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PANCYTOPENIA-Clinico-Hematological Study in a Capital City of Telangana State -India

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Original Research Article

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Abstract: Pancytopenia is the simultaneous presence of anaemia, leucopenia and thrombocytopenia. The etiology ranging from non-neoplastic, neoplastic to fatal leukemias. The management and prognosis depends both on the severity of pancytopenia and on the nature of underlying etiology. Thus identification of cause is the key to appropriate management. To study the clinical presentations, diagnosis and evaluation of various causes of pancytopenia by hematological parameters including bone marrow aspiration. It was prospective study. One hundred and fifty cases of Pancytopenia evaluated clinically with hematological parameters and bone marrow aspiration in a Yashoda hospital, Malakpet, Hyderabad, during period of January 2014 to February 2017. Out of 150 cases, age of patients ranged from 2 to 85 years with a mean age of 43 years. There was male preponderance. Fever and generalized weakness was common clinical presentation. The commonest physical finding was pallor and splenomegaly on systemic examination. The commonest peripheral smear was dimorphic picture & commonest bone marrow finding was hypercellular marrow with megaloblastic erythroid hyperplasia. The commonest cause for pancytopenia was Megaloblastic anemia (34%) followed by Hematolymphoid malignancy (26.6%). This study showed that clinical history, detail primary hematological investigations along with bone marrow aspiration, biopsy imprint in cytopenia patients are helpful to diagnose and to rule out the causes of pancytopenia. Megaloblastic anemia is commonest cause of pancytopenia in most indian and continent studies. Present study also shows increase in incidance of HLH (Hemophagocytic lymphohistiocytosis) and MDS are among emerging causes of pancytopenia and nutritional diet rich in vit B12 and folic acid prevents majority cause of pancytopenia in india.

Keywords: Pancytopenia, anaemia, leucopeni, thrombocytopenia, management.

INTRODUCTION

Pancytopenia is not a disease, but decreased in all three formed elements resulting from number of disease processes primarily or secondarily involving the bone marrow and symptoms attributable to anemia, leucopenia and thrombocytopenia. Pancytopenia therefore exists when hemoglobin level below 13.5g/dl in males or 11.5g/dl in females, Total leucocytes count below 4x10/l and platelet counts below 150x10/l [1, 2].

The etiology of pancytopenia varies in different states of Indian populations depending on the differences in age patterns, nutritional status, climate and the prevalence of infections [3]. As the severity of pancytopenia and the underlying pathology determines the management and prognosis of these patients, identifying the correct etiopathology in a given case is crucial and helps in implementing timely and appropriate treatment [4].

The present study was done to find the common causes of pancytopenia, its clinical presentation & utility of bone marrow examination in different causes of pancytopenia in order to help the management of patients with pancytopenia attending in our hospital.

SUBJECTS AND METHODS

This is a prospective study conducted by hematopatholgy section, Department of Laboratory medicine, Yashoda hospital hyderabad which includes patient attending OP and admitted inpatient and diagnosed as pancytopenia during year January 2014 to February 2017. Patients of all ages and both the sexes were included. Patients with Hb <10 gm/dl, WBC <4000/cumm³, platelets<1,50, 000/cumm³ were

included. Among exclusion criterias, patient who have recevied or receiving chemotherapy and radiotherapy and post-transplant patient on immuno-suppressive treatment. Clinical profile includes detailed history, clinical examination and haematological parameters at presentation. Haematological profile included hemogram, peripheral blood smear morphology and bone marrow aspiration/ biopsy imprint morphology/biopsy. Blood samples of patient were obtained by routine phlebotomy procedure. 3.0 ml EDTA (K2E 5.4 mg Ethylene diamine tetra acetic acid) Vacutainer (13x75mm) anticoagulated blood was collected by needle holder and processed through Automated Hematology analyser (Beckman-Coulter LH-750). 11Hematological parameters were consider as hemoglobin, packed cell volume, Red blood cell count, RBCs indices (MCV.MCH &MCHC), total WBCs count, Differential count, platelet counts and MPV.

A total of 150 patients who fulfilled the criteria for pancytopenia were taken up for the study. All the 150 cases were subjected to bone marrow aspiration examination after obtaining written consent from patient or guardian. Bone marrow aspiration done by Salahs needle no [16]. From Posterior superior iliac spine or sternum and 0.3ml sample collected for morphology and 1.5 ml in EDTA and 1.5 ml in Heparin vacutainer. Leishman stain and Giemsa stains performed on aspirated sample cytosmears. Disposable Jamshidi needle (11 GX100mm) was used for bone marrow biopsy. Bone marrow trephine biopsy was done from right posterior superior iliac spine. Whenever there is a scanty particulate marrow, blood tap or dry tap on aspiration. 1.5 to 2.0 cm long bone marrow biopsy core specimen was obtained and imprint and squash smears made and stained with leishman and giemsa stain before it fixed in fixative. Biopsy specimen was decalcified processed and sections were stained with Hematoxylene and Eosin (H&E) stain.

RESULTS

This study was carried out for 38 months in Hematopathology section, Department of laboratory medicine. A total of average 65,750 were received for Haemogram during each year. Out of these, 150 cases met inclusion criteria and bone marrow aspiration done in all cases. There were 91 males and 59 females. The mean age was 43 years with the range of 2 to 85 years. Most common affected age group was 51 to 65 years, followed by 36-50 years, 21-35 years, 02-20 years and least was more than 65 years age group (Chart 1). Male patients are predominance in almost all age groups except age group of 02-20 years were female patient found to have more pancytopenia cases.

The main chief complaints were fever, generalized weakness and loss of appetite. Among general examination pallor noted almost in all cases.

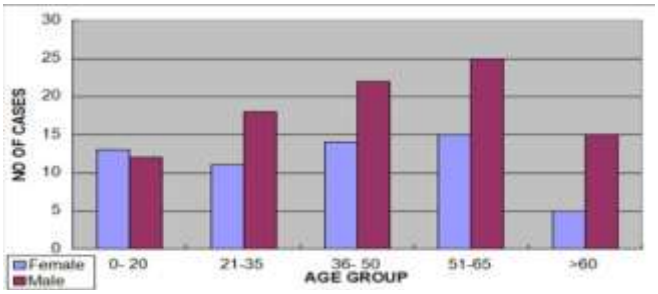

Chart-1: Age groups

Table-1: Chief complaints and Physical findings in 150 cases

S.No	Chief complaints and Physical Findings	No. Case	%
1	Fever	103	68.6
2	Generalised Weakness	81	54
3	Shortness of breath	37	24.66
4	Headache	15	10
5	Giddiness	11	7.33
6	Blurring of Vision	03	2
7	Loss of weight	12	8
8	Loss of Apetite	41	27.33
9	Body pain	21	14
10	Cough	25	16.66
11	Bleeding Manifestation	12	8.0
12	Vomittings	18	5.33
13	Loose Motion	07	4.66
14	Pallor	150	100
15	Jaundice	16	10.66
16	Lymphadenopathy	07	4.66
17	Oedema over feet	08	5.33
18	Hepatomegaly	23	10.66
19	Splenomegaly	55	36.66

Splenomegaly was more commonly seen than hepatomegaly (Table 1).

Hematological parameters as automated hematology analyzer sub grouped in to mild, moderate and severe form are shown in (Table: 2).

Table-2: Grading of formed element

Parameters	Range	Cases	%
Hemoglobin			
Severe	21 to 5.5 gm%	43	28.7%
Moderate	5.6 to 8.0 gm%	65	43.3%
Mild	8.1 to 10 gm%	42	28%
White blood cells	(WBCs)		
Severe	100 to 1000/cumm	15	10%
Moderate	1100 to 2500/cumm	68	45.3%
Mild	2600to 4000/cumm	67	44.7%
Platelets			
Severe	Less than30000/cumm	44	29.3%
Moderate	31000 to 80000/cumm	68	45.3%
Mild	81000 to 140000/cumm	38	25.4%

The most common peripheral blood RBCs picture was Dimorhic picture (28%). Hyper segmented neutrophils seen in 95% cases in megaloblastic anemia and 05% in mixed deficiency cases. Leucopenia and thrombocytopenia were seen in all cases.

Out of 150 cases of pancytopenia .the most common cause was Megaloblastic anemia (34%) (Table: 3).

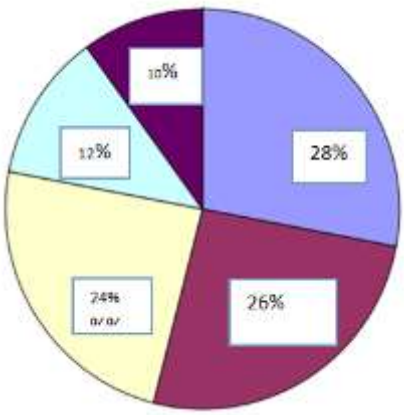

Chart 2
Dimorphic RBCs28%
Normocytic Normochromic RBCs26%
Macrocytic RBCs24%
Normocytic Hypochromic RBCs12%
Microcytic Hypochromic RBCs10%

Table-3: Distribution of Different etiology of Pancytopenia among 150 cases

Sr.no	Etiology	Number of cases	Percentage %	M	F	M:F
1	Megaloblastic anemia	51	34	34	17	2:1
2	Acute leukemia	21	14	09	12	0.7:1
3	Lymphoproliferative disorder	12	08	07	04	1.7:1
4	Myelodysplastic syndrome (MDS)	07	4.66	05	02	2.5:1
5	Aplastic anemia	17	11.33	14	03	4.6:1
6	Hypersplenism	13	8.66	04	09	0.4:1
7	Plasma cell dyscrasia	05	3.33	03	02	1.5:1
8	Hemophagocytic lymphohistiocytosis(HLH)	04	2.66	03	01	3:1
9	Disseminated Tuberculosis	03	2	01	02	0.5:1
10	Disseminated carcinomas	02	1.33	01	01	1:1
11	Mixed deficincy anemia	06	4.0	04	02	2:1
12	Hemolytic anemias	03	2	03	00	3:0
13	Sepsis	04	2.66	01	03	0.3:1
14	SLE	01	0.66	01	00	1:0
15	Drug induced	01	0.66	01	00	1:0

Megaloblastic anemia found in 51 cases with male predominance. Hemogram RBCs indices in megaloblastic anemia show average MCV 105fl (76-94fl) and MCH was 35pg (27-32 pg). Vitamin B12 deficiency alone more pronounced 78%, folic acid deficiency 04% and 18% cases in mixed deficiency. Hyper segmented neutrophils and macrovalocytes (Figure 1a) are predominant peripheral smear picture. Bone marrow aspirate mostly hyper cellular with increased erythroid: myeloid ratio. Megaloblasts (Figure 1b; red arrow) are large with sieve like nuclear chromatin, bluish cytoplasm. Giant metamyelocytes and stab forms (Figure 1b; blue arrow) commonly associated finding in aspirate smears.

Among Hematolymphoid malignancy, acute promyelocytic leukemia and acute monoblasic leukemia (figure 2) commonly encountered. Diluted marrow seen in acute lymphoblastic leukemia and imprint biopsy smears helps in early morphological diagnosis of leukemia. Erythroid and megakaryocytic series reduced in majority of cases of hematolymphoid malignancy.

Aplastic anemia commonly encountered in male and Bone marrow biopsy performed in all cases. Reactive lymphoplasmacytosis seen with increased fat spaces (figure3). Hypersplenism surprisengly found more in female. Significant Rouleaux formation and Erythrocyte sedimentation rate with A: G reversal seen in almost all cases (figure 4). Hem phagocytic lymphohistiocytosis (HLH) seen two paediatric age group of 4 and 13years, other two cases at 60 year and 39 year male (figure6). Hepato-splenomegaly, high ferritin, hypertriglyceridemia and increased lactate dehydrogenase seen all cases. Bone marrow granulomas (figure5) of tuberculus origin seen in two cases. Cervical tuberculosis seen in both the cases. Disseminated carcinoma seen in one female patient from carcinoma breast and other male patient had prostatic adenocarcinoma (figure7) deposit. Serum PSA was very high (1650 ng/ml).

We encountered 4 cases of sepsis with female predominance. Neutrophils toxic granules and cytoplasmic vacillations seen in these cases. Plasma procalcitonin level is more than 75 ng/ml on an average. Hemolytic anemia cases show reticulocytosis and positive coombs test. One case diagnosed as Evans syndrome.

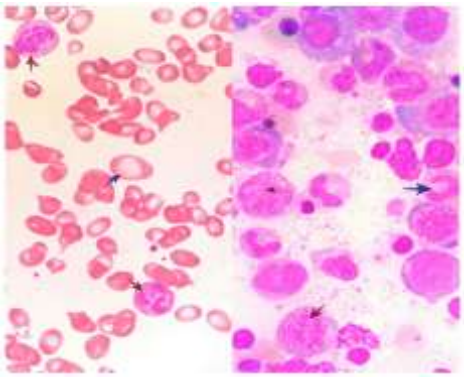

Fig-1: a, bMegaloblastic anemia (PS&BM images)

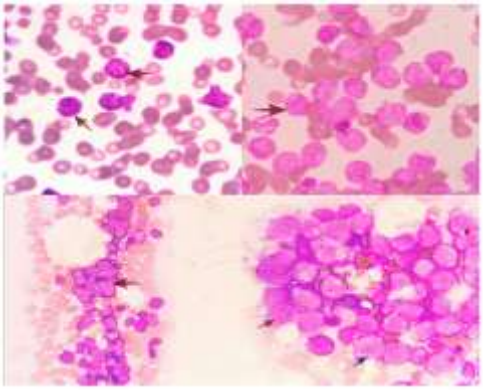

Fig-2: a, b acute leukemia (ALL &AML)

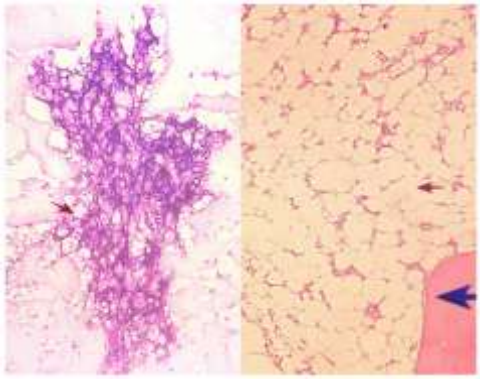

Fig-3: Aplastic anemia (BMaspiration & biopsy)

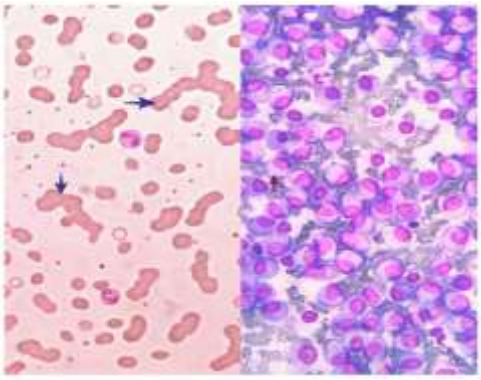

Fig-4: Multiple myeloma (PS& BM)

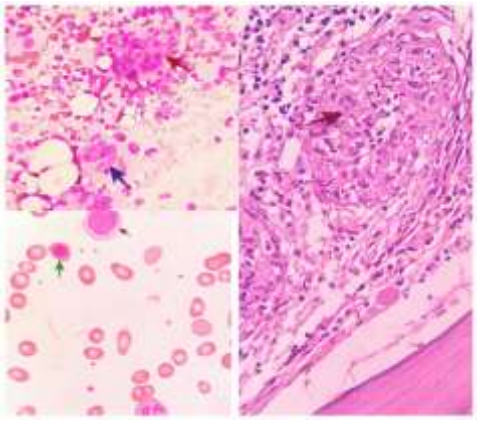

Fig-5: Bone marrow granulomas

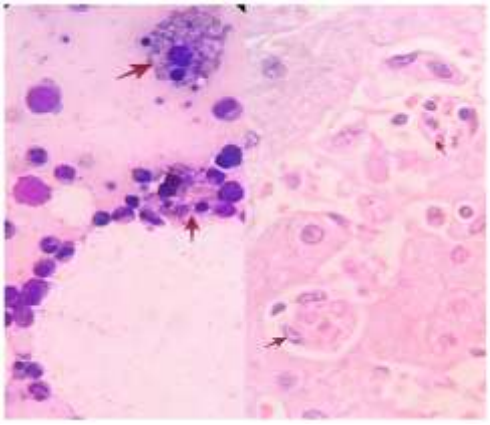

Fig-6: Hemophagocytic lymphohistiocytosis

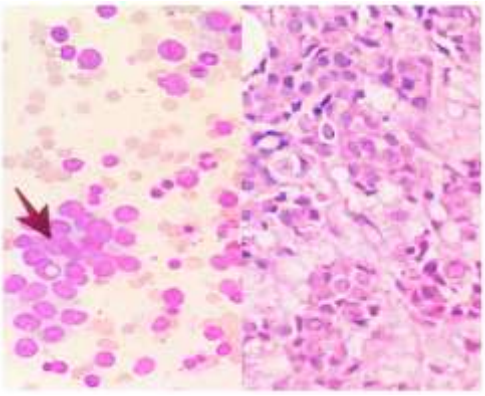

Fig-7: Disseminated carcinomas

Figure 1a: Peripheral smear (Leishman stain 40X) shows Macrovalocytes (blue arrow) & hypersegmented neutrophils (Red Arrow).
Figure 1b: Bone marrow aspirate smear (Giemsa stain 100X) Megaloblast with sieve like chromatin (Red arrow) & Giant stab forms (blue arrow).
Figure 2a: Peripheral smear (Leishman stain 40X) lymphoblast in peripheal smear,2b: lymphoblast in Bipsy imprint,2c: myeloblast in peripheral smear,2d; Atypical promyelocyte with auer rod.
Figure 3a: Bone marrow aspirate smear (Giemsa stain 100X) Increased fat with reactive plasmacytosis; 3b: Bone marrow biopsy (H&E Stain, 40X) increased fat spaces.
Figure 4a: Peripheral smear (Leishman stain 40X) show significant roulaux formation.
Figure 4b: Bone marrow aspirate smear (Giemsa stain 100X) Many plasma cells with eccenteric nuclei.
Figure 5a: (Leishman stain 40X) Bone marrow aspirate granulomas with epitheloid cells. 5b; Peripheral smear (Leishman stain 40X) show leucoerythroblastic picture. 5c; Bone marrow biopsy (H&E Stain, 40X) bone marrow granulomas.
Figure 6a: Bone marrow aspirate smear (Giemsa stain 100X) Hemophagocytes .6b; Bone marrow biopsy (H&E Stain, 40X) hemophagocytosis.
Figure 7a: Bone marrow aspirate smear (Leishman stain 40X) tumour cells in loose cohesive clusters .7bBone marrow biopsy (H&E Stain, 40X) adenocarcinoma cells from prostate.

DISCUSSION

During period of three years and two months, 150 cases of pancytopenia studied.Different etiology of pancytoipenia studied and compared with the national and little international published literature.

The mean age was 43 years in a patients ranged from 2 to 85 years ago with male predominance (60%), female (40%) and male to female ratio (M: F) of 1.5:1. Age and sex distribution was compared with other studies.

Table-4: Age, sex distribution compared to other studies done on pancytopenia

sr.no.	Authours	Country	Year	Number of case	Age ranges	M:F Ratio
1	Khunger *et al*. [4]	India	2002	200	02-70	1.2:1
2	Ashraf *et al.* [5]	Pakistan	2010	150	15-60	1.1:1
3	Gayathri BN *et al.* [6]	India	2011	104	02-80	1.2:1
4	Vandana *et al*.	India	2012	80	01-79	1:1.2
5	Sweta *et al.* [7]	India	2014	100	05-80	1.5:1
6	Present study	India	2017	150	02-85	1.5:1

Fever was the most common presenting complaint in our study (68.6%) followed by Generalized weakness (54%). The most common physical finding was pallor (100%), followed by splenomegaly (36%).Peripheral blood smear picture RBCs morphology Macrocytic and dimorphic together constitute 50%, follwed by Normocytic normochromic RBCs (28%),Normocytic hypochromic RBCs(12%) & microcytic hypochromic (10%). Leucoerythroblastic picture seen (12.6%) with dimorphic picture and commonly associated with megaloblastic anemia and infiltrative neoplastic lesion.

WBCs differential count lymphocyte predominance noted in 65%of hypoplastic anemia in our study compared to 50% in Tilak *et al*. [11], 51.3% in Gaythri & Rao *et al*. [6] and 85% in Khunger JM *et al.* [4] study. Hypersegmented neutrophils seen in seen in 90% of cases which was highest compared to 84.9% in Tilak V *et al*.[11] Study,51.3% in Gayathri *et al.* [6]. Platelet anisocytosis, large and giant platelets more pronounced in Myelodysplastic syndrome followed by megaloblastic anemia.

The commonest cause of pancytopenia reported in our study was megaloblastic anemia, similar to other studies conducted in asian countries .While commonest cause of pancytopenia in various studies throughout world has been aplastic anemia. In our study aplastic anemia was fifth common cause of pancytopenia.

All indian studies suggest more incidance of megaloblastic anemia among all etiology of pancytopenia. Incidance of megaloblastic anemia in our study was 34%, incidance of 74% in Gayathri & Rao *et al*. 72% was reported by Khunger JM *et al*. [4], 68% by Tilak *et al*. [11]. All these indian studies highlights higher prevalance of nutritional anemia in indians. Although Histogram RBCs Indices (MCV, MCH) & Peripheral smear examinations are more informative. Bone marrow aspiration performed to rule out possibility of marrow dysplasia. In our study serum Vitamin B12 and folic acid estimation done in those cases who are not treated with injectable or oral supplement before admission. Vitamin B12 deficiency found in 86.1% & folic acid 14% cases.

Table-5: Major causes of pancytopenia compare to other studies

Studies	Country	Year of study	Number of cases	Commonest cause	Second commonest cause
Keisu and Ost [8]	Israel & Europe	1990	100	Neoplastic disease radiation (32%)	Hypoplastic anemia (19%)
Hossain *et al*. [9]	Bangladesh	1992	50	Hypoplastic anemia	Chronic malaria and kalazar
Jha *et al.* [10]	Nepal	2005	148	Hypoplastic anemia (29%)	Megaloblastic anemia (23%)
Ashraf S *et al*. [5]	Pakistan	2010	150	Hypersplenism (68%)	Megaloblastic anemia (25.4%)
Tilak & Jain *et al*. [11]	India	1999	77	Megaloblastic anemia (68%)	Hypoplastic anemia (7.7%)
Kumar *et al*. [3]	India	2001	166	Aplastic anemia (29.5%)	Megaloblastic anemia (22.3%)
Gayathri BN *et al*. [6]	India	2011	104	Megaloblastic anemia (74%)	Aplastic anemia (18.3%)
Vandana R *et al.*	India	2012	80	Megaloblastic anemia (41.2%)	Dimorphic anemia (8.7%)
Sweta *et al.* [7]	India	2014	100	Megaloblastic anemia (66%)	Aplastic anemia (18%)
Vaddati T *et al*. [12]	India	2015	75	Megaloblastic anemia (56%)	Aplastic anemia (13.3%)
Present study	India	2017	150	Megaloblastic anemia (34%)	Hemato-lymphod malignancy (26.6%)

We encountred 26.6 % of hematolymphoid malignacy presenting as pancytopenia.Out of which 14% was acute leukemia, 08% of lymphoproliferative disorder and 4.6% of myelodysplastic syndrome. Incidence reported by Khunger JM *et al*. [4] (5%), 12 % Reported by Kumar *et al*. [3] and 3.85% by Gayathri and rao *et al*. [6]. Dry tap diluted marrow encountered in 20% cases. Bone marrow biopsy imprint smears play crucial role in early diagnosis especially in diluted and dry tap marrow. The diagnosis further confirmed on flow cytometry immune phenotyping and molecular study.

The incidence of Hypoplastic marrow in our study was 11.3% which very close to studies done by khunger *et al*. [4] (14%).While higher incidance reported by Kumar *et al*. (29.5%) [3]. Bone marrow biopsy done almost all cases of hypoplastic marrow. The cause of hypoplastic was idiopathic in 90% of cases. Methotrexate induced hypoplastic marrow seen in three cases.

Plasma cell dyscrasia constituting 3.33% compared to 4% reported by Khodke *et al*.1.3% by Tilak *et al*. [11] and Khunger *et al*. [4] who have reported an incidance of 1% in their studies. All cases show significant rouleaux formation on peripheral blood film and average ESR of 100 mm at the end of one hr by Westergrens method. Biochemical serum protein show A: G reversal seen in almost all cases with normal alkaline phosphatase levels.

We encountered four cases of Hemophagocytic lymphohistiocytosis (HLH).Two cases related to tuberculosis and other two was idiopathic.Major and monor criteria were considered for final diagnosis of HLH and. 50 % Mortality seen in our HLH.

Disseminated Tuberculosis and Disseminated carcinomas share incidance 2.0% and 1.33% respectively. Leucoerythroblastic picture seen in one case each. Prostate carcinoma infiltration observed in one case and breast carcinoma in other case of disseminated carcinomas and confirmed with bone marrow biopsy immunohistochemistry. Disseminated carcinoma was not found in other studies done by Khunger *et a*. [4], Khodke *et al.* Tilak *et al*. [11] and Gayathri & Rao *et al*. [6] Kumar *et al.* [3] reported 2 cases of marrow metastasis in his studies. Hemolytic anemia and sepsis share around 2% incidance while SLE was rare cause of pancytopenia in our studies.

The cause of pancytopenia was treatable in almost all cases of megaloblastic anemia. Mortality found in case of hematolymphoid malignancy, HLH and severe aplastic anemia, due to overwhelming infections.

CONCLUSION

Pancytopenia is not a disease entity. Prolonged fever, generalized weakness, prolonged anemia and tendency to bleed could be suspected for pancytopenia on clinical ground Megaloblastic anemia was the most common cause of pancytopenia, correlating with other studies done in India. Incidence of HLH and MDS emerging etiology compare to other studies. Haemogram with RBCs indices, Peripheral blood smear morphology, Bone marrow aspiration cytology and biopsy imprint smears morphology would be helpful in early identification and early intervention of patient with pancytopenia which helps in understanding disease process and early planning for further investigations for accurate diagnosis and management,to enhance survival rate in case of pancytopenia.

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