VOLUME-8, ISSUE-11, NOVEMBER-2019 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

General Medicine

TO ASSESS THE FREQUENCY OF ETIOLOGICAL CAUSES OF PANCYTOPENIA IN NORTH COASTAL ANDHRA PRADESH.

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KEYWORDS :

AIM OF THE STUDY:

To assess the frequency of etiological causes of pancytopenia in North Coastal Andhra Pradesh.

OBJECTIVE OF THE STUDY :

1. To study the clinical profile of a patient with pancytopenia.
2. To study the incidence of underlying etiology of the pancytopenia by Investigating

- Clinical Features
- Haemogram parameters
- serum ferritin, vitamin B12 levels
- bone marrow aspiration and biopsy

MATERIALS AND METHODS

STUDY DESIGN

This is a prospective descriptive study done in Department of General Medicine King George Hospital from July 2017 to June 2019. All the patients with pancytopenia seen in Haemogram will be evaluated for the cause of Pancytopenia and clinical history, required tests available in our institution will be done as per proforma.

SAMPLE SIZE

Total of 260 cases of pancytopenia as seen in Haemogram are studied. Of which 148 cases had Bone marrow aspiration.

INCLUSION CRITERIA

1) Patients aged >= 16 years of both sexes diagnosed with pancytopenia on Haemogram
2) Haemoglobin levels less than 10 g/dL
3) Total Leukocyte count less than 3.5 x 10^9/L
4) Platelet Count less than 1.0x10^9/L

EXCLUSION CRITERIA

1) Patients aged 15 years and less
2) Diagnosed case of Pancytopenia
3) Patients who received Chemotherapy or Radiotherapy
4) Patients with Recent Viral illness – Dengue fever

OBSERVATIONS AND RESULTS

DEMOGRAPHICS OF THE STUDY POPULATION

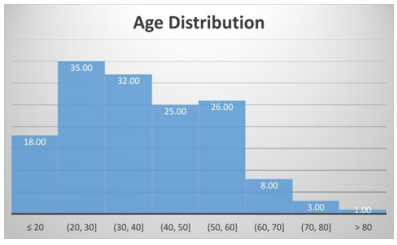
AGE AND SEX:

The age of the study population ranged from 16 years to 85 years with a mean age of 39.8 years and median age of 37 years. Majority of the population belonged to age group of 20 – 30 years

Table 2

Age Group	No. Of Cases
<20	18
20-30	35
31-40	32
41-50	25
51-60	26
61-70	8
71-80	3
>80	1

Figure 4

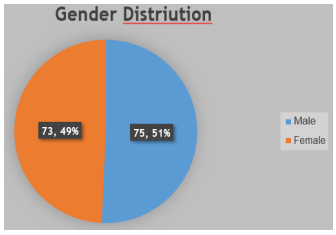


The sex distribution of study population is 75 males and 73 females. There is no significant difference in the distribution of disease in either population.

Table 3

Gender	No. of cases	Percentage
Male	75	51
Female	73	49

Figure 5



Etiological distribution

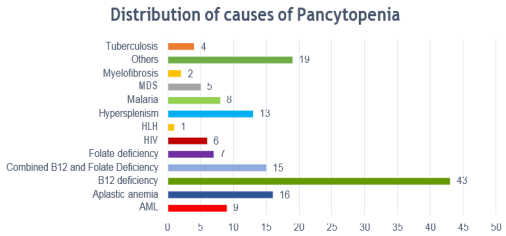
Of the 148 cases of Pancytopenia which underwent Bone marrow examination, 129 cases had a definitive diagnosis. Most of the cases of Pancytopenia are due to Megaloblastic Anaemia followed by Aplastic Anaemia. Other causes included, Malaria, HIV, Tuberculosis, Leukemias, Hypersplenism, Myelodysplasia and Myelofibrosis. A single case of HLH is reported.

Table 4

Diagnosis	No. of cases
AML	9
Aplastic Anaemia	16

Megaloblastic Anaemia	65
HIV	6
HLH	1
Hypersplenism	13
Malaria	8
MDS	5
Myelofibrosis	2
Others	19
Tuberculosis	4
Grand Total	148

Figure 6

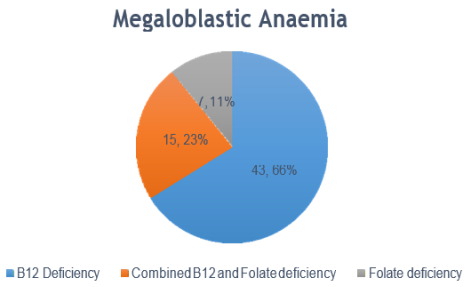


Of the Megaloblastic Anaemia, B12 deficiency is the comm onest and combined folate and B12 deficency is the next common cause.

Table 5

Megaloblastic Anaemia	No. Of cases
B12 Deficiency	43
Combined B12 and Folate deficiency	15
Folate deficiency	7

Figure 7



Mean age of presentation is in the middle aged population. Oldest is seen in AML and youngest is in HIV individuals.

Table 6

Diagnosis	Mean Age of Presentation
AML	50
Aplastic Anaemia	42
Megaloblastic Anaemia	39
HIV	32
Hypersplenism	38
Malaria	37.5
MDS	44
Myelofibrosis	45
Others	32.5
Tuberculosis	40.75

Distribution of gender in various causes of pancytopenia seen in the study

Table 7

Diagnosis	% Male	%Female
AML	55.5	44.5
Aplastic Anaemia	43.75	56.25
HIV	50	50
Hypersplenism	46	54
Malaria	50	50
MDS	40	60
Megaloblastic Anaemia	55.4	44.6
Myelofibrosis	50	50
Others	47.3	52.7
Tuberculosis	25	75

Figure 8

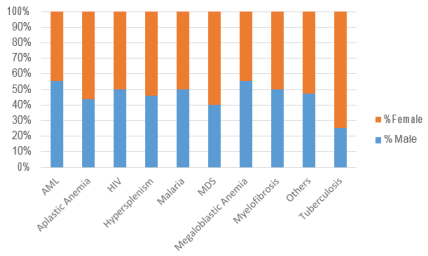


Figure 9

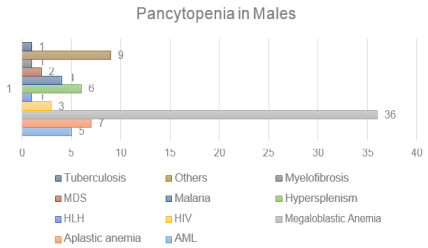
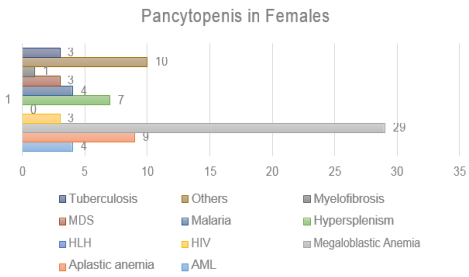


Figure 10



CLINICAL ANALYSIS:-

SYMPTOMS:-

Most of the patients had symptoms like Exertional fatigue, Petechial rash, Bleeding manifestations, Pedal edema, Fever, Frequent respiratory and Skin infections and Bone Pains. Most common symptom being exertional fatigue which is seen in 83.1

% of the cases. Next most common symptom is fever which was seen in 49%.

Table 8

Symptom	Number of patients	Percentage
Fatigue	123	83.1
Fever	73	49.3
Bleeding	35	23.6
Purpuric rash	25	16.8
Bone Pain	13	8.7
Frequent infections	43	29

SIGNS:-

On thorough clinical examination, most commonly seen signs with diagnostic importance are Pallor, Icterus, Lymphad enopathy, Pedal edema, Hepatomegaly, Splenomegaly, Bony tenderness, Hyper pigmented knuckles, melena. Pallor is the most common sign elicited.

Table 9

Sign	Number of Patients	Percentage
Pallor	146	98.6
Lymphadenopathy	24	16.2
Pedal edema	19	12.8
Hepatomegaly	18	12.1
Splenomegaly	35	23.6

Bone pains were seen in 44.4% of AML patients and 40% of Myelodysplastic syndrome which was less than 10% in other causes. Bleeding manifestations were most commonly seen in patients with hypersplenism. Recurrent skin and respiratory tract infections were more common in Aplastic Anaemia, Myelodysplastic syndrome and HIV.

Icterus was most commonly associated with malaria. It was seen in 62.5% of cases. Lymphadenopathy was frequently seen in Tuberculosis and HIV.

Table 10

Symptoms	AML	Aplastic Anaemia	Megaloblastic Anaemia	HIV	Hypersplenism	Malaria	MDS	Myelofibrosis	Others	TB
Total	9	16	65	6	13	8	5	2	20	4
Fatigue	100	81.25	83	100	70	87.5	40	50	90	100
Fever	66.6	43.75	38.5	100	38.5	87.5	60	50	53	75
Bleeding	22.2	25	23	16.6	38.5	25	0	0	21	50
Purpuric rash	11.1	18.75	17	33.3	38.5	12.5	0	0	10.5	0
Bone pains	44.4	6.25	4.6	0	7.6	0	40	0	0	0
Infections	22.2	43.75	29	100	23	0	40	0	15.7	25
Pallor	100	100	98.5	100	92.3	100	100	100	100	100
Icterus	33.3	6.25	23	33.3	46	62.5	20	0	0	25
Lymphadenopathy	22.2	18.75	10.7	50	15	0	0	0	15.8	100
Pedal Edema	33.3	6.25	10.7	16.6	15	12.5	0	0	15.8	25
Hepatomegaly	11	0	13.8	0	38.5	25	0	0	0	0
Splenomegaly	22.2	6.25	18.5	0	100	87.5	0	0	0	0

Figure 11

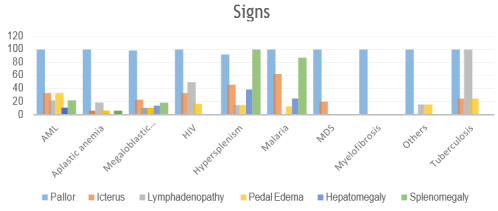
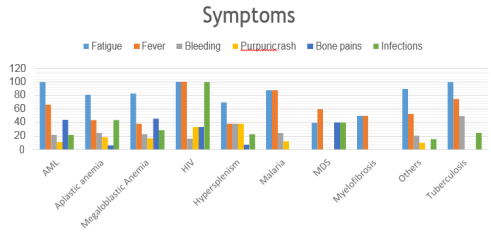


Figure 12



Hematological and Laboratory Findings

For every case of pancytopenia, a Haemogram with peripheral smear along with HIV, Smear for Malarial parasite and Bone marrow aspiration is done. In patients with dry tap, Bone marrow biopsy is done to confirm the cause.

Table 11

Diagnosis	Hb	TC	Platelets	MCV	MCH	MCHC
AML	3.9	2566	26667	90.25	29.7	31.7
Aplastic Anaemia	4.725	2173	32063	95.42	31.12	32.7
Megaloblastic Anaemia	4.5	2438	43100	102.7	29.5	31
HIV	5.25	2572	44500	80	27.8	33.2
Hypersplenism	4.9	2431	42154	81	24	27.6
Malaria	4.78	1910	42375	92	27.5	30.5
MDS	4.76	2128	40200	90.2	29.1	28.7
Myelofibrosis	4.1	1850	26000	99	32.65	32.7
Others	5.2	2714	42579	78	23.6	29
Tuberculosis	4.95	2355	54000	80	25.7	29.5

Table 12

Diagnosis	B12	Folate	Ferritin
AML	432	18	60
Aplastic Anaemia	307	18	50
Megaloblastic Anaemia	145	8.9	37
HIV	672	7.1	64.7
Hypersplenism	736	14.3	37.46
Malaria	690	14.5	56.25
MDS	449	10.4	53.6
Myelofibrosis	287	19	93
Others	420	11.7	52.9
Tuberculosis	340	10.75	22.75

Table 13

Megaloblastic Anaemia	MCV	B12 levels	Folate levels	Ferritin
B12 deficiency	102	110	13	42
Folate deficiency	110	458	0.63	34
Combine B12 and Folate Deficiency	100.5	100	0.97	25

Most of the peripheral smear findings of RBC were dimorphic followed by microcytic RBC.

Table 14

Peripheral smear finding	No. of cases
Normocytic	20
Microcytic	41
Macrocytic	16
Dimorphic	71

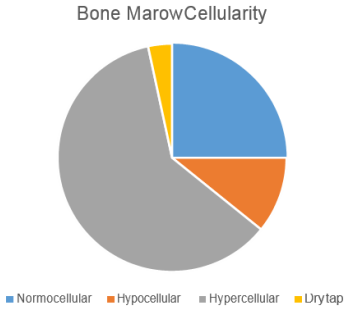
Bone marrow cellularity showed hypercellular marrow in most of the aspiration findings. The next common is normocellular marrow. 5 of the cases had drytap for which Bone marrow biopsy was done as part of further evaluation.

Table 15

Bone marrow Cellularity	No. of cases
Normocellular	37

Hypocellular	16
Hypercellular	90
Dry tap	5

Figure 13



DISCUSSION

Frequency of etiologies of pancytopenia varied in different population groups. This can be attributed to multiple factors such as diagnostic criteria, geographical distribution, follow up, genetic factors, infectious diseases in that particular area and exposure to drugs. Definition of pancytopenia itself is very vague as the cut-off values varied in various institutions. In our study male and female distribution is more or less similar in frequency and etiological causes. Total of 148 cases (n=148) were studied. All the cases fit the criteria taken into the study. Haemoglobin<10g%, WBC Total Count<4000/cu-mm, Platelets < 100,000/cu-mm. Haemogram, Peripheral smear, Bone marrow examination, B12 levels, Folate levels, Smear for malarial parasite, HIV, Ultrasound examination were done apart from thorough history taking and clinical examination. Most common age of presentation is the third decade (35 cases) which correlated with other studies like Arvind Jain et al[38], Khunger et al[39] and Khodke et al[40].Male female ratio in the present study is 1.03 which is concordant with some of the indian studies.

Table 16

Study	Male:Female Ratio
Kumar et al41	2.1
Khunger et al39	1.2
Santra G et al42	1.5
Gayathri B N et al43	1.2
Vandana et al44	0.83
Present study	1.03

In our study most common cause for pancytopenia is Megaloblastic Anaemia with 65 cases (43.9%) The next common causes were Aplastic Anaemia with 16 cases (10.8%) and Hypersplenism with 13 cases (8.7%). 19 cases (12.83%) in our study couldn't be attributed to any cause due to lack of further diagnostic modalities.

Megaloblastic Anaemia is the most common cause of pancytopenia in our study. It is seen in 43.9% of the cases. This is in concordance with studies of Khodke et al, Khunger et al, Tilak et al, Premkumar M et al, and Gayathri et al. Whereas in studies of Varma *et al*, Kumar et al, Santra et al Aplastic Anaemia is the most common cause.Zhou RH et al. stated that biopsy specimen will be more informative than an aspiration cytology regarding marrow cellularity, infiltration, residual hemopoietic cells, qualitative and quantitative abnormalities of megakaryocytes showing myelodysplastic features in AML cases.

Table 17

Study	Country	No. of cases	Most common cause	2nd most common cause
International agranulocytosis and aplastic Anaemia study group[48]	Israel &Europe 1987	319	Aplastic Anaemia (52.7%)	MDS(4.5%)
Keisu and Ost[49]	Israel and Europe 1990	100	Neoplastic disease, Radiation (32%)	Aplastic anaemia(19%
Khodke et al[40].	India 2000	50	Megaloblastic Anaemia (44%)	Aplastic anaemia (14)
Kumar et al[41]	India 2001	166	Aplastic Anaemia (29.51)	Megaloblastic anaemia (23%)
Khunger et al[39]	India 2002		Megaloblastic Anaemia (72%)	Aplastic Anaemia(23%)
Premkumar[62]	India 2008	140	Megaloblastic Anaemia (60.7%)	Leukemia (9%) Aplastic anaemia (8%)
Santra et al[42]	India 2010	111	Aplastic Anaemia (22%)	Hypersplenism (11%)
Gayatri et al[43]	India 2011	104	Megaloblastic Anaemia (71.04)	Aplastic anaemia(18.26)
Rashmi Kushwaha et al[50]	India 2012	60	Aplastic Anaemia (38.3)	Megaloblastic anamia (21.7%)
Sweta et al[51]	India 2014	100	Megaloblastic Anaemia (66%)	Aplastic Anaemia (18%)
Tejaswini et al[52]	India 2015	75	Megaloblastic Anaemia (56%)	Aplastic Anaemia (13.3%)
Present study	India 2018	148	Megaloblastic Anaemia (43.7%)	Aplastic Anaemia (10.8%)

Most common Symptom seen in present study is fatigue (83.1%), followed by fever(49.3%). Most common sign is pallor(98.6%) followed by splenomegaly(23.6%).

Tejaswini et al52 had fever as the most common symptom which is seen in 30.66%of cases whereas sithwath hyat et al study showed fatigue (97.64%) as the most common symptom and pallor(97.64%) as the most common sign which correlated with the present study.

Gupta et al had fever as the most common symptom which was seen in 64.28% fatigue was seen in only 34.28%.

Table 18

Clinical feature	Tejaswini et al[52]	Sitwat hayt et al[53]	Gupta et al54	Khodke et al[40]	Present study
Fatigue	28%	97.64%	34.28%		83.1%
Fever	30.66%	52.94%	64.28%		49.3%
Bleeding	8%	50.58%	34.28%	28%	23.6%
Bone pains		44.7%	41.42%	2%	8.7%
Splenomegaly	37.33%	55.29%		40%	23.6%
Pallor	25.3%	97.64%		100%	98.6%
icterus	2.66%	8.23%			23%

lymphadenopathy	1.3%	12.94%		12%	16.2%

Haemoglobin percentage varied from 2 to 8g%. Lowest Haemoglobin was recorded in a case of Megaloblastic Anaemia. Total Leukocyte count was in a range of 500 to 3800 /cu-mm with maximum cases falling in the range of 1500 – 2500 /cu-mm. Platelet counts ranged from 10,000 to 1 lakh /cu-mm with most number of cases between 20,000 and 30,000 / cu-mm. The predominant peripheral smear picture was dimorphic Anaemia seen in 47.97% of cases and followed by Microcytic picture in 27.7%. 13.5% cases had Normocytic picture and 10.8% had macrocytic picture in peripheral smear. Gupta et al found dimorphic Anaemia in 35.7% cases, Normocytic picture in 34% cases, Microcytic in 28.57% and macrocytic in 1.43%.

Most commonly seen bone marrow aspiration picture in the present study is Hypercellularity with megaloblastic picture. Gupta et al had hypocelularity as the most common finding. Swapna Kumari et al had Hyper cellularity as the most common finding in the study.

Table 19

Cellularity	Gupta et al54.	Swapna Kumari et al55.	Present study
Hypocellularity	44%	6.25	11.18
Normocellularity	12%	37.5	25.8
Hypercellularity	28%	56.25	62.93

Megaloblastic Anaemia is the most Common cause (43.9%) of Pancytopenia observed in the present study. Megaloblastic Anaemia is predominantly due to B12 deficiency. Combined B12 and Folate deficiency is the next common cause. Of the 65 cases 43 cases can be attributed to B12 deficiency alone. This accounts for 66% of Megaloblastic Anaemia cases. 7 cases are due to Folate deficiency alone, which is 11%. 15 cases (23%) are due to combined deficiency of folate and B12. The diagnosis of cause for megaloblastic Anaemia is made by sending serum B12 levels and Folate levels. B12 levels

$<$200ng/ml and Folate levels $<$ 5ng/ml are taken as deficiency.

Table 20

Vitamin deficiencies	Akinci et al56.	Prem Kumar et al62	Present study
B12 deficiency	58%	91.6%	66%
Folate deficiency	29%	5%	11%
Combined deficiency	12.3%	3.5%	23%

Next common cause for pancytopenia in the present study is Aplastic Anaemia. Pathogenesis of Aplastic Anaemia is not well understood. Autoimmunity targeting the stem cells is thought to be the cause. This aberrant immune response is thought to be due to environmental factors, drugs, Infections and endogenous antigens. In the present study it is reported in 16 cases accounting 10.8%. This correlated with other Indian studies by Tejaswini et al, Gayathri et al, Khunger et al, Khodke et al and Swetha et al. Only few indian studies had Aplastic Anaemia as the most common cause for pancytopenia. This is evidenced in studies by Kumar et al, Rashmi Kushwaha et al, and Santra et al[42]. International agranulocytosis and aplastic Anaemia study group[48] reported aplastic Anaemia(52.7%) as the most common cause of pancytopenia. This study was done in Europe and Israel. Further cause for aplastic Anaemia cannot be investigated in the present study due to lack of resources.

Acute Leukemias were seen in 9 cases (6%) whereas in Khunger *et al*[39] reported an incidence of 5%. Prem kumar *et al*. (9.2%) , BN Gayathri *et al*. (3.85%) , compared to Kumar *et al*.(12%). In our study all the cases were due to AML. One of the cases we got dry tap for which a bone marrow biopsy had to be done to diagnose.

Hypersplenism excluding malaria is seen in 13 cases which is 8.7 % of the cases. Peripheral pooling and destruction of the cells by enlarged spleen caused pancytopenia. Causes can be sepsis, Chronic Liver disease, infectious causes etc. The cause for hypersplenism is not included in the study. Hypersplenism is the most common cause of pancytopenia in the study by Arvind Jain et al and Hamid et al. Arvind Jain et al included Malaria in the hypersplenism group.

Malaria is seen in 8 cases accounting 5.4% of the cases. Malaria causes pancytopenia by hypersplenism, hemolysis, DIC, direct bone marrow invasion by parasite and Hemophagocytosis. In the present study marrow invasion by parasite was not seen. Gupta et al reported malaria in 30% of the cases making it the most common cause for pancytopenia in that study. Hamid et al. reported 17.3% of pancytopenia cases were due to Malaria which is third most common cause.

HIV caused pancytopenia in 6 cases (4%). Devi P.M. et al reported HIV in 6% of the cases in her study. Savage et al did a study in Zimbabwe which showed HIV as the third most common cause of Pancytopenia. Hematological manifestations are diverse in HIV. They can be due to direct and indirect effects of Virus, opportunistic infections, ART therapy and associated malignancies.Tuberculosis was seen in 4 cases (2.7%) in the present study. Although TB is a rare cause of pancytopenia, it has to be considered in countries like India. It is most of the times seen in association with miliary tuberculosis. Pathogenesis of pancytopenia is not well understood. Tuberculous bacilli were not seen in all the cases of pancytopenia in tuberculosis. This hypothesizes that Anti-tuberculous drugs may also cause pancytopenia. Tuberculosis is seen in 12.5% of the cases in the study done by Arvind Jain et al and 12.86% in the study done by Gupta et al.Myelodysplastic syndrome is diagnosed by presence of dysplastic cells and Auer rods in the bone marrow. This is seen in 5 cases (3.3%) in the present study. Gupta et al reported 1.73% of the cases to be MDS. International agranulocytosis and aplastic Anaemia study group reported MDS in 4.5% cases making it the 2nd most common cause. 2 cases of Myelofibrosis were diagnosed. We got a dry tap in bone marrow aspiration. Biopsy was taken and Reticulin stain was added anddiagnosed. One case of HLH was diagnosed. This case has increased ferritin levels of 4689 ng/ml.

STRENGTHS

- Being a descriptive observational study, information is quick to obtain and it involved low cost.
- The tests done in the study are routinely advised for pancytopenia as part of evaluation. Hence there are no ethical issues regarding that.
- Multiple parameters – Clinical features, Hematological findings, Bone marrow findings and laboratory values are studied.
- Sample size in the present study is comparatively higher than other studies done in this geographical area making it more significant.

LIMITATIONS

- This study is done in a Government hospital where further diagnostic modalities are not available.
- Study sample size needs to be higher for better results.
- Total of 260 cases of pancytopenia were found in Haemogram.
- Only 148 cases were subjected to bone marrow aspiration. These dropouts were due to fear of Bone marrow examination, and improper follow up.
- Follow up of the patients after treatment needs to be monitored for further information regarding the disease

and diagnosis.

- Patients with prior Chemotherapy and Radiotherapy were excluded for convenience.
- Berkesonian bias might effect the results as only patients from lower social strata attend this hospital.
- Unstable Pancytopenia cases with peripheral smear showing blast cells are intentionally omitted and referred to higher centre urgently as there is no department of Hematological oncology in our hospital

CONCLUSION

In a prospective descriptive study "Evaluation of Pancyt openia in adults and correlation between peripheral smear and Bonemarrow Findings" done on 148 patients in Department of General Medicine, King George Hospital, the salient conclusions are

- Pancytopenia is more common in 3rd and 4th decades
- Male:Female ratio is 1.03
- Most Common cause for Pancytopenia is Megaloblastic Anaemia
- second Most common cause for Pancytopenia is Aplastic Anaemia
- Third most common cause is Hypersplenism
- Fatigue is the most common presenting symptom followed by Fever
- Pallor is the most common sign seen in pancytopenia followed by splenomegaly
- Bone pains are most commonly associated with Leukemias
- Tuberculosis, Malaria and HIV should be ruled out in every case of pancytopenia in our geographical region.
- B12 deficiency is the most common cause for megaloblastic Anaemia followed by combined B12 and Folate deficiency.
- Most common peripheral smear RBC finding is dimorphic Anaemia
- Most common Bone marrow cellularity in pancytopenia is Hypercellularity

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