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Clinico Pathological Profile and Etiological Diagnosis in Patients of Pancytopenia.

KEYWORDS: Pancytopenia, Megaloblastic , Aplastic anemia

Rajesh Chetiwal	Sharath Kumar JV	Manoj Lakhotia
Associate Professor Depatt. of Medicine, ESI PGIMSR, New Delhi	Resident Deptt. of Medicine Dr. SN Medical College and attached hospitals, Jodhpur	Professor Deptt. of Medicine Dr. SN Medical College and attached hospitals, Jodhpur

ABSTRACT

Background: *There has been a wide variation of etiological diagnosis of Pancytopenia and its clinical presentation. This can be attributed to difference in methodology and stringency of diagnostic criteria, geographic area, period of observation, nutritional status and varying exposure to myelotoxic drugs. There are limited number of studies in Indian subcontinent and few studies are available from the other parts of the worlds on the frequency of various causes.*

Objective : *To Analyze the clinico pathological profile in pancytopenia. To identify various causes of pancytopenia.*

Study design : *Prospective observational study, on 210 Subjects of pancytopenia older than 13 years, meeting inclusion criteria during the period of 18 months since January 2010 , were included.*

Methodology : *The study was conducted at tertiary care teaching institute. detailed clinical and laboratory workup was done including complete blood count, peripheral smear examination, serum Lactate Dehydrogenase, bone marrow aspiration, biopsy and staining with special stains.*

Results : *In our study 210 cases of pancytopenia 116 (55.3%) were males and 94 (44.7%) females. The majority of the patients were in younger age group 13 - 30 years (64.7%).*

Megaloblastic anemia was the most common cause of pancytopenia in 83 (39.52%) , followed by aplastic anemia in 57 (27%), malaria in 17 (8.09%) and hypersplenism in 16 (7.61%) of patients. Acute leukemia, myelodysplastic syndrome, SLE, HBV , multiple myeloma, and sepsis were uncommon etiology.

Conclusion : *Megaloblastic anemia and aplastic anemia were amongst the common etiological diagnosis of pancytopenia, comparising 2/3 of all cases. Severe Anemia was more common in megaloblastic anemia. Where is thrombocytopenia was more common in patients of aplstic anemia, resulting in bleeding manifestations.*

Introduction :

Pancytopenia is a relatively common hematological entity. It is defined as reduction in all three formed elements of the blood, erythrocytes, leucocytes and platelets. The condition is often equated with aplastic anemia, which is recognized as primarily due to failed blood cell production. As the result of a study of thirty nine cases, Wintrobe suggested in 1959 that the term Aplastic anemia be reserved for use in cases of pancytopenia where severe hypoplasia or aplasia of the marrow is present, and there is evidence of primary disease infiltrating, replacing or suppressing active haemopoietic tissue.[1,2]

Pancytopenia is not a disease entity but a triad of findings that may result from a number of disease processes. The defect can be in the bone marrow, periphery or both. Like reduced bone marrow activity, defective or ineffective erythropoiesis and increased destruction of cells by overactive reticulo endothelial system.

The aplasia of bone marrow has long list of causes, primary being the idiopathic variety attributed to immunological destruction, leading to bone marrow suppression and hence causing aplastic anemia. These include drugs like chemotherapeutic agents , chloramphenicol, interferon and sulpha drugs. Various infections like parvo virus , human immunodeficiency virus (HIV), Hepatitis virus. Destruction of the bone marrow can also occur due to radiation, sepsis or connective tissue disorder, invasion by hematological malignancies and other cells.[3,4,5]

Patient of megaloblastic anemia due to folic acid and vitamin B 12 deficiency many times present with pancytopenia[6]. Tropical infectious diseases like malaria can cause transient pancytopenia or it could be persistent in tropical splenomegaly syndrome due to hypersplenism.

The clinical presentation of pancytopenia is different in each disease so clinico pathological evaluation of such patients may help in establishing the etiological diagnosis. In view of wide spectrum of etiology it is important to know specific cause, for a definitive treatment. Hence the current study was carried out.

Aim : To Analyze the spectrum of clinical presentation in pancytopenia.

To identify etiological diagnosis and pathological profile in pancytopenia.

Material and Methodology : A Prospective observational study done in 210 cases of pancytopenia, older than 13 years of age admitted in Medicine ward at a tertiary care teaching institute, during *the period of 18 months since January 2010* Diagnostic criteria for pancytopenia, 1.Hemoglobin level <13.5 g/dl in males <11.5 g/dl in females, 2. Leukocyte count $<4x10^9$/L, 3.Platelet count $<150x10^9$/L. Patients on chemotherapy, radiation therapy for various malignancy and on whom bone marrow aspiration/biopsy was not done were excluded.

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The patients were evaluated in detail clinically as per Performa and laboratory workup, viral markers, immunological tests, hematological profile including complete blood count, red cell indices, peripheral smear, serum lactate dehydrogenase, bone marrow aspiration and biopsy with special stains were carried out.

Quantitative data tabulated in Microsoft excel sheet and presented in proportion.

Results : 210 cases of pancytopenia meeting inclusion criteria were enrolled comprising of 116 (55.3%) males and 94(44.7%) females .The majority of the patients with pancytopenia were in younger age group 13 - 30 years (64.7%). Males were more common in 13-20 years age group whereas females were more between 21-30 years.

In our study megaloblastic anemia was the most common cause of pancytopenia in 83 (39.52%) , followed by aplastic anemia in 57 (27%), malaria in 17 (8.09%) and hypersplenism in 16 (7.61%) of patients (Table 1). Acute leukemia, myelodysplastic syndrome, SLE, HBV , multiple myeloma, and sepsis were also observed in etiology of pancytopenia.

Commonest symptom was easy fatigability (68.9%) in the study group.The other common symptoms were fever (64.2%), breathlessness (45.23%) and palpitation (16.19%). Bleeding manifestation was seen in (27.6%) cases, epistaxis was most common bleeding manifestation. The pallor was observed in (95.7%) , signs of bleeding in 27% , icterus in 20% , lymphadenopathy in 8% , hepatomegaly was found in (43.8%) and splenomegaly in (42.8%) of patients.

The hemoglobin level varied from minimum of 1.4 gm% to 12gm% and the mean hemoglobin level was 5.29±2.56 gm%. among all the patients, WBC count was in range from 340 /cumm to 3970/cumm, the mean WBC count was 2491±856/cumm .the mean platelet count of 210 cases was 50161±33000/cu.mm the range was between 3000 / cu.mm to 1.3 lac /cu.mm.

Megaloblastic anemia and aplastic anemia were the two most common etiological diagnosis were observed, comprising (66.66%) 140 cases so clinico - pathological profile of these two commonest observed conditions were also compared in this study. The most common mode of presentation was easy fatigability in both megaloblasic (84%) and aplastic anemia (68.4%), breathlessness on exertion 64.6% and 50.8%, fever 57.3% and 45.6%respectively. Bleeding was the major presenting complaint (66.6%), whereas low in megaloblastic anemia (6.09%)(Table 2).

The physical signs of the patients with megaloblastic anemia in the study shows that 80/83 cases had pallor , 22/83 cases had icterus ,40/83 cases had hepatomegaly , 32/83 cases had splenomegaly , 29/83 cases had haemic murmur. Hepatosplenomegaly was one of the significant finding on examination of these patients (Table 2).

The laboratory evaluation of patients of Megaloblastic and Aplastic anemia shows that hemoglobin level varied between as low as 1.6 gm to 12 gm%,the mean level of 4.49±2.11 gm%, in megaloblastic anemia, where as it was 1.4 to 12 gm% and mean of 5.4 ±2.7% in Aplastic anemia. Total leukocyte count in megaloblastic anemia varied between 340 to 3970/cumm with mean value 2692±836.82 and 1100 to 3690/cumm in aplastic anemia. Platelets was low in aplastic anemia with 3000/cumm, when compared to megaloblastic 4000/cumm. Megaloblastic patients have high Mean Corpuscular Volume (MCV) values, the average level was 111±8.96. Serum lactate dehydrogenase (LDH) varied between 700 to 1580 with an average of 983 (Table 2).

Sixteen of the cases attributed to hypersplenism. These patients had moderate to large splenomegaly, bone marrow aspiration showing hypercellular marrow. Most of the patients were having chronic liver disease and portal hypertension, two of them had tropical splenomegaly.

Acute leukemia was seen in 12 cases of which 2 were acute myeloid leukemia and 10 were acute lymphoid leukemia . They presented with fever (11/12), bleeding manifestation seen in 7/12 of these cases. On clinical examination all had pallor, 5/12cases had lymphadenopathy and 11/12 cases had splenomegaly, bone marrow examination confirmed the diagnosis of leukemia in all the cases.

Eight cases of myelodysplastic syndrome (MDS) presented with pancytopenia. Easy fatigability, and fever as their main presenting complaint. Pallor was seen in all patients, three patients also had splenomegaly. Four of these were diagnosed as MDS, RAEB (Refractory Anemia with Excess Blasts), two as MDS, RA(Refractory Anemia) and rest two as MDS unclassified .

Three cases of SLE (Systemic Lupus Erytheromatosis) were found to have pancytopenia. All were females in their second decade one of them presented with fever and butterfly rash on face, other presented with joint pain. On clinical examination they had pallor, two of them had splenomegaly.

Two cases of multiple myeloma were having pancytopenia, marrow infiltrated with plasma cells causing pancytopenia. One of the patient was in post partum presented with fever, easy fatigability, breathlessness, had sepsis with multi organ dysfunction results in bone marrow suppression to cause pancytopenia.

Discussion:

In our study 116 (55.3%) were males and 94 (44.7%) females. Male preponderance was noted in all groups except aplastic anemia where females were more than males (2:1) as aplastic anemia is more common in females. Most of the patients were in second and third decade. The mean age in the present study was 32.97 years, which is in concordance with **Kumar et al** where mean age was 30.6 years. In a study done by **Tilak et al**,[8] 32.47% of patients were seen under 20 years of age, this was because they also included pediatric patients in their study.

In our study we noted various etiological diagnosis of pancytopenia, but the two common causes seen were megaloblastic anemia (39.5%), aplastic anemia (27.1%) followed by malaria (8%) and hypersplenism (7.6%). Others disease like acute leukemia, MDS, SLE, HBV also observed. Multiple myeloma and sepsis were also noted in very few cases.

Megaloblastic anemia was the most common cause of pancytopenia in 83 (39.6%) patients. Peripheral smear in all the cases showed macrocytes. Mean corpuscular volume (MCV) was elevated in most of these patients with mean value of 111± 8.96 and 40/83 of them had hypersegmented neutrophils. Serum LDH varied between 700 to 1580 with an average mean of 983±196, p value <0.0001 (Table 2).

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Similar results have been reported in hematological study from other Indian centers. **Kale et al**, [6] from Mumbai in a study of 65 pancytopenia patients detected megaloblastic anemia in 25.4% of cases. **Sen et l**, [7] from Rohtak found megaloblastic anemia in 39% of the 191 patients studied. **Tilak et al**, [8] quotes an incidence of 68 % whereas **Kumar et al,**[9] gives an incidence of 22.3% for megaloblastic anemia. **Khunger JM et al**[11] studied 200 cases in Sufdar jung hospital Delhi found 72% of cases with megaloblastic anemia. **Jha A et al**[12] from Nepal found 30.18% of cases had megaloblastic anemia**. Kishore khodke et al**[13] from Dr RML Hospital New Delhi found that in 50 cases of pancytopenia 44% were due megaloblastic anemia. This high incidence can be attributed to the nutritional deficiency common in our country. A study done in Israel did not find megaloblastic anemia as a very common cause of pancytopenia.

Comparing the hemoglobin level in the four major groups of pancytopenia, the mean hemoglobin level in megaloblastic anemia group was (4.49±2.11gm%),which is lower than the other groups. Similar results were noted **Kumar et al**,[9] where hemoglobin level noted was 4.6 gm%.

Aplastic anemia was the second common (27.14%) cause of pancytopenia .This is comparable with the above mentioned studies, however aplastic anemia was most common cause of pancytopenia in studies by **Vermal et al**[13] and **Hossain et al**[14] .The mean age of patients in this group was 26.7±10.22 years. Male to female ratio was 1:2. In **Kumar et al**,[9]study the mean age was 29 years and male preponderance (1.45:1) was noted. Bleeding is a common early symptom of aplastic anemia, p value <0.0001 (Table 2). In the present study 38 out of 57 (66.6%) cases had bleeding manifestation at presentation. On comparing the platelet count in the four major diseases causing pancytopenia it was noted that the platelet count was lowest in aplastic anemia group. Mean platelet count in this group was 38,000/ cumm. Similar results have been documented by **Kumar et al**.[9]

The etiology of aplastic anemia was idiopathic in most of cases. Similar observation has been made by **Kumar et al**,[9] where 73.46% cases were idiopathic , study by **Keisu et al**[10] also found idiopathic variety as the commonest cause.

In the present study 19 (9.04%) of cases of pancytopenia were due to malaria. **V Gupta et al** found malaria to be responsible for pancytopenia in 2.9% of the cases. The incidence of malaria was high in the present study when compared to **V Gupta et al**, none of the other studies mentioned above had malaria as one of the cause. This could be seen in view of prevalence of malaria in the western Rajasthan

CONCLUSION:

Megaloblastic anemia and aplastic anemia were amongst the common etiological diagnosis of pancytopenia comparising 2/3 of all cases. Severe Anemia was more common with high mean corpuscular volume and high serum lactate dehydrogenase levels in megaloblastic anemia. Where is thrombocytopenia was more common in patients of aplastic anemia with bleeding manifestations.

Malaria and hypersplenism were not uncommon etiology of pancytopenia, where autoimmune disorder and sepsis and other causes were less common in our study.

Table 1: Etiology of Pancytopenia

S.No.	Etiology	No of Cases n=210	Percentage (%)
1	Megaloblastic Anemia	83	39.52
2	Aplastic Anemia	57	27.14
3	Malaria	17	8.09
4	Hypersplenism	16	7.61
5	Acute Leukemia	12	5.7
6	MDS	8	3.8
7	Lymphoproliferative Disorder	4	1.9
8	SLE	3	1.4
9	HBV	4	1.9
10	Multiple Myeloma	2	0.95
11	Sepsis	1	0.4
12	No Cause	3	1.4
	Total	210	100%

TABLE -2 Clinico - pathological profile of megaloblastic and aplastic anemia

S. No.	Clinico-pathological parameter	Megaloblastic anemia, n = 83	Aplastic Anemia, n= 57	P value
1	Easy fatigability	69 (84.1)	39 (68.4)	0.300
2	Breathlessness	53(64.6)	29 (50.8)	0.1052
3	Palpitation	19 (23.1)	16 (28.0)	0.5040
4	Fever	47 (57.3)	26 (45.6)	0.1754
5	Pedal Edema	11 (13.4)	5 (8.7)	<0.0001
6	Bleeding manifestation	5 (6.09)	38 (66.6)	<0.0001
7	Pallor	80 (97.5)	52 (91.2)	0.932
8	Icterus	22 (26.8)	2 (3.5)	0.0005
9	Lymphadenopathy	0 (0)	5 (8.7)	0.0070
10	Hepatomegaly	40 (48.7)	13 (22.8)	0.0024
11	Splenomegaly	32 (39.0)	0(0)	<0.0001
12	Haemic Murmur	29 (35.3)	21 (36.8)	0.8563
13	Hb (gm/dl)	4.49±2.11	5.46±2.77	0.0202
14	TLC (/cu mm)	2692±836.82	2294.9±780.9	0.0053
15	Platelet (l/ cumm)	0.57±0.29	0.38±0.31	0.0003
16	MCV	111±8.96	88.24±11.15	0.0588
17	LDH	983±196	289.85±126.5	<0.0001

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