Original Article

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TO STUDY ETIOLOGICAL SPECTRUM OF PANCYTOPENIA BASED ON BONE MARROW EXAMINATION

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ABSTRACT:

Introduction : Pancytopenia is a relatively common hematological entity. It is a feature of many life threatening illness ranging from simple drug induced hypoplasia to megaloblastic anemia to aplastic anemia to leukemia. The severity of pancytopenia and underlying cause determines the management and prognosis.

Aim : To find out causes of pancytopenia. Bone marrow examination was done to find out underlying cause.

Method : It was a prospective study and 100 pancytopenic patients were evaluated by detailed hematological examination comprising complete blood count, peripheral blood smear and bone marrow aspiration in pathology deptt of SRMS-IMS.

Result : the age of patients ranged from 1 month to 80 yrs. The most common cause of pancytopenia was aplastic anemia (24%) followed by dimorphic anemia (21%) ,Megaloblastic anemia (17%) , Leishmania Donovani bodies (07%), Acute leukemia (06%) , Myelodysplastic anemia (06%) , Infective pathology (05%), Iron deficiency anemia (04%), Multiple myeloma (02%) , Drug induced (02%) , Metastatic (02%), ITP (01%), Hemophagocytic lymphohistiocytosis (1%) and Inconclusive (02%).

Conclusion : The present study concludes that detailed primary hematological investigations along with bone marrow examinations in cytopenic patients and to rule out causes of pancytopenia. These are also helpful in management.

Key words : Bone marrow aspiration, Aplastic anemia, Pancytopenia.

INTRODUCTION:

Sir William Harvey described blood as “The fountain of life and primary seat of the soul. The marrow of our bone is the seedbed of our blood”.(1) Peripheral pancytopenia is reduction in all three major formed elements of blood to levels below their lower normal limits leading simultaneous presence of anemia, leucopenia and thrombocytopenia. Thus, it is not a disease entity by itself, but rather a triad of finding.(2)

It is an uncommon clinical problem encountered in clinical practice and should be suspected on clinical ground when a patient presents with unexplained anemia, prolonged fever and bleeding tendency. The presenting symptoms are usually attributable to anemia, leucopenia or thrombocytopenia. Pancytopenia is a

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striking feature of many serious and life threatening illnesses and may caused by several disorder ranging from simple drug- induced bone marrow hypoplasia and megaloblastic anemia to fatal aplastic anemia and leukemia. The mechanism of development of pancytopenia varies from decrease in hematopoietic cell production as in aplastic anemia, trapping of normal cells in hypertrophied and overacting reticuloendothelial system as in hypersplenism, ineffective hematopoiesis in megaloblastic or replacement by abnormal or malignant tissue in the marrow.[2,3]

Although pancytopenia is a relatively common hematological entity and a serious clinical problem with exhaustive differential diagnosis, there is relatively little discussion on this abnormality in major text books of hematology and internal medicine. [4]

The mechanisms contributing to pancytopenia include, decrease in hematopoietic cell production, marrow replacement by abnormal cells, suppression of marrow growth and differentiation, ineffective hematopoiesis with cell death, defective cell formation, antibody mediated sequestration or destruction of cells in a hypertrophied and overactive reticuloendothelial system[5] .

Bone marrow examinations is now being widely used in the investigation and follow up of many disease processes and sometimes it may be the only mean to diagnose a variety of hematological and non hematological conditions.

A disturbance of each of the principle blood element is reflected much earlier and the changes are more conspicuous in the marrow than the peripheral blood. As the severity of pancytopenia and the underlying pathology determines the management and prognosis of these patients [6], identifying the correct etiopathology with the twin aims of diagnosing the patients with pancytopenia and finding out the common disease entities responsible for pancytopenia.

This study will help to evaluate the various causes of pancytopenia and to correlate the peripheral blood findings with bone marrow aspirate and trephine biopsy whenever possible. There by, it will help in planning the diagnostic and therapeutic to patients with pancytopenia.

Aims and objectives - To find out causes of pancytopenia. Bone marrow examination was done to find out underlying cause.

MATERIALS AND METHODS:

The present prospective study was done on the patients of all age group and both sexes. Case selection was based on clinical features and supported by laboratory evidence, which included lowered value of hemoglobin, lowered value of total leukocytes count and lowered platelets counts which are features of pancytopenia.

All outdoor and indoor patients diagnosed as pancytopenia referred to department of pathology, SHRI RAM MURTI SMARAK INSTITUTE OF MEDICAL SCIENCES, BAREILLY. During the period of two 2014 to 2016 was included.

Inclusion Criteria- Patients who showed peripheral pancytopenia.[5]

Hemoglobin-< 10gm%,

WBC count-<4000 cells/cumm,

Platelet count-<1.4x10^9/cumm]

- Patients who consented for bone marrow aspiration.

Exclusion criteria-

- Patients not diagnosed with pancytopenia on peripheral blood smears.
- Patients presenting with pancytopenia but bone marrow aspiration was not done.

A detailed clinical history was taken and physical examination to be performed in each case. Complete blood count (Hb, TLC, DLC, Platelet count) by automated blood counters, peripheral smear study, reticulocyte count and bone marrow aspiration/ biopsy to be performed in needed cases.

I. Blood sample of patients were obtained by routine phlebotomy procedure.

II. 2ml of EDTA (ethelenediamine tetra-acetic acid) anti coagulated blood was collected and processed through automated hematology analyzer.

III. Blood counts were done by semi automated electronic cell counter (sysmex KX – 21, Transasia Biomedicals) and were again cross checked manually by peripheral smear examinations.

IV. Nine hematological parameters were obtained by coulter, will be noted –

- Hemoglobin,
- Red blood cell count,
- Total leukocyte count,
- Differential count,
- Platelet count,
- Mean corpuscular hemoglobin (MCH),
- Mean corpuscular hemoglobin concentration (MCHC),
- Mean cell volume (MCV),
- Packed cell volume (PCV).

V. In every case both manual as well as coulter review is performed.

VI. Peripheral smear stained by leishman stain and general blood picture was examined in detail.

VII. Buffy coat preparation stained by leishman stain was used whenever the TLC was markedly reduced.

Bone marrow studies using standard methods were done whenever indicated

and possible, avoiding the cases where the cause for pancytopenia was obvious.

All patients underwent a detailed medical history and physical examination followed by blood sampling for the investigations .i.e. complete blood count with peripheral film, erythrocyte sedimentation rate (ESR) , malarial parasites (MP), liver function tests , renal function tests , PT and viral profile (HBsAg, Anti HCV).

RESULTS:

Seven hundred ninety two all outdoor and indoor patients were diagnosed as pancytopenia, out of which 100 patients underwent bone marrow exanimation between September 2014 and May 2016. These constitute the subject of the present study.

Prevalence and Incidence of pancytopenia in the patients attending Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly IPDs and OPDs was 0.0007 and 0.0006 respectively.

Table I. Age wise distribution of Pancytopenia

Age group (years)	Total no. of cases	Percentage
0-10	14	14%
11-20	26	26%
21-30	18	18%
31-40	13	13%
41-50	9	9%
51-60	13	13%
>60	7	7%
TOTAL	100	100%

Most of the patients were in the age group of 11-20 years (26%) and least occurrences was seen in the age group of >60 years (7%).

Table-2 Sex distribution of patients of pancytopenia.

Female	30
Male	70

The sex distribution of pancytopenia showed a male preponderance. The male to female ration was 2.3:1.

Table-3 Different presenting symptoms of pancytopenia

Symptoms	No. of cases	Percentage
Fever	65	43%
Generalized weakness	33	22%
Bleeding	27	18%
Abdominal distension	26	17%

Fever (43%) was commonest symptom in Pancytopenic patients, followed by generalized weakness (22%), bleeding manifestation (18%), and abdominal distension (17%). Most common cause of abdominal distension is hepatosplenomegaly.

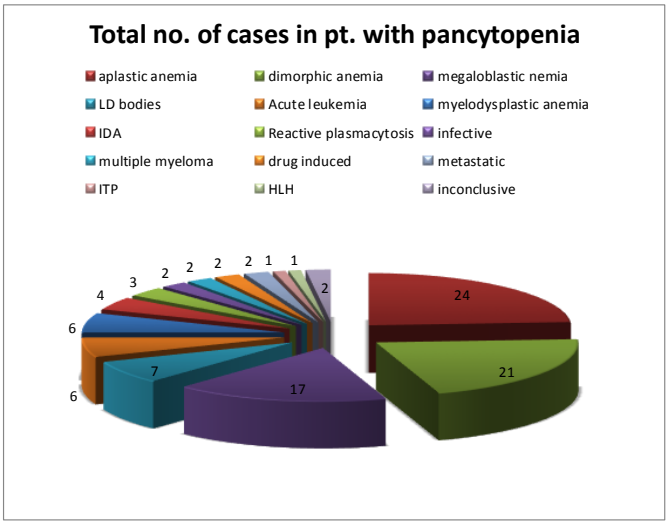

Figure-1 incidence of different causes of pancytopenia

Aplastic anemia was the commonest cause(24%) followed by dimorphic anemia(21%).

PANCYTOPENIA WITH DIFFRERENT MARROW

Table-4 Pancytopenia with different marrow

Etiology	Total no. of cases	Hypercellular		Hypocellular		Normocellular		Hemodiluted	
Megaloblastic anemia	17	15	88%	01	6%	00	00%	01	0 6%
Nutritional anemia	21	15	71%	01	05%	04	19%	01	05%
Acute leukemia	06	04	67%	00	00%	00	00%	02	33%
Myelodysplastic syndrome	06	05	83%	00	00%	00	00%	01	17%
LD bodies	07	04	57%	00	00%	03	43%	00	00%
IDA	04	03	75%	01	25%	00	00%	00	00%
Reactive plasmacytoisis	03	00	00%	02	67%	01	33%	00	00%
Infective	02	01	50%	01	50%	00	00%	00	00%
Multiple myeloma	02	02	100%	00	00%	00	00%	00	00%
Drug induced	02	01	50%	01	50%	00	00%	00	00%
Metastatic	02	01	50%	01	50%	00	00%	00	00%
ITP	01	00	00%	00	00%	01	100%	00	00%
HLH	01	01	100%	00	00%	00	00%	00	00%
Inconclusive	02	00	00%	01	50%	00	00%	01	50%

Hypercellular bone marrow was observed in 53 patients, Normocellular bone marrow was observed in 09 patients, Hemodiluted bone marrow was observed in 08 patients and 03 patients were observed in Hypoplastic bone marrow.

Most common etiology noted was nutritional anemia (27%), followed by megaloblastic anemia (22%), Leishmania Donovani (9%), acute leukemia (8%), Myelodysplastic syndrome (8%), Iron deficiency anemia (5%) other are Reactive plasmacytosis (4%), (3%) Infective, Multiple myeloma, Drug induced, Metastatic and (1%) ITP, HLH (Hemophagocytic lymphohistiocytosis), and (3%) was Inconclusive

DISCUSSION:

In the present study, pancytopenia was due to the following causes.

1. Aplastic anemia
2. Dimorphic anemia
3. Megaloblastic anemia
4. Leishmaniasis Donovani bodies
5. Iron deficiency anemia
6. Reactive plasmacytosis
7. Malignant disease-leukemia
8. Myelodysplastic syndrome
9. Others
    a) Infective
    b) Multiple myeloma
    c) Drug induced
    d) Metastatic
    e) Hemophagocytic Lumphohistiocytosis (HLH)

In the present study, Aplastic anemia (24%) was the commonest cause of pancytopenia, followed by megaloblastic anemia (17%) , dimorphic anemia (21%), LD bodies (07%), iron deficiency anemia (6%), Myelodysplastic anemia (06%), acute leukemia (6%), iron deficiency anemia (04%), others include uncommon cause like Reactive plasmacytosis (3%), infective , multiple myeloma, metastatic, drug induced are (2%),and HLH (1%).

In 1976, the study by Relief FP, Heyns AD [7] revealed that bone marrow failure (67.7%) was the commonest cause of pancytopenia and sever infection (9.7%) was the second common cause.

In 1987, the international agranulocytosis and aplastic anemia study group [5] found aplastic anemia in 52.7% and MDS in 10.5% of patients. Hossain MA et al.[8] . (1992) found aplastic anemia fallowed by chronic malaria and kalaazar to be the commonest cause of pancytopenia.

Verma N,Dash S[4] (1992) found aplastic anemia in 40.6% and megaloblastic anemia in 23.2% of patients. Tilak V, Jain R[9] (1998) found megaloblastic anemia (68%) to be the commonest cause of pancytopenia fallowed by aplastic anemia (7.7%). Savage DG et al.[11] (1999) found megaloblastic anemia to be the commonest cause followed by aplastic anemia. Kumar et al.[12] (1999) found hypoplastic anemia (29.5%) to be the commonest cause fallowed by megaloblastic anemia.

Khodke et al.[2] (2000) observed megaloblastic anemia (44%), followed by hypoplastic anemia (14%) as the common cause of pancytopenia. Naeem Khan et al.[13] (20001) found aplastic anemia (20%) as the commonest of pancytopenia followed by megaloblastic anemia (16.7%).

Osama [14] found megaloblastic anemia (39%) as the commonest cause of pancytopenia fallowed by hypersplenism (19%). Muzzarat Niazi [15] (2004) found aplastic anemia (38.3%) as the commonest anemia (24.7%). Mobina Ahsan Sodhy (2005) found megaloblastic anemia (35.9%) followed by hypersplenism (16.3%) as the commonest cause . Jha A et al.[3] (2008) found hypoplastic bone marrow (29%) followed by megaloblastic anemia (23.64%) as the common causes.

Tariq Ayub et al[16].,(2009) analysis of bone marrow findings showed megaloblastic anemia in (57.5%), bone marrow hypoplasia/ aplasia in (20%) and leukemia in (15%) patients.

Pathak R et al.[17] (2012) found maximum number of cases was seen in age group of 15-30 years. Hypoplastic anemia was the commonest cause followed by hematological malagnancies, megaloblastic anemia (6.8%), leishmaniasis (1.9%) and Gaucher disease (0.9%).

Arvind Jain et al.[18] (2013) observed, the male to female ratio 2.6:1. The majority of cases were encountered in 3rd and 4th decades. Hypersplenism (29.2%), Infection (25.6%), myelosuppressant (16.8%) and megaloblastosis (13.2%) were the four most common causes in this large series on pancytopenia from a single centre in india.

Rajendra Kumar et al77. (2014) observed the M:F ratio was 1.28:1. Most common diseases were megaloblastic anemia (41.81%), dimorphic anemia (16.72%), hypoplsatic anemia (9.09%), ITP (8.36%) and infective pathology (4.72%). Most common presenting symptoms were fever, melena, hematuria and hematemesis. Splenomegaly, hepatomegaly and lymphadenopathy were found in 35.65%, 21.15% and 14.78% of cases respectively.

In the present study, Aplastic anemia (24%) was the commonest cause of pancytopenia fallowed by megaloblastic anemia (17%) and nutritional anemia (21%).

The commonest cause of pancytopenia, reported from various studies throughout the world has been aplastic anemia.

This is in sharp contrast with the result of present study where the commonest cause of pancytopenia was megaloblastic anemia. This seems to reflect the higher prevalence of nutritional anemia in India subjects as well as in developing countries. However similar result has been reported has been in studies from other Indian centers.

Table 5. Causes of pancytopenia in various studies

SI.NO	Study	Country	Year	No.of cases	Common cause	Second M/C cause
1.	Retief FP,Hyens AD	South Africa	1976	195	Bone marrow failure (67.7%)	Severe infection (9.7%)
2.	International agramilocytosis and aplastic anemia	Europe	1987	389	Aplastic anemia (52.7%)	MDS (10.5%)
3	Imbert M et al.	Europe	1989	213	Malignant myeloid disorder (42%)	Malignant lymphoid disorder (18%)
4	Keisn M et al	Sweden	1990	100	Neoplastic disease (32%)	Aplastic anemia (16%)
5	Hossain M et al.	Bangladesh	1992	50	Aplastic anemia	Chronic malaria and kalaazar
6	Varma N, Dash S	India	1992	202	Aplastic anemia (40.6%)	Megaloblastic anemia (22.3%)
7	Tilak V.Jain R	India	1998	77	Megaloblastic anemia (68%)	Aplastic anemia (7.7%)
8	Javage DGet al.	Zimbabwe	1999	134	Megaloblastic anemia	Aplastic anemia
9	Khodke et al.	India	2000	166	Hypoplastic anemia (29.51%)	Megaloblasti-c anemia (22.3%)
10	Naeem Khan M et al.	Pakistan	2001	30	Aplastic anemia (20%)	Megaloblasticanemia(16.7%)
11	Kumar R et al.	India	2001	166	Aplastic anemia(29.5%)	Megaloblastic anemia (22.3%)
12	Osama Ishtiaq et al.	Pakistan	2002	100	Megaloblastic anemia (39%)	Hpersplenism(16.3 %)
13	Mussafrat Niazi et al.	Pakistan	2004	89	Aplastic anemia (38.3%)	Megaloblastic anemia (27.7%)
14	Mobina Ahsam Dodhy et al.	Pakistan	2005	392	Megaloblastic anemia (35.95%)	Hypersplenism (19%)
15	Jhazia Memon et al	Pakistan	2008	230	Aplastic anemia (23.9%)	Megaloblastic anemia (13.04%)
16	Jha et al.	Nepal	2008	148	Hypoplastic anemia (29.5%)	Megaloblastic anemia (23.64%)
17	Tariq Ayub et al	India	2009	40	Megaloblastic anemia (57.5%)	Hypoplasia/ Aplasia (20%)
18	Pathak R et al	Nepal	2012	102	Megaloblastic anemia (6.8%)	Leishmaniasis(1.9%)
19	Arvind Jain et al	India	2013	250	Hypersplenism (29.2%)	Infection (25.6%)
20	Rajendra kumar et al.	India	2014	345	Megaloblastic anemia (41.8%)	Dimorphic anemia (16.72%)
21	Present study	India	2016	100	Aplastic anemia (24%)	Nutritional anemia (21%)

CONCLUSION:

Pancytopenia is a common hematological entity that comes across in routine practice. In the present study, the incidence of pancytopenia on peripheral blood smear is 0.0006 predominantly observed among

younger age group (11-20years) with male predominance.

In present study the main cause of pancytopenia is Aplastic anemia, dimorphic anemia and Megaloblastic anemia. The cause of Aplastic anemia was unknown. Also one case of hemophagocytic lymphohistiocytosis was present in the study.

Aplastic anemia is more common in age group of 11 – 20 yrs with male predominance. While Leishmaniasis Donovani Bodies show maximum prevalence between 21-30 years with M: F ratio 6:1. Uncommon etiological factors like malignant disease, Myelodysplastic anemia; Infective, Iron deficiency anemia, multiple myeloma, metastatic, drug induced and Hemphagocytic lymphohistiocytosis are identified in this study.

A comprehensive clinical, hematological and bone marrow study of patients with pancytopenia usually helps in identification of the underlying cause. However, in view of a wide array of etiological factors,pancytopenia continues to be a challenge for hematologists.

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