Clinical Etiological Evaluation of Pancytopenia in Adults in a Tertiary Care Hospital

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Abstract
Introduction: *Pancytopenia refers to reduction in all three formed elements of blood erythrocytes, leucocytes and platelets[1]. It is not a disease entity, but rather a triad of findings that may result from a number of disease processes. Although it is a common clinical problem with an extensive differential diagnosis, there is relatively little discussion of this abnormality in major textbooks of internal medicine and hematology [2].*
Aim and Objectives: *To determine the common etiological causes of Pancytopenia. To determine the most common clinical manifestations of pancytopenia. To determine, if a critical analysis of peripheral smear provides a clue to the underlying pathology. To determine how frequently Bone marrow aspiration yields the Diagnosis.*
Materials and methods: *the present study entitled "clinical and etiological evaluation of pancytopenia in adults" was undertaken at Yashoda hospital-Malakpet-Hyderabad, a tertiary care hospital.*
Results: *60 patients with pancytopenia on the Hemogram were tabulated. Based on bone marrow findings and relevant investigations with clinical data, the following aetiological categories were recognized. Megaloblastic Anaemia 53 %, Aplastic Anaemia 10 %, Acute promyelocytic Leukemia 6.6%, Acute Lymphoblastic Leukemia 6.6%, Myelodysplastic Syndrome 3%, Hodgkins Lymphoma 3%, Non Hodgkins Lymphoma / Visceral TB 1.7%, Myelofibrosis 1.7%, Hemophagocytic syndrome 3%, Hypersplenism 3%, Septicemia 3%, Systemic Lupus Erythematosus 3%.*
Consclusion: *Nutritional Megaloblastic Anemia is the commonest cause of Pancytopenia in this study. Acute Leukemias and Aplastic anemia are two other conditions to be considered commonly during evaluation of Pancytopenia. Pallor is the most common clinical feature followed by shortness of breath. Except in megaloblastic anemia, no specific features were found on peripheral smear, to point out to a specific diagnostic, as the cause of pancytopenia. Concurrent Iron deficiency is usually associated, resulting in masking of typical features of Megaloblastic anemia. Macrocytes and hypersegmented neutrophils indicate megaloblastic anemia as the underlying cause of pancytopenia. Bone marrow aspiration is sufficient to diagnose the underlying cause of Pancytopenia Bone marrow biopsy is not routinely necessary.*
Key Words: *Megaloblastic Anemia, Pancytopenia,*

I. Introduction

Pancytopenia refers to reduction in all three formed elements of blood erythrocytes, leucocytes and platelets[1]. It is not a disease entity, but rather a triad of findings that may result from a number of disease processes.

Although it is a common clinical problem with an extensive differential diagnosis, there is relatively little discussion of this abnormality in major textbooks of internal medicine and hematology [2]. Pancytopenia can be due to decrease in hemopoietic cell production in the bone marrow e.g by infections, toxins, malignant cell infiltration or suppression or can have normo cellular or even hyper cellular marrow, without any abnormal cells, e.g infective hematopoiesis and dysplasia, maturation arrest of all cell lines and peripheral sequestration of blood cells[3].

The frequency with which each condition is associated differs considerably. For example, it is always present at some stage in the course of aplastic anaemia, very common in subleukemic leukemia, relatively uncommon in lymphomas and rare in metastatic carcinoma involving the bonemarrow. Prognosis also depends on both the severity of the pancytopenia and nature of   the underlying condition. Thus   the cause of the pancytopenia ,vary from treatable causes like Vit B12 - Folate deficiency and Hypersplenism to virtually an untreatable cause like Aplastic anemia   except by Bone marrow Transplantation which is out of reach for most of our patients.

Pancytopenia is generally equated to Aplastic anemia and , prognosis considered is grim. Even in textbooks of Hematology[4,5] pancytopenia has been discussed along with Aplastic anemia,though it was not considered it`s most common cause[4].

A review of available literature revealed only one international study(Imbert et al) [6] and a few Indian studies on common etiological causes of pancytopenia are present, and most of them are from North India.

This study was, therefore taken up to find out the common etiological Causes of pancytopenia, common clinical presentation, and to determine the value of peripheral Smear examination, Bone marrow aspiration,and Bone marrow biopsy in making correct diagnosis.

II. Material And Methods

The present study entitled "CLINICAL AND ETIOLOGICAL EVALUATION OF PANCYTOPENIA IN ADULTS" was undertaken at YASHODA HOSPITAL-MALAKPET-HYDERABAD, a tertiary care hospital.

Methodology:-

Study design:- An institutional based cross-sectional study.
Study Settings:- Department of General Medicine, Yashoda Hospital, Malakpet, Hyderabad.
Study Period:- Two years extending from October 2008 to October 2010.
Inclusion Criteria:- All patients with age more than 12 years admitted to medical wards & medical ICU in Yashoda Hospital with following indices on hemogram [1]

Hemoglobin - <12gm%
W.B.C count - <4000/cu.mm
Platelet count - < 1,00,000/cu.mm.

Patients with above indices, either in the initial hemogram or in the subsequent hemograms during the workup prior to diagnosis are included.

Exclusion criteria:- All those patients who developed pancytopenia due to cancer chemotherapy.
Data Collection:- 60 patients admitted into the medical wards and ICU of YASHODA SUPER SPECIALITY HOSPITAL MALAKPET, between October 2008 to October 2010 [study period of 24 months] and meeting exclusion and inclusion criteria were studied. They were subjected to detailed history, physical examination and their dietary habits were also enquired. The following investigations were done in all patients.

1] Hemogram
2] Basic Biochemical parameters
   [LFT, Blood Urea,Serum Creatinnine,Electrolytes]
3] Basic Radiological investigation
   [Xrays,US abdomen and pelvis]
4] Bonemarrow aspiration and Trephine biopsy
   If needed

Additional investigations were done as required and where ever feasible depending upon the history and physical examination and initial investigation findings.

1] Serum B12, Serum Folic acid, Serum Iron studies
2] Serum LDH
3] Lymphnode Biopsy
4] Immunohistochemistry, Flow cytometry
5] Blood culture
6] ANA, dS DNA

The following features were noted in the peripheral smear.

1] Morphology of red cells
2] Morphology of W.B.C
3] Presence of hypersegmented
   neutrophils
4] Degree of anisocytosis &
   poikilocytosis
5] Blast cells.

The Bonemarrow was evaluated for the following features.

1] Cellularity
2] E/M ratio
3] Erythropoiesis

4] Leucopoiesis

5] Thrombopoiesis

6] Blasts cells

If the initial bone marrow aspiration resulted a dry tap Bonemarrow biopsy was considered.

III. Results And Observations:

60 patients with pancytopenia on the Hemogram were tabulated. Based on bone marrow findings and relevant investigations with clinical data, the following aetiological categories were recognized.

Aetiology	Number of Cases (n=60)	percentage (%)
Megaloblastic Anaemia	32	53
Aplastic Anaemia	6	10
Acute promyelocytic Leukemia	4	6.6
Acute Lymphoblastic Leukemia	4	6.6
Myelodysplastic Syndrome	2	3
Hodgkins Lymphoma	2	3
Non Hodgkins Lymphoma / Visceral TB	1	1.7
Myelofibrosis	1	1.7
Hemophagocytic syndrome	2	3
Hypersplenism	2	3
Septicemia	2	3
Systemic Lupus Erythematosus	2	3

(TABLE 1)

As shown in TABLE 1 Megaloblastic anemia was the leading cause of pancytopenia in my study [53%].

The same can be charted in a Pie diagram
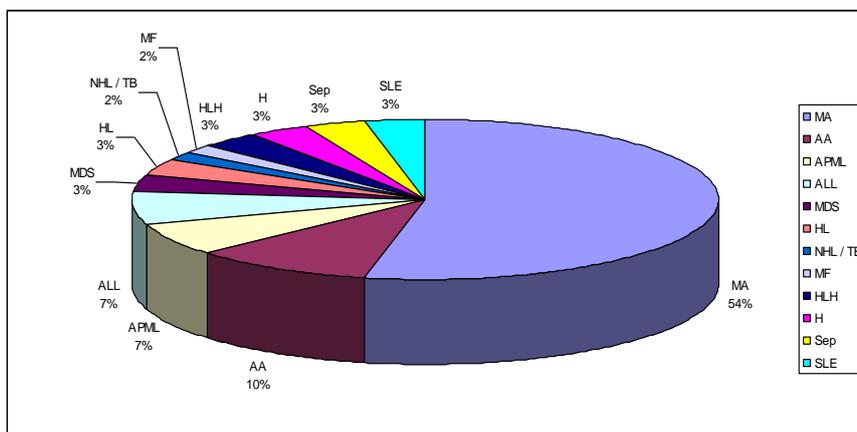
(FIGURE 1)

MA	= Megaloblastic Anaemia	
AA	= Aplastic Anaemia	
APML	= Acute Promyelocytic Leukemia	
ALL	= Acute Lymphoblastic Leukemia	
MDS	= Myelodysplastic Syndrome	
HL	= Hodgkins Lymphoma	
NHL/TB	= Non Hodgkins Lymphoma / Visceral TB	
HPS	= Hemophagocytic syndrome	
MF	= Myelofibrosis	
H	= Hypersplenism	
Sep	= Septicemia	
SLE	= Systemic Lupus Erythematosus	

AGE AND SEX DISTRIBUTION

AGE DISTRIBUTION

No. OF PATIENTS (y-axis, 0–30)

Legend:
- ■ No. of Patients
- ■ No. of Patients with Megaloblastic Anemia

AGE IN YEARS (x-axis: 12-20, 21-30, 31-40, 41-50, 51-60, 61-70)

SEX DISTRIBUTON

No.OF PATIENTS (y-axis, 0–18)

Legend:
- ■ MALES
- ■ FEMALES

AGE IN YEARS (x-axis: 12-20, 21-30, 31-40, 41-50, 51-60, 61-70)
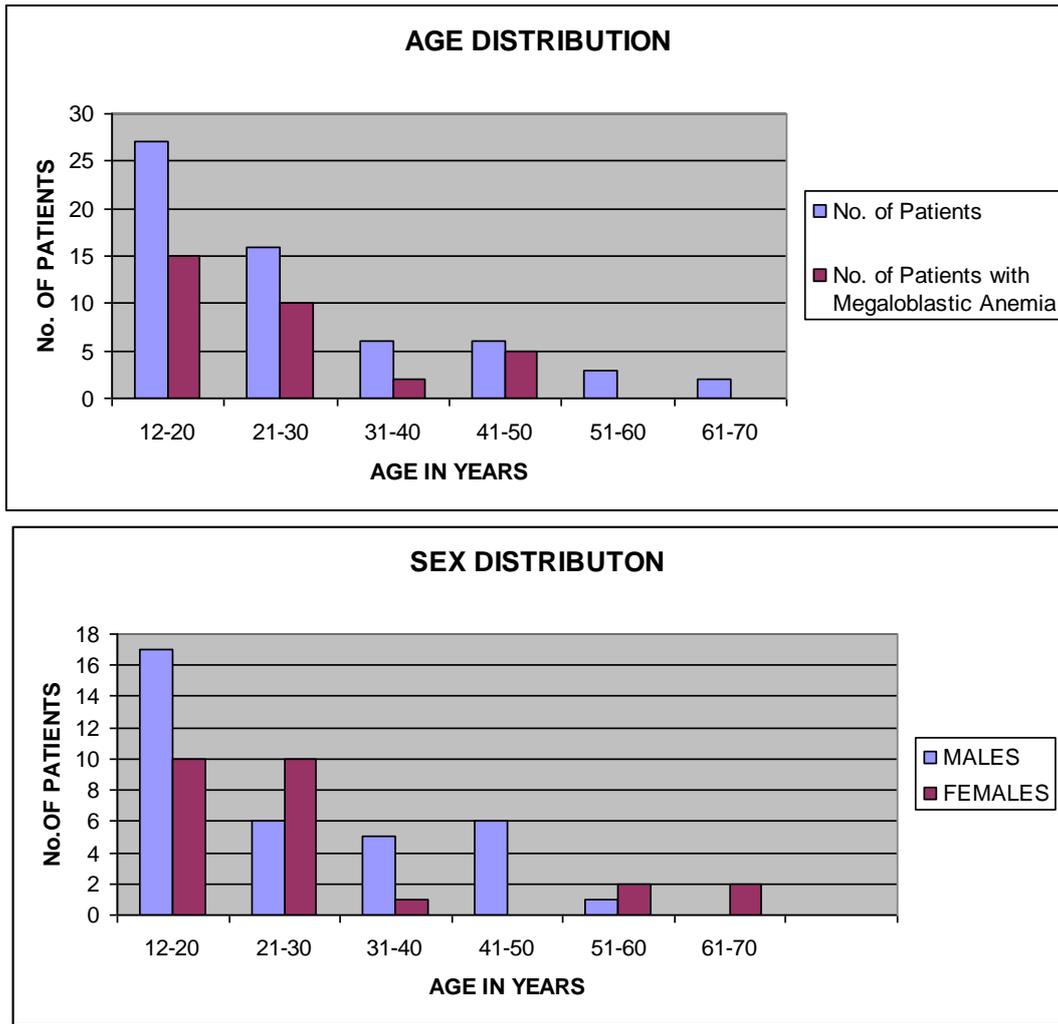
(FIGURE 2 AND 3)

As shown in FIGURE 2and 3 there were no patients below the age of 12 years as they were admitted at a separate hospital. 45% of the patients (27 of 60) were in the second decade and 27% of them (16 of 60) in the third decade. There were 35 Male patients and 25 Female patients. The age distribution of Megaloblastic Anemia, which accounted for the maximum number of cases in this study is shown in the bar diagram.

DIETARY HISTORY ANALYSIS OF PATIENTS WITH MEGALOBLASTIC ANEMIA

(y-axis, 0–30)

Legend:
- ■ 0/7 days Grp.I
- ■ 1-3/7 days Grp.II
- □ 4-7/7 days Grp.III

(x-axis: Eggs, Gr.Lf, Pls, Milk, meat)
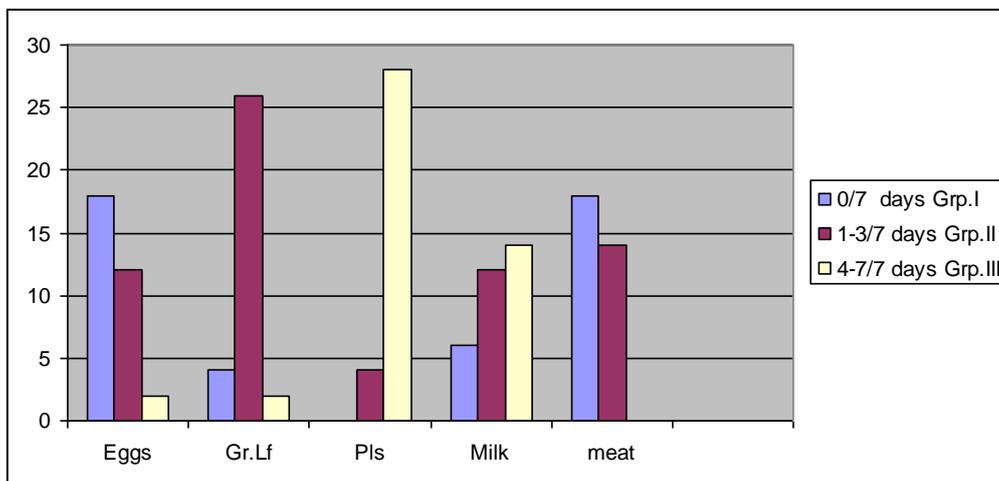
(FIGURE 4) Gr.LF: Greanleafy vegetables, Pls:Pulses

As shown in Figure 4, of 32 cases of megaloblastic anemia 18 patients (55%)
were either strict Vegetarians or ate Meat usually on festival days. 10 patients in Group II ate meat once a weak.
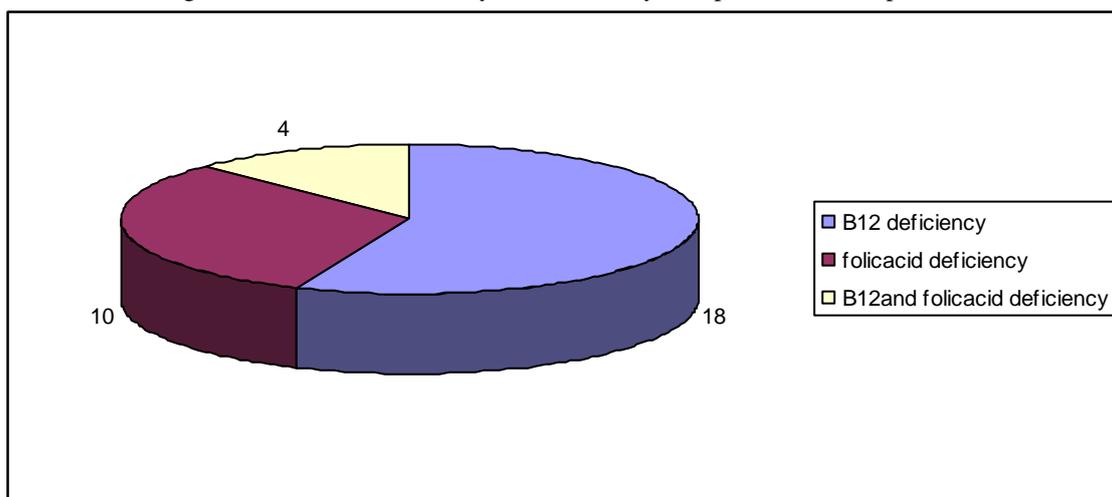
(FIGURE 5)

Of 32 cases of megaloblastic anemia, 18patients had B12 deficiency, 10patients had Folic acid deficiency and 4 patients had deficiencies of both.

Major clinical features at presentation were as follows

Clinical Features	Number	Percentage
Fatigue and Shortness of breath	52	87
Fever	45	75
Pallor	60	100
Bleeding	24	40
Hepatomegaly	34	57
Splenomegaly	36	60
Lymphadenopathy	12	20

(TABLE 2)

As shown in the table 2, the commonest symptoms were, fatigue and shortness of breath followed by mild to moderate fever. Bleeding manifestations at the time of presentation were present in 24 patients (40%). On physical examination, all the patients had moderate to marked pallor. Hepatomegaly was present in 34 patients (57%) and splenomegaly in 36 patients (60%). Lymphnodes were palpable in 12 of them (20%). None of the cases of megaloblastic anemia had evidence of either cord or peripheral nerve involvement.

HAEMATOLOGICAL CHARACTERISTICS: HEMOGRAM ANALYSIS
The total Hemoglobin ranged from 2 – 9.5 g%

Hb – gm%	Number	%
2.0 -4.9	30	50
5.0 -7.9	18	28
8.0 -9.9	12	22
(TABLE 3)	n =60	100%

The total count ranged from 700 to 4000 cells / cumm. All those with an absolute Neutrophil count of less than 1800 cells/cumm were considered Neutropenic by definition [28]. The neutrophil counts were as follows in 46 patients with neutropenia (77%).

Neutrophil Count	Number	%
0 – 600	15	32.6
601 – 1200	16	34.8
1201 – 1200	15	32.6
(TABLE 4)	n =46	100%

The platelet counts ranged from 20,000 to 1,00,000 and their distribution was as follows

Platelet	Number	%
20,000 – 40,000	23	38
40,001 – 60,000	4	7
60,001 – 80,000	19	32
80,001 – 1,00,000	14	23
(TABLE 5)	n =60	100%

CLINICAL CORRELATIOIN OF HEMOGRAM DATA

Though all the patients had pallor of mucous membrane on clinical examination and hemoglobin was in the anemic range, only 52 patients (87%) had fatigue and shortness of breath.

Fever was present in 45 in patients (75%) and the commonest cause was infection. In all cases it could not be correlated with neutropenia.

	Number
Fever	45
Neutropenia	46
Fever with Neutropenia	35
Fever without Neutropenia	10
Neutropenia without fever	11

(TABLE 6)

10 patients had fever though there was no neutropenia. Neutrophil dysfunction could be a contributing cause. 11 patients had neutropenia but did not have fever.

Bleeding manifestations were present in 24 patients (40%)

Platelet Count	Number of patients with bleeding manifestation
20,000 – 40,000	18
40,000 – 60,000	1
60,000 – 80,000	5
(TABLE 7)	n =24

18 patients developed bleeding manifestations when platelet counts dropped below 40,000. Five patients with Megaloblastic marrow developed bleeding manifestations with a platelet count of 60,000, which can be explained by functional platelet dysfunction which has been known to occur in megaloblastic anemia[5].

HEPATOMEGALY:

Of the 34 (57%) patients who had hepatomegaly, 18 belonged to the Megaloblastic group. Leukemias and Lymphomas accounted for 8 cases and 4 cases respectively.

Hepatomegaly (n = 34)
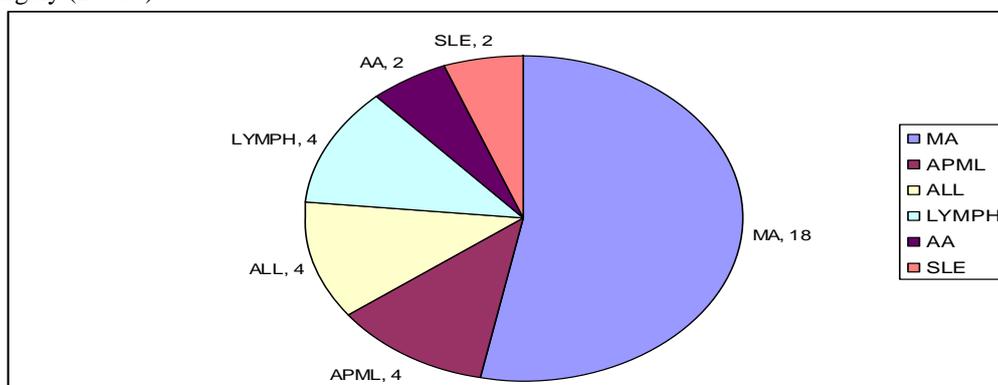
(FIGURE 6)

SPLENOMEGALY:

The spleen was palpably enlarged in 36 cases of which majority belonged to Megaloblastic Anemia (20 cases). Acute Promyelocytic Leukemia and Lymphomas accounted for 4 each and Acute Lymphoblastic Leukemia, Hypersplenism, SLE, Aplastic Anemia accounted for 2 each.

Splenomegaly (n = 36)
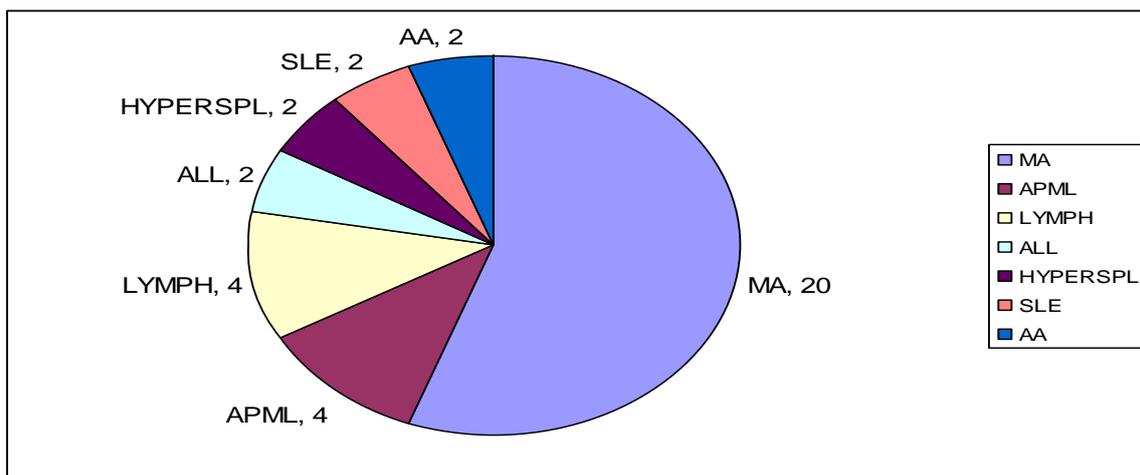
(FIGURE 7)

Lymphadenopathy was present in 12 cases out of which 8 cases were Hematological malignancies and 4 belonged to Aplastic Anemia, suggesting infection as an underlying cause for the enlarged nodes in these 4 patients.

BONE MARROW DIAGNOSES
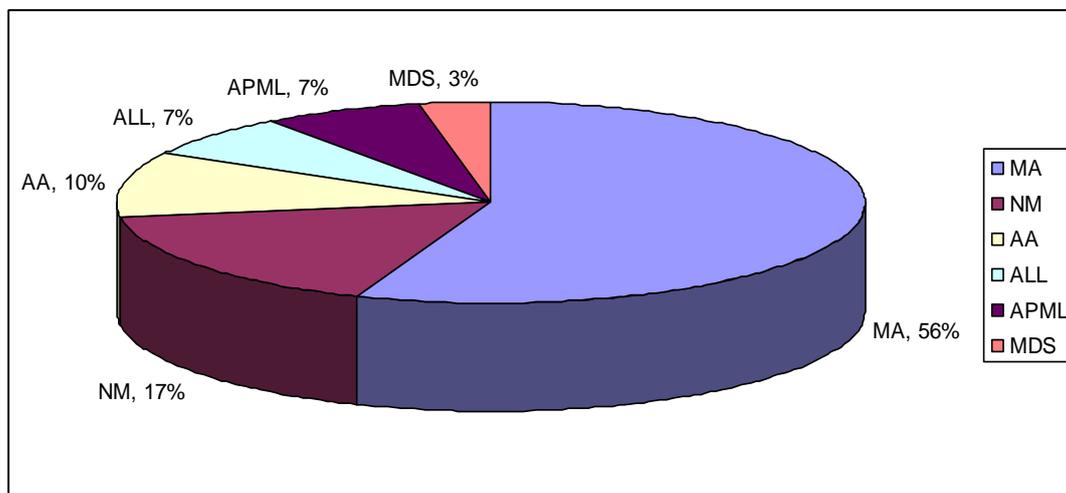
(FIGURE 8)

MA   =   Megaloblastic Anemia (32/58) = 55%
NM   =   Normoblastic Marrow   17%
AA   =   Aplastic Anemia   10%
ALL   =   Acute Lymphoblastic leukemia   7%
APML =   Acute Promyelocytic Leukemia   7%
MDS   =   Myelodysplastic Syndrome   4%

Bone marrow aspiration was performed in 60 cases and it yielded diagnostic material in 58 cases. 2 cases resulted in a dry tap. In 1 case of Hodgkins disease with Pancytopenia diagnosis was arrived at by a Lymph node biopsy. Similarly in a patient with Myelofibrosis there was a dry tap on bone marrow aspiration, so diagnosis was done on the basis of Trephine biopsy which revealed a grade three Myelofibrosis.

ANALYSIS OF BONE MARROW CHANGES:
CELLULARITY
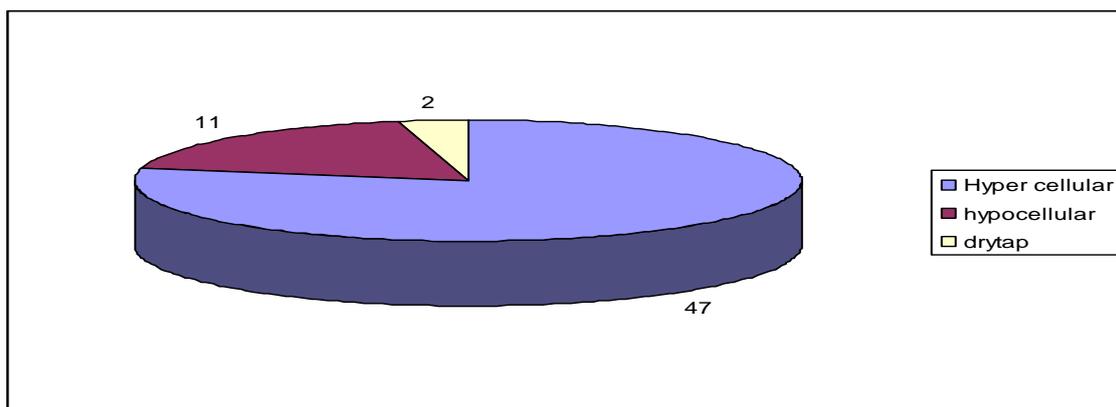
(FIGURE 9)

ERYTHROPOIESIS
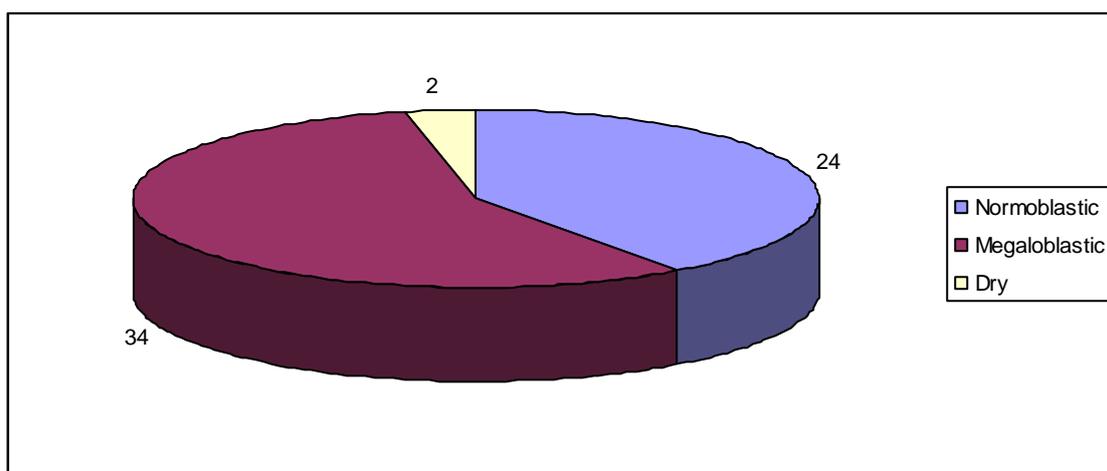
(FIGURE 10)

As shown in Figure 7 and 8, of the 58 of successful bone marrow aspirations 34 are Megaloblastic erythropoietic marrow. Of these 34 ,32 are Megaloblastic anemias and rest of the two are due to Myelodysplastic Syndrome showed the typical Megaloblastoid change with Micromegakaryocytes change which are characteristic of this condition. Two cases are dry tap. 47 bone marrow aspirations revealed celluar marrow and 11 cases are hypocelluar.

Of the 24 cases of normoblastic erythropoietic marrow, 11 were of Acute Leukemias (ALL – 4 cases, Acute Promyelocytic Leukemia – 4 cases Hodgkins lymphoma 1,NHL/TB 1) and 6 were of Aplastic Anemia in whom the cellularity was markedly decreased. Hypersplenism, Hemophagocytic syndrome, SLE and Septicemia accounted for two cases each. Among two cases of sepsis, one is due to Peritonitis and another is due to Salmonella sepsis.

One female patient with pancytopenia and a normoblastic marrow remained undiagnosed for 6 months and was maintained on multiple blood transfusion. A Splenic aspiration revealed infiltration with lymphocytes suggestive of Non Hodgkins Lymphoma. She underwent laparatomy for suspected primary splenic lymphoma and splenectomy. At operation the abdominal viscera were studded with miliary nodules. Splenetomy was carried out and a liver biopsy done. Both revealed caseating granulomas. She was started on anti-TB drugs but returned 6 months later with generalised lymphadenopathy and a biopsy revealed Non Hodgkins Lymphona. She expired in the post operative period. A diagnosis of visceral TB and Non Hodgkins Lymphoma was made.

IV. Discussion

After evaluating 60 patients with Pancytopenia, Nutritional Megaloblastic Anemia was found to be the most common cause (53%), Acute Leukemias accounted for 18% and 10% of the cases had Aplastic Anemia. All other cause were scattered with two cases each and there was one case of Myelofibrosis.

This is in contrast to the study by Imbert et al[6,] where Vitamin deficiencies (specific details not mentioned) accounted for only 7.5% of cases. The radically different dietary habits, and a proportion of strict

vegetarian, explain the discrepancy. This also explains why hematological malignancies (including lymphoid malignancies) were their commonest cause (60%) but second most common cause (18%) in this study. Myelofibrosis constituted 31% in the study by Imbert et al but this study could record one such case. 80% of the patients in this study were below 30 years, during which myelofibrosis is uncommon, its peak incidence being between 40-70 years age.

Results of this study are very similar to the study by Tariq Aziz et al[129] in which megaloblastic anemia is the most common cause(40.9%) followed by Aplastic anemia(31.88%).

V. **Conclusion**

1. Nutritional Megaloblastic Anemia is the commonest cause of Pancytopenia in this study.
2. Acute Leukemias and Aplastic anemia are two other conditions to be considered commonly during evaluation of Pancytopenia.
3. Pallor is the most common clinical feature followed by shortness of breath.
4. Except in megaloblastic anemia, no specific features were found on peripheral smear, to point out to a specific diagnostic, as the cause of pancytopenia.
5. Concurrent Iron deficiency is usually associated, resulting in masking of typical features of Megaloblastic anemia.
6. Macrocytes and hypersegmented neutrophils indicate megaloblastic anemia as the underlying cause of pancytopenia.
7. Bone marrow aspiration is sufficient to diagnose the underlying cause of Pancytopenia Bone marrow biopsy is not routinely necessary.

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