giant band forms. This finding was similar to the study of Gayathri et al [13] in which 74.04% cases showed megaloblastic maturation. Erythroid hyperplasia was a significant finding in megaloblastic anaemia with a 'p' value 0.0005

Bone marrow trephine study in this study shows hypercellularity in 69.44% cases of which 17 cases showed megaloblastic maturation with giant metamyeloctes and giant band forms and were disgnosed as Megaloblastic anaemia. In four cases the bone marrow trephine biopsy showed increased cellularity with myeloid hyperplasia. Immature cells were noted in all four of them and were diagnosed as acute myeloid leukemia. In two cases, normal haematopoiesis was decreased with infiltration by plasma cells and was diagnosed as plasma cell myeloma. Another case showed bone marrow with interstitial and nodular infiltration by lymphoma cells and it was diagnosed as non Hodgkin's lymphoma. One case showed bone marrow with dyserythropoeisis, dysmyelopoiesis and dysmegakaryopoiesis and it was diagnosed as Myelodysplasic syndrome. These findings was comparable to findings noted by Santra et al[9] in which cellular marrow showed Hypersplenism, megaloblastic anaemia, bone marrow lymphoma, acute leukemia,Myelodysplastic syndrome, multiple myeloma,tuberculosis,falciparum malaria

Normal bone marrow cellularity[Table 9] was noted in 3 cases, among which 2 were megaloblastic anaemia and 1 was lymphoma. Hypocellularity [Table 8]in bone marrow trephine was noted in 8 cases in which bone marrow of 6 cases showed replacement of normal hematopoietic cells by fat cells in all patients There was relative increase in plasma cells and lymphocytes and was diagnosed to be Aplastic anaemia. Bone marrow of one case showed decreased normal hematopoietic cells with a few lymphocytes, plasma cells and a focus showing abnormal localization of immature precursors and was diagnosed to be hypoplastic myelodysplastic syndrome. Another case showed reduced normal marrow elements with increase in the number of macrophages showing ingested amastigote forms of Leishmania donovani [Fig 3]and Visceral leishmaniasis was diagnosed in this case. Study done by Mussarat et al in 89 cases showed visceral leishmaniasis in one case, Santra et al noted 10 cases of Visceral leishmaniasis out of 111 cases , Kishore khodke et al noted 7 cases of Kala azar out of 50 cases.

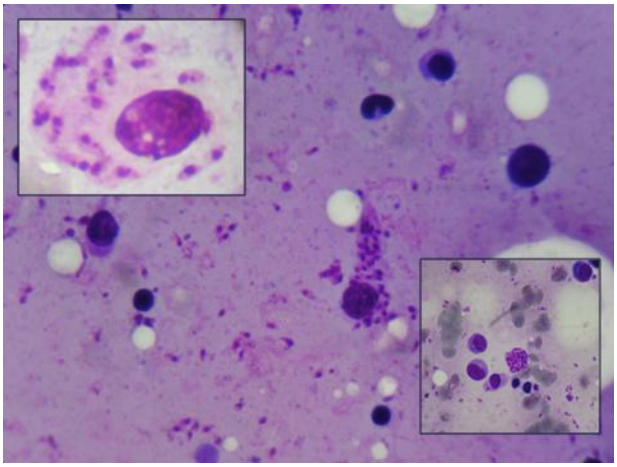

Figure 3: Bone marrow aspirate showing macrophages (40X) with ingested amastigote form leishmania,inset(100X) showing macrophage and kinetoplast

5. Summary

Pancytopenia cases attending Thrissur Government Medical College during the period between Aug 2009 to Aug 2011 were studied. Paediatric cases and patients on chemotherapy were excluded from this study. Peripheral smears, bone marrow aspirates, bone marrow trephine biopsies of Pancytopenia cases were studied. Females were found to be more common than males. Male to female ratio was 1:1.4. Commonest age group in this study were between 60 to 70 years. Megaloblastic anaemia was the commonest cause of pancytopenia in this study, this seems to reflect the higher prevalence of nutritional anaemia in our population.

The haematological parameters in patients with megaloblastic anaemia and aplastic anaemia were comparable to the findings of other study. Uncommon etiologies like Leukemia, Multiple myeloma, Lymphoma, Myelodysplastic syndrome and Kala azar were also identified in this study. Though the results of this study was in concordance with the other studies in India, the main limitation that we encountered was that of the small sample size and which may probably be due to the unavailablity of bone marrow aspirates and trephine biopsies in many of the pancytopenic patients.

6. Conclusion

Pancytopenia basically is a laboratory diagnosis. Bone marrow aspiration and trephine biopsy are mandatory for the diagnosis of the various causes of pancytopenia. Comprehensive clinical and haematological study on pancytopenia cases is needed to identify the cause with certainty. In view of the wide range of etiologies, pancytopenia continues to be a diagnostic challenge for haematologists.

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