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Clinico-Haematological Study of Pancytopenia

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Abstract

Introduction: *Pancytopenia is a clinical condition, which refers to a combination of anaemia, leucopenia and thrombocytopenia. It often poses diagnostic challenge to physician and the knowledge of accurate etiologies of this condition is crucial in the management of the patient.* ***Materials and Methods:*** *The study was a prospective study done over a period of October 2011 to December 2011 and 50 patients were evaluated clinically along with haematological parameters, bone marrow aspiration and wherever required, a trephine biopsy was performed in Haematology department of Armed forces institute of pathology (AFIP), Dhaka cantonment, Dhaka. In all patients, a detailed relevant history along with a physical examination was done and data was collected using pre designed proforma.* ***Results:*** *Among the 50 cases studied, age of the patients ranged from 3 to 80 yrs with a mean age of 37.5 yrs and male predominance. Fever and generalized weakness were the most common symptoms. The commonest physical findings were pallor followed by splenomegaly and hepatomegaly. Anisopoikilocytosis and relative lymphocytosis was the most prominent peripheral blood findings in patients. The commonest cause of pancytopenia was Aplastic anaemia (36%), followed by Myelodysplastic syndrome (18%), visceral leishmaniasis (12%), Megaloblastic anaemia (8%), Acute leukaemia (6%), Myelofibrosis (4%), Multiple myeloma (4%), Hypersplenism (4%), Malaria (2%).* ***Conclusion:*** *As a large number of pancytopenic patients have a reversible aetiology, early & proper diagnosis may be life saving. Maximum diagnostic yield can be achieved by correlation with clinical findings & laboratory parameters.*

Keywords: *Pancytopenia, Bone marrow examination, Aplastic anaemia.*

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Introduction:

Pancytopenia is an important clinico-haematological entity encountered in our day to day clinical practice. There are varying trends in its clinical pattern, treatment modalities and outcome[1].

The incidence of pancytopenia around the world is not mentioned in the textbook. Different studies done at different places showed variable frequency of pancytopenia. The study conducted by Shazia Memon et al[2] in Hyderabad within three years periods showed, 3.57%, while Habibur Rehman et al[3] , Kanchanalak et al[4] and Adil et al[5] reported 0.8%, 1.2% and 12.6% respectively. The aetiology of pancytopenia varies in different populations depending on the differences in age patterns, nutritional status, climate and the prevalence of infections[6].

It is always present in some stages in the course of aplastic anaemia, very common in subleukaemic leukaemia, relatively uncommon in lymphoma and rare in metastatic carcinoma involving the bone marrow. The prognosis depends on the severity of pancytopenia and on the nature of underlying pathology[7].

Pancytopenia is not a disease entity but a triad of findings that may result from various disease processs, which can be defined by reduction in all three formed elements of blood below the normal reference range(Haemoglobin< 13.5gm/dl in males or 11.5 gm/dl in females, Leucocyte count< $4X10^9$ /L and Platelet count< $150X10^9$ /L)[8].

The presenting clinical symptoms are usually due to anaemia, leucopenia and thrombocytopenia. Fatigue and weakness due to anaemia, increased susceptibility to infections because of leucopenia

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and bleeding tendency due to thrombocytopenia are the usual presenting symptoms[9].

Red blood cell indices help us to classify anaemias as microcytic, normocytic, and macrocytic depending on low, normal or high MCV. Most of the causes of pancytopenia present with normal RBC indices, but causes like megaloblastic anaemia, aplastic anaemia, myelodysplastic syndrome and paroxysmal nocturnal hemoglobinuria presents with high MCV[10].

Bone marrow examinations, such as bone marrow aspiration and biopsy, are extremely helpful in the evaluation of pancytopenia[11]. The bone marrow picture may vary depending on the etiology, from normocellular with non-specific changes to hypocellular, hypercellular or being replaced completely by malignant cells. According to aetiology, degree and duration of the bone marrow impairment, clinically these can lead to fever, pallor, infection or serious illness and death. Knowing the exact etiology is important for specific treatment and prognostication[12].

Few clear recommendations can be found as to the optimal investigative approach to pancytopenia. Some experts suggest that marrow examination is essential to the diagnosis, but it has not been established whether the procedure is necessary in all pancytopenic patients. Bone marrow aspiration is one of the most frequent and relatively safe, invasive procedure done routinely to evaluate the cause. Though an invasive procedure, it can be easily performed even in the presence of severe thrombocytopenia with little or no risk of bleeding. This study was carried out with the aim to obtain detailed information of a common disorder in our set-up regarding its causes and diagnostic approaches and there by automatically enhance the management process.

Early diagnosis of various causes of pancytopenia are very crucial and require prompt clinical examination and investigations like complete blood count, peripheral blood flim study and bone marrow examination. In Bangladesh the causes of pancytopenia are not well defined, for this purpose, this study will be helpful to findout the underlying etiopathology of pancytopenia.

Materials and Methods:

This study was a prospective study conducted at Armed Forces Institute of Pathology (AFIP), Dhaka cantonment, Dhaka from October to December 2011. Total 50 patients presenting with pancytopenia were found out by using a preformed questionnaires and blood counts obtained prior to transfusion done on an automated haematology analyzer. In all patients, a detailed relevant history including the treatment history, history of drug intake, radiation exposure, along with a physical examination of pallor, jaundice, hepatomegaly, splenomegaly and lymphadenopathy, were taken. Peripheral blood film study was done by staining the blood smears with leishman stains.

Peripheral Smear Preparation and Staining

Peripheral smear was prepared and stained according to the guidelines in Practical Hematology, Dacie and Lewis, 10th Edition[13].

Bone Marrow aspiration[14]

Under aseptic measures aspiration was done through posterior iliac crest. The patient was placed in a prone position, a pillow under their head. Lidocaine was used as the anaesthetic, providing the patient has no history of an allergic reaction to this medication. During this process, local anaesthetic is first infiltrated into the skin and subcutaneous tissue to anaesthetize an area approximately 1 cm. in diameter. After the skin is numb, lidocaine is infiltrated directly over the periosteum to numb an area approximately 2-3 cm in diameter. Salah needle is advanced with steady pressure and a slight twisting motion to the center of the posterior iliac prominence. The needle was rotated back and forth (90^{o}-180^{o}) and careful pressure was applied to advance the needle through the cortical bone. A decreased resistance indicated penetration of cortex and entry into the marrow cavity. Needle was advanced about 1 cm into the marrow cavity. The obturator was unlocked and slowly removed 0.3 ml of marrow fluid was aspirated into a 10 ml syringe and specimen slides were prepared. A folded piece of gauze was placed over the site with a pressure bandage. The patient was asked to lie supine for at least 30 minutes.

Steps of preparing aspirated smear and staining methods[13]

Prepared slides were examined under scanner and low power to assessed cellularity, megakaryocytes and metastatic carcinoma cells. The area where cells were very well spread out was selected and under oil immersion at least 500 marrow cells were counted.

Bone Marrow Biopsy[15-17]

The bone marrow biopsy was obtained through the same skin incision site used for the marrow aspiration. Jamshidi needle was used for this procedure. Once the needle fixed in the bone, the stylet was removed. Using firm pressure, slowly rotate the needle in an alternating clockwise-counterclockwise motion and advance it into the bone marrow cavity to obtain an adequate bone marrow specimen measuring approximately 1.5-2 cm in length. Needle was rotated along its axis to help cut the specimen. Following this procedure slowly pulled the needle out rotating in an alternating clockwise and counterclockwise motion. Then, removed the specimen from the needle with the probe through the distal cutting end. If the aspiration was a dry tap, the core biopsy may be used to make touch preparations prior to placing the specimen in fixative. Obtained material kept in 10% formalin. After the procedure, pressure was applied for a 2 minutes and an elastoplast was applied after placing the gauze on the top of the site. The patient was instructed to check the site frequently, to report any bleeding, and to keep it dry. The dressing was removed after 48 hours only. Biopsy

specimen stained with haematoxylin and eosin (H&E). Prepared slides were examined under microscope.

Ethical Consideration

Ethical clearance was obtained from the Research Committee of DGMS office. Permission to use the records was obtained from the Haematology department of AFIP, Dhaka. Written informed consent was taken from the patient's or legal guardian for the use of any photographs. Patient confidentiality was strictly maintained. No names, addresses or contact details of the patients were divulged.

Method of data processing & statistical analysis

Data were analyzed by using Microsoft excel & statistical analysis was done by using descriptive statistics.

Results:

Among all study patient 80% patients are male and 20% are female. Male to female ratio was 4:1. The most common causes (figure 1) of pancytopenia was aplastic anaemia (36%), followed by MDS (18%), and visceral leishmaniasis (12%). Other less common causes of pancytopenia include acute leukaemia (12%), megaloblastic anaemia (8%), myelofibrosis, Hypersplenism, multiple myeloma (each one constitute 4%). Uncommon causes in this study was malaria (2%). Maximum number of patients was found in the age group (Table I) of 11-20 years and incidence of aplastic anaemia, ALL was more in 11-20 yrs of age. Similarly MDS was more in 61-70 yrs of age and AML & megaloblastic anaemia was more in 51-60 yrs.

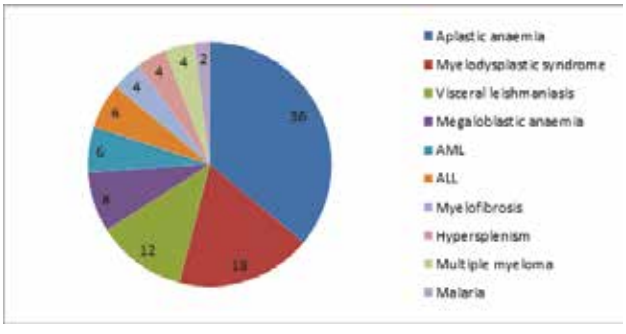

Figure 1: Different causes of pancytopenia.

Table I: Age and etiology wise distribution.

Age in yrs	Aplastic anaemia	MDS	Viscearal leishmaniasis	AML	ALL	Megaloblastic anaemia	Multiple myeloma	Misc.
0-10	3	0	1	0	1	0	0	0
11-20	4	0	2	0	2	0	0	1
21-30	3	1	2	0	0	0	0	1
31-40	3	0	1	1	0	1	1	0
41-50	1	0	0	0	0	1	1	1
51-60	2	1	0	2	0	2	0	1
61-70	2	4	0	0	0	0	1	1
71-80	0	3	0	0	0	0	0	0

MDS-Myelodysplastic syndrome, AML- Acute myeloblastic leukaemia, ALL- Acute lymphoblastic leukaemia, Misc.- Myelofibrosis, Malaria, Hypersplenism

The bone marrow study showed that (Table II) 36%of the patients had hypocellular marrow, 60% had cellular marrow including normocellular marrow (6%) and hypercellular marrow (54%) and 4% had blood tap. Increased erythropoiesis seen (Table II) in 44% cases. Decreased erythropoiesis seen in 38% cases and normal erythropoiesis seen in 14% cases, 32% cases was showed dyserythropoiesis. Granulopoiesis decrease in most cases of (32%) aplasic anaemia. Whereas increases granulopoiesis seen in 28% cases (MDS 12%, megaloblastic anaemia 8%, acute leukaemia 6%, visceral leishmaniasis 2%). Twenty study (40%) cases also showed normal granulopoiesis. Dysgranulopoiesis was seen, only in cases of MDS (10%). Decreased megkaryopoiesis (Table II) seen in 48% cases. Increased megkaryopoiesis seen in 12%cases and normal megakaryopoiesis seen in 32% cases. Dysmegkaryopoiesis was seen in patients having MDS (14%) and megaloblastic anaemia (4%). Overlap of common haematological parameters in major causes of pancytopenia without any clue to diagnosis. However, more severe anaemia, leucopenia and thrombocytopenia were found in cases of visceral leishmaniasis (Table III).

Table II: Cellularity, Erythropoiesis, Granulopoiesis & Megakaryopoiesis in different causes of pancytopenia.

Condition	Hypocellular	Normocellular	Hypercellular	Blood tap
Cellularity	18(36%)	3(6%)	27(54%)	2(4%)
Condition	**Normal**	**Increased**	**Decreased**	**Dyerythropoiesis**
Erythropoiesis	7(14%)	22(44%)	19(38%)	16(32%)
Granulopoiesis	20(40%)	14(28%)	18(26%)	5(10%)
Megakaryopoiesis	16(32%)	6(12%)	24(48%)	9(18%)

Table III: Mean hematological parameters in five common cause of pancytopenia.

Disease	Hb g/dl	Total Count(x10^9/L)	Platelets Count(x10^9/L)	ESR mm	MCV fl	MCH pg	MCHC
Aplastic anaemia	7.93	2.49	34.97	88.6	83.5	28.54	33.77
MDS	8.03	3.01	62.55	80.22	82.8	28.28	34.13
Visceral leishmaniasis	6.02	2.83	43.66	100.8	70.71	25	31
Acute leukaemia	7.62	2.41	62.16	109	85	29	33.33
Megaloblastic anaemia	8.31	2.25	85.25	83.5	90.8	29	35.12

The most common clinical complaint in this study was fever 30 (60%), followed by general weakness (figure 2). Fever affects all patients of visceral leishmaniasis & generalized weakness was more common in cases of aplastic anaemia. Pallor as a clinical sign was universal (70%), followed by splenomegaly (30%) which was more often seen in all patients of visceral leishmaniasis (figure 2). Table IV shows comparison of peripheral blood film findings of different diseases of present study with other studies done by Gayathri and Rao et al[1] and Tilak V et al[18]. Table V shows comparison of first and second causes of pancytopenia in different studies with present study.

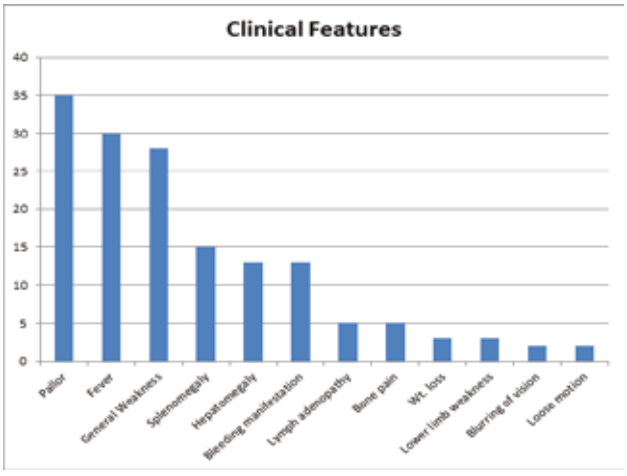

Figure 2: Clinical features according to causes of pancytopeni

Table IV: Comparison of peripheral blood findings with those in other studies.

Diagnosis	Total no of cases			Anisopoikilocytosis			NRBC			Hypersegmented neutrophils			Immature WBC			Relative lymphocytosis		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Aplastic anaemia	18	19	6	1	17	2	-	-	-	-	5	-	-	-	-	12	10	3
MDC	9	-	-	7	-	-	4	-	-	-	-	-	5	-	-	1	-	-
Visceral leishmaniasis	6	-	-	2	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Acute leukaemia	6	4	1	-	1	1	1	1	1	-	-	-	6	2	1	-	-	-
Megaloblastic anaemia	4	77	53	2	68	51	1	-	13	2	38	45	-	20	-	-	-	-
Multiple myeloma	1	1	1	-	1	1	1	-	-	-	-	-	-	-	-	-	-	-
Malaria	1	2	3	1	2	1	-	-	-	-	-	-	-	-	-	-	-	-

A- Present study
B- Study done by Gayathri and Rao et al[1]
C- Study done by Tilak V et al[19].

Table V: A comparison of the first and second most common causes of pancytopenia.

Study	Country	Year	No of cases	Commonest causes	Second most common cause
Keisu & Ost[20]	Israel & Europe	1990	100	Neoplastic disease, radiation (32%)	Aplastic anaemia (19%)
Hossain et al[18]	Bangladesh	1992	50	Aplastic anaemia	Cr. Malaria & Cr. Kalazar
Verma & Das[11]	India	1992	202	Aplastic anaemia (40.6%)	Megaloblastic anaemia (23.26%)
Tilak & Jain[19]	India	1999	77	Megaloblastic anaemia (68%)	Aplastic anaemia (7.7%)
Kumar et al[21]	India	1999	166	Aplastic anaemia (29.51%)	Megaloblastic anaemia (22.3%)
Khodke et al[22]	India	2000	50	Megaloblastic anaemia (44%)	Aplastic anaemia (14%)
International arganulocytosis and aplastic anemia study group[23]	Israel & Europe	1987	319	Aplastic anaemia (52.7%)	Myelodysplastic syndrome (4.5%)
Present study	Bangladesh	2011	50	Aplastic anaemia (36%)	Myelodysplastic syndrome (18%)

Discussion:

Pancytopenia is not an uncommon hematological problem encountered in our clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anaemia, prolonged fever and tendency to bleed[24]. There are varying reports on the underlying aetiology of pancytopenia from various parts of the world[25].

In present study among 50 patients with pancytopenia 40 were males and 10 were females, with male: female ratio of 4:1. It was 2.6:1 in the study done by Lakhey et al, [26] and 2:1 in the study by Mussarrat Niaze and Fazil-i-Raziq[27]. In this study of pancytopenic patients the highest incidence was in the age group of 11-20 years,followed by 41-60 yrs of age. Mussarrat Niaze and Fazil-i-Raziq in their study also found most common age group of pancytopenia in the range from 12-30 years[27]. The mean age was 37.5 years with a range of 3-80 years. Osama Ishtiaq et al[24] and Gayathri B N et al[1]. in their studies found mean ages to be 36.7 years and 41 years respectively. Lakhey et al[26] also found the mean age was 40 years in their study.

The commonest cause of pancytopenia in present study was Aplastic anaemia (36%). Table V shows comparison of 1st and 2nd most common causes common causes of pancytopenia in different studies conducted in different countries[11,19,23]. Hypoplastic anaemia was commonest cause of pancytopenia. However, in some studies hypoplastic anaemia was next to megaloblastic anaemia and latter was the commonest cause of pancytopenia[19,22]. But in a study done by Keisu et al[20] neoplastic disease was the commonest cause of pancytopenia, unlike present study in which it was third in the list. The high frequency of malaria and kalazar in their study may be due to study done in an endemic area. In our study 6 cases of pancytopenia showed leishmaniasis and malaria was detected in 1 case. Only a single study showed MDS as the second commonest cause of pancytopenia[23] like present study. The incidence of aplastic anaemia quoted from west is 10–25%[28]. In present study Aplastic anaemia was the predominant causes of pancytopenia (36%), similar to study conducted by Deepak B Kumar et al[28] (33.33%), Jha et al,[29] (29.5%). Aplastic anaemia was the commonest causes of pancytopenia in some studies ranging from 24%-49% and the second cause in other studies. High incidence of aplastic anaemia was reported in Philippine (54%)[30] and Nepal (30%)[31]. In those two studies, males were affected with aplastic anaemia much more than females which might be a result of a higher incidence of occupational exposure to chemicals and pesticides[32]; the reverse is seen in Iraqi rural community as females use these substances more than males[28].

Over 60% of patients are over the age of 70 at diagnosis, with males more likely to be diagnosed with MDS than females by a ratio of 1.4 : 1.[33] Similarly in present study all the cases of MDS was found within the age group of 61-70 yrs, with male, female ratio was 2:1. The incidence of MDS as a cause of pancytopenia was 8.33% in a study conducted by Deepak B kumar et al[28]. while in present

study MDS was the 2nd most common causes of pancytopenia (18%).

Visceral leishmaniasis was the third most common causes of pancytopenia in present study as found in 12% cases. Similar findings was reported by Najlaa Badir Al-Awadi et al[34]. All the cases of visceral leishmaniasis were from Gajipur, Dhaka, near the endemic zone of this disease, in Bangladesh. Sud A et al.[35] and Sever-Prebilic M et al.[36] have reported the presence of visceral leishmaniasis in non -endemic areas. So, if there is pancytopenia with history of splenomegaly and fever one should think of visceral leishmaniasis even if patient is not from endemic area or not exposed to such area. Visceral leishmaniasis is one of the common cause of pancytopenia and frequency is very high in some studies done in India and Pakistan[37].

The incidence of megaloblastic anaemia in other studies varied from 0.8% to 68%[28]. This wide variation of incidence of megaloblastic anaemia depends on the status of the nutritional anaemia in that particular region of the study. The incidence was 8% in present study, most of the cases was found between the age group of 51-60 yrs and all the cases were male. Out of 4 patients 1 had evidence of malabsorption syndrome, and the remaining 3 cases the underlying disorder could not be established and evaluation of serum folate or vit B-12 was not available in this study.

Pancytopenia can be seen in 30% cases of acute leukaemia at the time of presentation[22]. Acute leukaemia constituted 12% of total cases of pancytopenia in present study which is low as compared to study of Jha et al[29]. in which it constituted 19.59% of total cases of pancytopenia. However, in study of Deepak B Kumar et al[28] no cases of acute leukaemia was detected and in study of Tilak et al[19] only 1 case of acute leukaemia was detected as a cause pancytopenia. On the other hand in the study of Bashwari et al[38] the main indication of bone marrow examination (BME) in case of pancytopenia was investigation of acute leukaemia. Acute leukaemia constituted third most common cause of pancytopenia in the study of Savage et al[39] and similar finding was seen in study of Varma and Dash[11]. In the study of Aziz et al[40] acute leukaemia constituted almost 10% of cases of pancytopenia and was third most common cause of pancytopenia.

In France, Imbert et al[41] founded myelofibrosis on bone marrow biopsy of adult patients with pancytopenia in 31% of them; while in present study, only 4% cases of myelofibrosis was found and all the cases were was diagnosed by bone marrow trephine biopsy.

Erythroid hyperplasia was present 4% cases of the present study and Splenomegaly was seen in both the cases of erythroid hyperplasia in present study. Some of these cases may represent one phase in the evolution of hypoplasia, while some may be cases of refractory anemia. The criteria for differentiation of these groups remain unsatisfactory and these patients should be kept under follow-up. Hypercellular or normocellular marrow in cases of pancytopenia can also be seen in cases with ineffective hematopoiesis with cell death within the marrow. Similarly, hypercellular marrow in the presence of peripheral pancytopenia can be a manifestation of myelodysplastic syndrome[29]. Focal hyperplasia of erythroid or granulocytic cells at a similar stage of maturation may be observed in hot spot. A correlation with BME, clinical parameters and other laboratory parameters are required to trace the cause of pancytopenia in these cases. A possible hypersplenism needs to be ruled out in addition to different haemolytic anaemias in cases of marrow showing erythroid hyperplasia[42].

The annual incidence of Multiple myeloma is 4 per 1,00,000. It represents approximately 1% of all malignant diseases and 15% of all haematological malignancies. The incidence of MM is lower in Asian populations and in blacks is twice that in whites; MM is slightly more frequent in men than in women. The median age at diagnosis is 65 – 70 years. Only 15% and 2% of the patients are younger than 50 and 40 years, respectively[43]. In present study of the remaining causes multiple myeloma accounted for 2 cases (4%).The age of the patients with multiple myeloma were 45 and 65 yrs and both were male. A single case was diagnosed as a cause of pancytopenia in the study done by Pathak et al[42] and Jha et al[29] which shows similarity to this study.

Pancytopenia, a decrease in all the three types of cells in the peripheral blood, commonly presents with symptoms of anaemia or thrombocytopenia. Leucopenia is an uncommon cause of the initial presentation of the patient, but can become fatal during the subsequent course of the disorder. Sometimes pancytopenia is detected as an incidental feature of a disorder that is capable of depressing the levels of all cellular elements in the blood[28]. Figure 2 shows that fever affects all patients of visceral leishmaniasis, while generalized weakness was most often seen in aplastic anaemia. Pallor as a clinical sign was universal in all case of aplastic anaemia, followed by splenomegaly which was found in all cases of visceral leishmaniasis. In another study by Niazi and Raziq weakness (68.2%) was the commonest symptom, followed by fever (47.7%) and bleeding manifestations (33.7%)[27]. With reference to the commonest clinical sign that we came across, pallor was the most common sign, followed by pallor with splenomegaly and pallor with hepatosplenomegaly. In studies conducted by Khodke et al[22], Deepak B Kumar et al[28] and Niazi and Raziq[27], pallor and hepatosplenomegaly were the commonest sign, as in the present study.

We found that the routine hematological parameters were non-specific and showed a significant overlap among the major causes of pancytopenias. Table III shows comparison of common haematological parameters in five major causes of pancytopenia. However, the peripheral

blood films were valuable in pointing toward the cause in patients with megaloblastic anaemia and leukaemia. Bone marrow aspirate was found to be sufficient for diagnosis in most cases of leukaemia and megaloblastic anaemia. Peripheral blood flim findings of present study were comparable with those in other studies shown in Table IV hypersegmented neutrophils were noted in 50% cases of megaloblastic anaemia in present study, compared to 49.35% in Gayathri and Rao[1] study and 84.9% in Tilak V et al[19] study, but Khunger et al[44] in their study demonstrated no hypersegmented neutrophils in megaloblastic anaemia. Also relative lymphocytosis in aplastic anaemia was noted in 66.66% caes in present study compared to 52.63% study done by Gayathri and Rao et a[10] and 50% in study done by Tilak V et al[19].

Conclusion:

The various causes of pancytopenia can be attributed to the geographic area, genetic differences, stringency of diagnostic criteria, and differences in methodology used. Aplastic anaemia is the most common cause of pancytopenia in this study. Severe pancytopenia has significant correlation with poor disease outcome and can be used as a prognostic indicator. There are varying trends in its clinical pattern, treatment modalities, and outcome depending on the different causes of pancytopenia which should kept in mind while managing it. Causes such as megaloblastic anaemia, and infections such as visceral leishmaniasis and malaria are reversible. As a large proportion of pancytopenia is of reversible etiology, early an accurate diagnosis may be life-saving.

Conflict of Interest: None

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