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CLINICOHAEMATOLOGICAL ANALYSIS OF PANCYTOPENIA: A STUDY IN A TERTIARY CARE CENTRE.

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ABSTRACT **Introduction:** Pancytopenia is an important clinicohaematological entity encountered in our day to day clinical practice. There are varying trends in its clinical pattern, treatment modalities and outcome. A reduction in all three types of cellular components in peripheral blood is termed as pancytopenia and this includes anemia, neutropenia and thrombocytopenia. Underlying etiology determines the management and prognosis of the patients.

Methodology: Total 100 cases with age group between 18-80 years were studied in this study by examining peripheral smears of blood samples. Bone marrow samples were obtained by routine bone marrow aspiration and biopsy procedures if indicated. Biochemical and other special investigations were done to confirm the diagnosis.

Results: In our study mean age of the patients were 42 years with slight male predominance. Majority of the patients presented with pallor, fatigability, exertional dyspnoea and fever. The common physical findings were pallor followed by splenomegaly and hepatomegaly. The commonest marrow finding was hypercellularity with megaloblastic erythropoiesis. Megaloblastic anemia followed by aplastic anemia was two major causes for pancytopenia.

Conclusion: The present study concludes the importance of workup of all cases of pancytopenia to diagnose and treat the reversible causes and to reduce mortality and morbidity. Megaloblastic anemia is the commonest cause of pancytopenia in our studies like other most Indian and subcontinent studies. Hematological and biochemical investigations along are helpful to diagnose or to rule out the causes of pancytopenia. Invasive procedures like bone marrow aspiration and biopsy can be avoided to diagnose in most cases of pancytopenia.

KEYWORDS : Pancytopenia, Pallor, Hyper cellular Bone Marrow, Megaloblastic Anemia.

BACKGROUND

Pancytopenia is common among patients attending hospital[1]. Pancytopenia by itself is not a disease but is the result of various diseases[2]. It should be suspected on clinical grounds when a patient presents with pallor, easy fatigability, prolonged fever and a tendency to bleed. Cytopenia is a reduction in the number of each type cell in peripheral blood. Pancytopenia refers to a reduction in all three components of blood e.g. red blood cells, white blood cells and platelets. It is an important clinicohaematological entity encountered in our day to day clinical practice. It is not a disease entity but a triad of findings that may result from a number of disease processes primarily or secondarily involving the bone marrow[3].

Major causes of pancytopenia in developing countries are megaloblastic anemia, parasitic infection, hypersplenism and aplastic anemia. Aplastic anemia is one of the most serious causes of pancytopenia. Marrow failure leads to pancytopenia. The presenting symptoms are often attributable to anemia or thrombocytopenia leading to pallor, fatigue and dyspnoea. Leucopenia is an uncommon cause of initial presentation but can become the most serious threat to life during the course of disorder.

Infections usually occur with commensal organisms of the skin or gastrointestinal tract. Early manifestation of neutropenia is often a sore throat or chest or soft tissue infection which typically show incomplete response to antibiotics. Unfortunately, patients with pancytopenia may develop overwhelming septicemia without any focal sign of infection, the only clinical features being malaise and fever. The commonest offending organisms include coliforms, klebsiella sp, pseudomonas species and staphylococci.

The severity of pancytopenia and underlying pathology determine the management and prognosis of the patient [4]. There are varying trends in its clinical pattern, hematological change, treatment modalities and outcome.

AIMS AND OBJECTIVES:

1. To know the spectrum of diseases presenting with pancytopenia.
2. Common clinical presenting features.
3. Early identification of causes and planning for management so that burden of hospital admission can be minimized.

METHODS

Study Participants: This study was conducted in the department of medicine, at a tertiary care hospital in north east part of India with the patients attending at OPD and indoor medicine patients department at MJN Medical College and Hospital , Cooch Behar, WB. Patients of all age groups and both sexes were included.

Study Period: The present prospective study was undertaken for a period of 2 years from March 2019 to February 2021.

Inclusion Criteria:

Inclusion criteria were presence of all three of the following[3].
1. Hemoglobin, <10 g/dl;
2. Total leukocyte count (TLC), <3500/ µl ;
3. Platelet count, <1 lac/ µl

Exclusion Criteria:

1. Patients on myelotoxic chemotherapy.
2. Patient on radiotherapy.
3. Patient <18yaers

Study Design:

This is a hospital based observational study .Case selection was based on clinical features and supported by laboratory evidence, which included peripheral blood smear. A total of 100 cases of pancytopenia are analyzed with clinico-hematological features. Bone marrow aspiration smears and trephine biopsy sections, in patients, fulfilling the criteria of pancytopenia were examined. Criteria for diagnosis of pancytopenia were1) hemoglobin less than 10gm/dl, 2) TLC less than 3500/mm^3 and 3) platelet count less than 1,00,000/mm^3 [(3).] Bone marrow aspiration was performed by pathologist under local anesthesia with informed consent. The relevant clinico-hematological parameters were recorded. The causes of pancytopenia are analyzed based on clinico-hematological parameters, including peripheral blood film. Bone marrow aspiration, bone marrow biopsy (in cases of dry tap and as needed in selected cases) are performed with written

consent from patient or guardian, besides this LFT, abdominal ultrasonography, malaria parasite, serology for HIV, enteric fever, vitamin B12 level, chest x-ray and other investigation as indicated. Clinical features, age, gender are compared with the various studies published in literature.

Statistical Analysis:
Data were collected, assembled and transferred to Excel Spread sheet (MS Excel 2007) and analyzed using IBM-SPSS ver. 16, Chicago. The continuous variables were expressed as mean and ± standard deviation, while categorical variables were expressed as percentages. A P-value <0.05 was considered as statistically significant Descriptive statistics were used to interpret results.

RESULT& ANALYSIS:
Total 100 patients of pancytopenia were studied in our study group among them 54(54 %) were males & 46(46%) were female (Table-1). Of these patients pallor (94%) and fatigability (82%) were the most common presenting symptoms, other common presentation in sequence were palpitation(45%), dyspnoea on exertion (36%), fever(48%), bleeding (24%), splenomegaly(35%), lymphadenopathy (6%) and hepatomegaly (15%) of cases (Table-2).

Table 1: Distribution of Sex

Sex	Frequency	Percentage
Male	54	54%
Female	46	46%

Table 2: Distribution of Symptoms.

Symptoms	No of pt.	%
Pallor	94	94%
Fatigability	82	82%
Dyspnoea	36	36%
Chest Pain	12	12%
Palpitation	45	45%
Fever	48	48%
Bleeding Manifestation	24	24%
Hepatomegaly	15	15%
Splenomegaly	35	35%
Lymphadenopathy	6	6%
Icterus	5	5%

Table3: Distribution of Diagnosis

Diagnosis	No. of cases	Male	Female	Percentage (Total)
Megaloblastic anemia	39	22	17	39%
Aplastic anemia	32	14	18	32%
Kala azar	5	4	1	5%
CLD	12	9	3	12%
MDS	1		1	1%
Acute leukemia	4	3	1	4%
HIV	2	2		2%
MM	1	1		1%
Typhoid	1	1		1%
Drug	2		2	2%
Viral Fever/Puo	12	8	4	12%
Tuberculosis	1	1		1%

Table 4: Distribution of Common Causes

	MA	AA	Hypersplenism	Infection
Male	22	14	9	6
Female	17	18	4	4

Table 5: Distribution of Age

Age(yr)	MA	AA	Hypersplenism	Infection
18 - 30	3	9	1	2
30-45	15	14	5	6
46-60	18	6	6	4
61-80	3	3	1	0

Table 6: Hematological Parameters In Three Subgroups of Pancytopenia

	Megaloblastic anemia	Aplastic anemia	CLD	Infection
Hb (gm/dl)	3 - 8-6	2- 8	4 -9	7.5 -9.8
WBC (/µL)	1400-3500	800-3500	2500-3500	3000-3400
PLT (/µL)	25000-95000	15000-76000	40000- 98000	15000-85000

Peripheral blood picture includes complete haemogram showed Hb% ranging from 3gm/dl to 9.8gm/dl with a mean Hb concentration of 6.8 g/dl. TLC 1400 to 3500/cmm blood (mean 3,300/cmm) and platelet count 25000 to 98000 /cmm mean 73×10^3)/mm^3 of blood.(Table-6).

The predominant blood picture was dimorphic anemia macrocytic normochromic anemia with hypersegmented neutrophil in majority of smears and MCV >100(64%), NNA(12%),, MHA(8%), dimorphic anemia (16%)of cases.

Megaloblastic anemia was diagnosed by examination of peripheral blood which showed macrocytic with hyper-segmented neutrophil. Bone marrow aspirate are hyper-cellular with increased erythropoiesis and presence of megaloblasts.[5]

Bone Marrow finding in our study had hypercellular with marked erythroid hyperplasia and presence of megaloblasts. Megakaryocytes is depressed. Megaloblastic change is characterized by sieved nucleus chromatin, asynchronous nuclear maturation and bluish cytoplasm.

Aplastic anemia was characterized by pancytopenia in peripheral smear and bone marrow showing hypocellular fatty patchy marrow with depressed all cell lines with absence of megakaryocytes. Lymphocytes and plasma cells were within normal limits.

Major etiological group in our study were megaloblastic anemia, aplastic anemia, infection, leukemia. (Table-3)

Megaloblastic anemia was found in 39% cases of which 22% male and 17% are female. Aplastic anemia in 32% of cases and among them14% and 18% are male and female respectively. Infection was an important group causing pancytopenia. In our study we found seasonal viral fever/puo in 12%, kala azar in 5%, HIV 2%, tuberculosis1%, typhoid 1% of cases. We also found pancytopenia in chronic liver disease with hypersplenism (10%), leukemia (4%), multiple myeloma in 1%, MDS in 1% and drug induced in 2% of patients.

We measured blood vitamin B12 & folate level in all patients having MCV >100, macrocytes, hyper segmented neutrophil in peripheral smear. Vitamin B12 deficiency (68%) was found to be more common than folate deficiency (14%) and was present in most of the cases of megaloblastic anemia in our study.

Macrocytosis without anemia may be an indication of early folate or Cobalamin deficiency as macrocytosis preceded development of anemia. The average Indian vegetarian diet is deficient in Cobalamin.

DISCUSSION:
Pancytopenia is a clinical condition which refers to a combination simultaneous presence of anemia, leucopenia and thrombocytopenia. The causes of pancytopenia may be due to various conditions and its etiology differs in different population, different methodology and diagnostic criteria, genetic difference, nutritional status, prevalence of infection and exposure to toxic drugs[6].

Total 100 pancytopenia cases were studied of which 54% & 46% were male & female respectively. In a similar study conducted by Das makheja et all. the male female ratio in their study was 1.38 :1[7].

In our study incidence of megaloblastic anemia was 39% and was the commonest cause for pancytopenia followed by aplastic anemia in 32% of cases. One study done by Bhaskar B Thakkar et al,; in 2001 showed incidence of megaloblastic anemia 37% as a cause for pancytopenia which is close to our study[8].

Incidence of megaloblastic anemia in 72% was reported by Khunger JM et al.; in 200 patients and 68%, by Tilak V et al. [9,10]. All the above studies have been done in India, and they stress the importance of megaloblastic anemia being the major cause of pancytopenia. Savage et al in Zimbabwe studied 134 patients identifying megaloblastic anemia to be the most common followed by aplastic anemia and acute leukemia. Jha et al in Nepal studied 148 pancytopenic patients and found hypoplastic bone marrow in 29%, megaloblastic anemia 23.6%, haematological malignancy 23.6% [11].

Hence findings of the present study correlate well with other reports from India and other subcontinent. The incidence of megaloblastic anemia in our study was 39% whereas in other studies it varies from 0.8%to 68%.[4,14,15,16,17]

Incidence of aplastic anemia varies from 10% to 52% among pancytopenic patients[12]. The incidence of hypoplastic anemia in our study was 32%, which correlated with the corresponding figures 29.5% in studies done by Kumar R et al[12]. Khodke K et al. and Khunger JM et al., Both observed an incidence of 14%.[12,9]

In one study each from India, Bangladesh and Pakistan the commonest cause of pancytopenia was aplastic anemia. One international study also found aplastic anemia as commonest cause of pancytopenia.

Premkumar et al. study showed that infectious diseases is an important cause of pancytopenia in country like India in contrast to developed country where pancytopenia is mostly due to malignancy and marrow aplasia[13]. Seasonal viral fever 12%, kala azar 5%, HIV 2% typhoid fever 1% ,tuberculosis 1% were responsible for pancytopenia in our study group,(combined=21%)which is a major group causing pancytopenia also support their study.

Other important causes of pancytopenia in our study was chronic liver disease with hypersplenism in 12%, acute leukemia(aleukemic) 4%, multiple myeloma in 1%, MDS in 1% and drug induced in 2% of patients. Khodke K et al. reported incidence of aleukemic leukemia about 7%[12].

Pancytopenia can be seen in approximately 30% cases of acute leukemia at time of presentation.

The high incidence of megaloblastic anemia correlates with high prevalence of nutritional anemia in the subcontinent[12].

Common clinical presentation was pallor 94%, fatigability 82%, dyspnea 36%, fever 48%, palpitation 45%, petechial hemorrhage 24%, splenomegaly 35%. Khan et al showed 81% cases with pallor followed by fever, then bleeding manifestation.[14]. In one study by Khunger JM et al ; reported pallor in 100% cases, splenomegaly in 32.5% and hepatomegaly in32.5% of patients[9].

This was quiet similar to our study which show 94% pallor followed by fatigability 82%, fever 48% splenomegaly 35% and bleeding manifestation in 24% cases.

Vitamin B12 deficiency was found to be more common than folic acid and the major cause of megaloblastic anemia and therefore pancytopenia in our study. From different studies and many study reports from India show vitamin B12 deficiency is the predominant cause of megaloblastic anemia followed by folic acid. Other causes of MA include parasitic infections like Diphyllobothrium latum, alcoholism, vegetarianism, gastrectomy drugs like oral contraceptives and anticonvulsants. This is consistent with the similar studies and their results done from different parts of India (Pune, Pondicherry, Delhi)[18] and our neighborhood countries[19].

CONCLUSION

Pancytopenia is a frequently observed hematological condition which consistent with the combination of anemia, leucopenia and thrombocytopenia and should be suspected on clinical grounds when a patient presents with unexplained anemia, exertional dyspnoea, prolonged fever and tendency to bleed.

However there is limited number of studies available from Indian subcontinent on the frequency of various causes of pancytopenia. Study on pancytopenia is also less in this region of eastern India which is a drainage area of the people of a few countries like Bangladesh, Nepal, Bhutan and of a few states like Bihar, Assam, Meghalaya. The high incidence of megaloblastic anemia correlates with high prevalence of nutritional anemia in the subcontinent[8]. It is a rapidly correctable disorder and should be promptly notified[6] which if not diagnosed at an early stage, may be fatal. The underlying pathology determines the management and prognosis of the patients. This study was done to analyze the presentation, to identify the causes also invasive procedures like bone marrow biopsy and aspiration can be avoided with the help of detailed primary hematological and other supportive investigations and to find out treatment modalities. Peripheral blood smear examination and bone marrow aspiration gives a fairly accurate diagnosis of pancytopenia in a short time period reducing laboratory burden.

The commonest cause of pancytopenia is megaloblastic anemia followed aplastic anemia are two major cause in present study correlated well with other Indian and sub continent studies. Pallor and fatigability are most common findings in all patients with megaloblastic anemia. Vitamin B12 deficiency was found to be the major cause of megaloblastic anemia and therefore pancytopenia and is easily manageable. Early diagnosis also helps to reduce morbidity and mortality in serious disease by early intervention.

Small sample size is one of the limitations of our study. The variability in etiology and other finding can be attributed to the geographic area, genetic differences, stringency of diagnostic criteria, and differences in methodology used, yet it is important that a good quality of peripheral blood film examination is often helpful to reach the diagnosis.

Abbreviation:

TLC - total leucocyte count
OPD - out patient department.
WB - west Bengal.
LFT - liver function test.
HIV - human immunodeficiency virus.
CLD - chronic liver disease.
MDS - myelodisplastic syndrome
MM - multiple myeloma.
PUO - pyrexia of unknown origin.
AA - aplastic anaemia.
MA - Megaloblastic anaemia
Hb - haemoglobin
MCV - mean corpuscular volume
NNA - nomocytic normochromic anaemia
MHA - microcytic hypochromic anaemia

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