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# Pancytopenia: Etiological Patterns In 50 Cases Admitted In General Medical Wards

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**Abstract: Objective:** To determine the frequency and to identify the various causes of pancytopenia in patients admitted in General Medical Wards.

**Methods:** We conducted a descriptive cross sectional study on fifty patients of pancytopenia admitted in medical wards of Liaquat University Hospital, Jamshoro / Hyderabad from 1st Mar'14 - 30th Sep'14. Out of 50 patients, 33 were males and 17 were females. Patients on cancer chemotherapy, those with a history of recent blood transfusion and those refusing bone marrow examination was not included. Medical History, physical examination and hematological factors at presentation were documented. Hematological summary comprised of hemoglobin level, differential and total leucocytes count, platelet count, reticulocyte count, peripheral smear and bone marrow aspiration/biopsy. The data was analyzed on SPSS version 18.

**Results:** A total of 50 patients with mean age of 37.02 years (± 8.64 SD) were included in the study. Throughout the research period, in a total of 4800 admissions in medical wards, 182 had Pancytopenia on investigation of patient's peripheral blood smear (3. 79%). Those out of 182 subjects suffering from pancytopenia, fifty randomly selected patients were included in the study. Cause of Pancytopenia was identified in 48 cases on the basis of examination of their bone marrow, while 02 cases remained undiagnosed. Megaloblastic anemia came out to be the most common diagnosis (n=17). Hypersplenism due to portal hypertension was the second most common diagnosis (n= 07). Aplastic anemia (n=5), Acute Lymphoblastic leukemia (n=5), Acute Myeloid Leukemia (n=4), Sepsis (n=3) and Myelodysplasia (n=2) were other important causes. Systemic Lupus Erythromatosis (SLE), falciparum malaria, Hodgkin's disease, multiple myeloma were noted one in each case. Viral hemmohagic fever was suspected in one patient. The most frequent clinical presentations were fatigue, pallor, fever, petechial hemorrhages, visceromegaly, nose bleeding and GIT (gastrointestinal tract) bleeding.

**Conclusion:** Pancytopenia is relatively a frequent problem in general medical wards. A thorough assessment is necessary to find out the underlying cause. Megaloblastic anemia, Hypersplenism, Aplastic anemia and acute leukemias were the most common causes. Bone marrow aspiration and trephine biopsy are found to be useful tools in evaluation of Pancytopenia.

**Keywords:** *Pancytopenia, Bone marrow aspiration, Trephine biopsy*

## 1. INTRODUCTION

Pancytopenia is a serious and comparatively common hematological ailment in which all three cellular elements of blood are deficient (Gayathri, 2011, Tariq, 2010). A patient is supposed to have pancytopenia when the hemoglobin is less than 10 g/dl, the leukocyte count is <4000/mm$^3$ and platelet count is fewer than 150000/mm (Lakhey, 2012, Rajput, 2002, Khan, 2001). It generally represents with symptoms of anemia for instance pallor and dyspnea or thrombocytopenia for example bleeding or bruising. At presentation Leucopenia is unusual, but it can instigate life threatening infection later in the disease' (Kumar, 2012). There are wide varieties of etiologies that can cause Pancytopenia, leading to a diagnostic stalemate. In a suspected case of pancytopenia a Complete Blood Count with peripheralsmear and reticulocyte count are the basic investigations. A thorough clinical history and bone marrow examination is requisite to reach an accurate diagnosis (Elizebath *et, al.,* 2013). Investigation of bone marrow is principally believed essential to exclude leukemia or any other malignant infiltration (Aziz, *et, al.* 2013). An invasive but easy process, bone marrow assessment can be of remarkable help to the clinician. It can be carried out in secondary care hospitals consequently greater part of the cases of pancytopenia can be supervised at these centers and do not necessitate referral. Trephine biopsy is usually suggested when there is hypoplasia or aplasia on aspiration (Tariq, *et. al.* 2010, Memon, *et, al.* 2008).

There are varied etiologies of Pancytopenia. Similar to acquired aplastic anemia, Pancytopenia with hypocellular bone marrow can be hereditary or acquired. The inherited cause of pancytopenia includes Fanconi anemia, Diamond-Blackfan anemia and congenital dyskeratosis. Pancytopenia with cellular marrow caused due to Myelodysplastic syndromes, Paroxysmal nocturnal haemoglobinuria, Myelophthisis, Bone marrow lymphoma, Hairy cell leukemia, Systemic lupus erthymatosus, Hypersplenism, B12 and folate deficiency, Overwhelming infection (HIV most common), Alcohol, Sarcoidosis, Tuberculosis and Leishmaniasis (Rajput, *et, al.* 2002). Pancytopenia can seldom crop up after acute viral hepatitis. An acute aplastic emergency usually occurs abruptly after viral

infection (Akoum, *et, al.,* 2007). A gradual onset pancytopenia may take place in patients with liver cirrhosis. T-cell-mediated immune reaction and peripheral sequestration from hypersplenism in combination can lead to pancytopenia Pancytopenia has been hardly reported in patients with hyperthyroidism. Thyroid hormones have been known to potentiate erythropoiesis through the β-adrenergic receptors and lessen the life-span of whole blood component. Immunological systems have also been reported to be concerned in the decrease of the life-span of platelets and blood cells (Hatipoglu, et, al., 2004). Brucellosis can seldom present with pancytopenia (Ishtiaq, *et, al.,* 2004). Geographical conditions and genetic disorders ascertain the incidence of diverse sources of pancytopenia. The management and prognosis depends on severity of pancytopenia and the underlying pathology.

The pathophysiology of these disorders comprises of the following mechanisms of action: (1) a reduction or damage to the hematopoietic stem cells such as by infections, toxins, malignant cell infiltration, resulting in hypoplastic or aplastic bone marrow; (2) ineffective hematopoiesis, for example vitamin B-12 or folate deficiency; (3) differentiation defects, such as Myelodysplasia and (4) peripheral sequestration of blood cells, such as hypersplenism (Tariq, *et, al.,* 2010, Lakhey, *et, al.,* 2012,Yokus, *et, al.,* 2010).

Megaloblastic anemia has been established to be the most frequent cause of Pancytopenia internationally. Nutritional dynamics, recurrent infections, malabsorption syndromes and vitamin B12 and folate deficiencies looks to be linked strongly with megaloblastic anemia. Insufficient dietary vitamin B12 intake is one of the frequent cause of deficiency among vegetarians as vitamin B12 is known to found mostly in animal sources. Megaloblastic anemia is a simple treatable cause of pancytopenia but it by and large presents with imprecise symptoms such as memory loss, irritability and depressed mood and is hard to diagnose. The patient may have walking difficulties because of Sub-acute combined degeneration of spinal cord, which is possibly reversible if diagnosis and treatment is done early. Vitamin B12 deficit should be taken into consideration for the patients with pancytopenia, high LDH levels and neurological symptoms, even though if vitamin B12 and MCV levels are within normal limits (Savage, *et, al.,* 1999). The infants are more at risk of developing severe developmental abnormalities, growth failure, and anemia are more in infants who are breast-fed by vitamin B12-deficient mother (Aziz, *et, al.,* 2010). The causes of pancytopenia are not clearly defined in Pakistan; we undertook the present study to evaluate the various causes on the basis of bone marrow examination. This will help in defining the optimal diagnostic approach in patients with pancytopenia.

## 2. METHODOLOGY

**Study Design:** This was a descriptive cross sectional study.

**Study Place and Duration:** Medical unit III LUMHS Jamshoro from 1st Mar – 30th Sep' 2014.

**Study population:** 50 patients of Pancytopenia on blood CP

**Sample Selection procedure:** Non-probability convenient sampling

**Inclusion Criteria:** Patients aged between 20-60 years and of either sex were included in the study. Criteria for inclusion were presence of all of the following: hemoglobin<10 g/dl; total leukocyte count (TLC) <4,000 / µl and platelet count<150 ,000/ µl.

**Exclusion Criteria:** Those who were already diagnosed on bone marrow examination, those who have recent blood transfusions, those not willing for admission and patients on cancer chemotherapy were excluded.

**Data collection procedure:** Fifty randomly selected patients with pancytopenia, who meet inclusion criteria, were included in the study. After recording age and informed consent, all patients were subjected to complete relevant history including the presenting features, treatment history, history of drug intake, blood transfusion, toxin exposure, dietary history with special focus on intake of vegetables and animal products such as meat, eggs and milk, loose and /or bulky stools, malena, episodes of worms in stool, recent viral infections (e.g. hepatitis), radiation exposure, and socio-economic status. A thorough physical examination was done for pallor, fever, jaundice, hepatomegaly, splenomegaly, lymphadenopathy, purpura, petechie, gum bleed, nose bleed. Neurological examination was carried out to detect any sensory or motor abnormality. Blood samples were drawn in all patients for complete blood count including total leucocytes count, differential count, platelets and reticulocyte count, hemoglobin level and hematocrit. Absolute values including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were calculatedin every patient. Pancytopenia was diagnosed in the presence of anemia (Hb <10 mg/dl), leucopoenia (WBC < 4.01x $10^9$/L) and thrombocytopenia (platelets < 150 x $10^9$/L). Blood smears were obtained for RBC morphology and malaria parasite. Blood counts were conducted on an automated blood analyzer (Sysmex) while differential leukocyte count and red cell morphology was done manually by staining the blood smears by Giemsa stains. Chest X-ray and ultrasound of abdomen was done in selected patients. Bone marrow aspiration was performed from posterior superior iliac

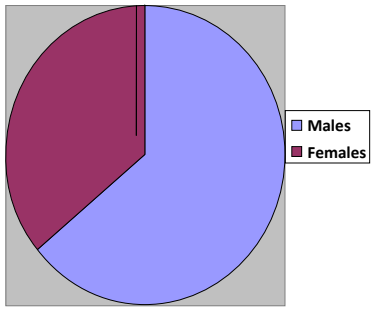
spine under aseptic technique and where required trephine biopsy was also done. The procedure was explained to the patient in detail and an informed written consent was taken. Findings of aspiration and trephine biopsies were interpreted in the light of history, clinical examination and peripheral blood findings.

**Data analysis procedure:** Simple1statistical methods, which include descriptive statistics (mean, median, SD), were used to analyze the results. Cross tabulation was carried out to find out the correlation among different variables. Analysis was done on statistical package for social science (SPSS) version 18. A p value of <0.05 was taken as statistically significant.

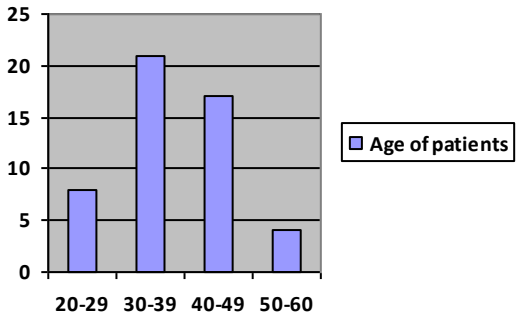
## 3. RESULTS

During the study period, 4800 patients were admitted in general medical wards and out of those, 148 (3.77%) had pancytopenia on blood CP. Among the fifty randomly selected patients who were included in the study, 33 were males and 17 were females (M: F ratio 2:1). Graph no.1 shows the sex distribution of the patients. Mean age was 37.02 years ± 8.64 (SD) with the range of 20-60 year. Majority of the patients were between 30-50 years (n=38). Graph no.2 shows the age distribution of patients. Megaloblastic anemia came out to be the most common diagnosis (34%) followed by hypersplenism due to portal hypertension (14%). Aplastic anemia (10%), Acute Lymphoblastic leukemia (10%), Acute Myeloid Leukemia (8%), Sepsis (6%) and Myelodysplasia (4%) were other important causes. Systemic Lupus Erythromatosis (SLE), falciparum malaria, Hodgkin's disease and multiple myeloma were noted one in each case. Viral hemmohagic fever was suspected in one patient and it came out to be dengue fever. Two cases remain undiagnosed even after bone marrow examination. The etiological breakup of pancytopenia is shown in the **(Table 1)**. Among the presenting features, fatigue was the most common symptom (90%) and pallor was the most common sign (100%). **(Table 2)** shows the presenting features of the patients. Mean hemoglobin of the subjects was 5.08 g/dl with the range of 1-10 g/dl ± 2.76 (SD). Gross anemia (Hb < 4g %) was detected in 21 (42%) patients which includes patients of Aplastic anemia (5), ALL (5), AML (4) and megaloblastic anemia (7). Graph no. 3 shows the hemoglobin status of patients. Thrombocytopenia (platelet count < 150×109/L was present in all patients studied and four of them presented with epistaxis and gastrointestinal bleeding whose platelet counts were < 10×109/L. Two of them had aplastic anemia and one each hypersplenism and megaloblastic anemia. The most common finding on peripheral smear examination was anisocytosis (69%), followed by macrocytosis (54%) and hypersegmented neutrophils (28%). The MCV was > 110 fl in fifteen patients (30%) who had megaloblastic anemia. Hypersegmented neutrophils were detected in 14 patients of megaloblastic anemia (82.35%). This indicates the importance of peripheral smear examination in the evaluation of pancytopenia.

**Graph No.1: Sex distribution of subjects**




**Graph No.2: Age distribution of the Subjects**




**Graph No.3: Hemoglobin status of patients studied.**

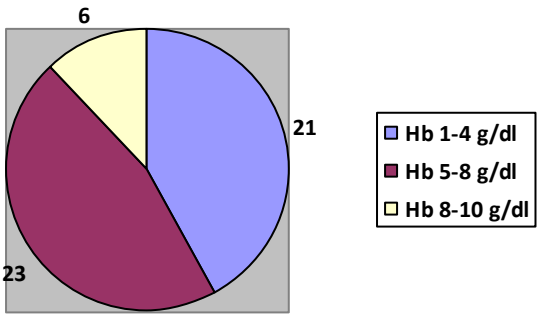


**Table 1. Causes of Pancytopenia in subjects studied (n = 50)**

| Diagnosis | Frequency | % |
|---|---|---|
| Megaloblastic Anemia | 17 | 34 |
| Hypersplenism | 07 | 14 |
| Aplastic Anemia | 05 | 10 |
| ALL | 05 | 10 |
| AML | 04 | 8 |
| Sepsis | 03 | 6 |
| Myelodysplasia | 02 | 4 |
| Malaria | 01 | 2 |
| SLE | 01 | 2 |
| Myeloma | 01 | 2 |
| Hodgkin Disease | 01 | 2 |
| Dengue fever | 01 | 2 |
| No Cause | 02 | 4 |

**Table No.2: C/F of Pancytopenia in subjects (n = 50)**

| C/F | Number | Percentage |
|---|---|---|
| Pallor | 50 | 100 |
| Fatigue | 45 | 90 |
| Dyspnea | 26 | 52 |
| Fever | 23 | 46 |
| Splenomegaly | 16 | 32 |
| Jaundice | 08 | 16 |
| Lymphadenopathy | 05 | 10 |
| Hepatomegaly | 04 | 8 |
| Bleeding | 04 | 8 |
| Petechiae/purpura | 03 | 6 |
| Bone Tenderness | 02 | 4 |
| Weight loss | 02 | 4 |
| Edema | 01 | 2 |

## 4. DISCUSSION

Pancytopenia is not an uncommon hematological problem encountered in general medical wards and it should be suspected when a patient seeks medical advice for unexplained anemia, prolonged fever and tendency to bleed. Underlying it are various causes which are diagnosed on bone marrow examination. The early diagnosis of the cause of Pancytopenia is important because most of these causes are treatable. We undertook this study to find out the frequency and causes of pancytopenia. Present research during the six months study period, find out that a little over percent of patients admitted in general medical wards had pancytopenia on blood CP. (Memon, *et, al.,* 2008) showed that pancytopenia was also quite common in children (3.5%). The mean age of our patients was 37 years with the male to female ratio of 2:1. Different male to female ratio and age range were observed in different studies. **(**Tariq, *et, al.,* 2010, Lakhey, *et, al.,* 2012, Kumar, and Raghupathi, 2012). In our study, megaloblastic anemia makes the largest group among the causes of pancytopenia which is consistent with the studies by Savage, *et, al.,* 1999, Iqbal, *et, al.,* 2001, Aziz, *et, al.,* 2010, Gayathri, *et, al.,* 2011, Khalid, *et, al.,* 2005, Dodhy, *et, al.,* 2005 and Qazi, *et, al.,* 2002. In the West, megaloblastic anemia is less common and only 13.7% cases were reported in patients with pancytopenia in a study done in New York *(Gamal and Safa 2008)*. In India, it is common because of vegetarianism as vitamin B12 is present in animal products (Aziz, *et, al.,* 2010). In Pakistan poverty and poor quality of food may be responsible for high prevalence of megaloblastic anemia. Moreover megaloblastic anemia usually presents with vague symptoms so it should be suspected in patients who presents with symptoms of anemia or pancytopenia as the consequences may be devastating (Savage, *et, al.,* 1999). The incidence of megaloblastic anemia in other studies varied from 0.8% to 68% (Kumar and Raghupathi 2012). This wide variation of incidence of megaloblastic anemia depends on the status of the nutritional anemia in that particular region of the study. The second most common diagnosis in our study was hypersplenism due to portal hypertension. It is understandable because of prevailing situation of hepatitis B and C in our country. These patients had positive anti hepatitis C antibodies and their ultrasound report shows cirrhosis with dilated portal vein. Our finding is in agreement with Ishtiaq, *et, al.,* 2004, Dodhy, *et, al.,* 2005, Yokus, *et, al.,* 2010, Qazi and Masood 2002 who also noted hypersplenism as the second most common diagnosis. In a study done in Yemen, hypersplenism due to malaria, Kalazar and other infectious diseases was the second most common diagnosis of pancytopenia (Niazi and Raziq, 2004) Other studies also reported hypersplenism among the common causes of pancytopenia (Khodke, *et, al.,* 2001). Although the commonest cause of pancytopenia, reported in various studies throughout the world has been aplasticanemia, in our study it came out to be third on the list. Aplastic anemia is more common in developing world than in western population. This is just opposite to that for leukemias. The incidence of aplastic anemia in west varied between 10-25% (Aziz, *et, al.,* 2010) whereas studies done in developing countries show higher results (36%-41%) (Aziz, *et, al.,* 2010). Environmental exposure to toxic chemicals, pesticide use in agricultural field and indiscriminate use of medicines in poor countries may be responsible for this state of affairs. Moreover hepatitis is more prevalent in developing world and hepatitis associated aplastic anemia is a known entity which can occur after acute attack of hepatitis. Besides HBV and HCV, HGV may cause aplastic anemia. The incidence of hypoplastic anemia was14% to 19% in studies conducted in subcontinent (Jha and Sayami, 2010). A higher incidence, viz, 33.33%, was reported by (Kumar and Raghupathi, 2012).

In our study, Leukemias were among the common underlying diagnosis presenting in nine patients. ALL (10%) was more common than AML. In a study done

by Tariq, *et, al.,* 2010, similar trends were noted with ALL presenting in 12% cases. The incidence of ALL in our country is lower as compared to the developed countries, as is the case in India and China (Tariq, *et, al.,* 2010). In a study done in Nepal, 27.78% of patients presented with hematologic malignancy. AML was the most common malignancy diagnosed in 12.96% of the total cases (Lakhey and Talwar, 2012). Savage, *et, al.,* 1999, Jha, *et, al.,* 2008 and Qazi, *et, al.,* 2002 describe leukemias as the 3rd most common cause of pancytopenia.

In our study, we found MDS in percent cases of pancytopenia. Similar trend was observed in a study done by Aziz, *et, al.,* 2010. Slightly higher results (7-8%) were reported in other studies (Lakhey & Talwar, 2012). **(Table 3)** compare the diagnosis in different studies.

Among the clinical features, pallor was the most common sign and fatigue was the most common symptoms in current study. Other clinical features which were noted in decreasing order of frequency were dyspnea, fever, splenomegaly, Jaundice, lymphadenopathy, hepatomegaly, bleeding, Petechiae/purpura, weight loss and bone tenderness. Almost similar findings were observed in other studies (Gayathri, *et, al.,* 2011, Tariq, *et, al.,* 2010). In a study done by Aziz, *et, al.,* 2010, the common presentations were pallor weakness and shortness of breath. A significant finding was edema in 24% cases whereas edema was noted in only one patient in our study. In a study done in Yemen (Niazi & Raziq, 2004), the commonest presenting complaint was fever in 86.7% cases followed by fatigue in 76% and dizziness in 64% of the cases. Pallor was seen in all patients.

In our study, the most common finding on peripheral smear examination was anisocytosis, followed by macrocytosis and hypersegmented neutrophils. In another study, anisocytosis (79.1%) was the most important peripheral blood finding followed by microcytosis (Kumar, D. B. and Raghupathi, A. R. 2012). An interesting finding in our study was the raised MCV above 100 fL in patients with megaloblastic anemia. Almost similar results were seen in studies done by Savage, *et, al.,* 1999, Iqbal, *et, al.,* 2001, Qazi, *et, al.,* 2002 and Ishtiaq *et, al.,* 2004. Given the above observations, one should consider megaloblastic anemia1on top when MCV is above 100 fL.

**Table No.3: Comparison of etiology of pancytopenia with other studies**

| Study | No. of cases | First cause | 2nd cause |
|---|---|---|---|
| Kumar, et, al.[6] | 48 | Aplastic Anemia (33.3%) | Erythroid hyperplasia (27.08%) |
| Aziz, et, al.,[8] | 88 | Megaloblastic Anemia (40.9%) | Aplastic Anemia (31.8%) |
| Lakhey, et, al.,[3] | 54 | Aplastic Anemia (29.6%) | Leukemias (27.7%) |
| Iqbal, et, al.,[16] | 208 | Megaloblastic Anemia (28.3%) | Aplastic Anemia (22.1%) |
| Niazi, et, al.,[22] | 89 | Aplastic Anemia (35.3%) | Megaloblastic Anemia (24.7%) |
| Dodhay, et, al.,[18] | | Megaloblastic Anemia (35.9%) | Hypersplenism (16.3%) |
| Yemen[21] | 75 | Hypersplenism (45%) | Megaloblastic Anemia (14.7%) |
| Osama, et, al.,[13] | 100 | Megaloblastic Anemia (39%) | Hypersplenism (19%) |
| Gayathri, et, al.,[1] | 104 | Megaloblastic Anemia (74.04%) | Aplastic Anemia (18.26%) |
| Savage, et, al.,[15] | 134 | Megaloblastic Anemia | Aplastic Anemia |
| Jha, et, al.,[25] | 148 | Aplastic Anemia (29%) | Megaloblastic Anemia (23.6%) |
| Santra and Das[27] | 111 | Aplastic anemia (22.72) | Hypersplenism (11.7) |
| Gupta, et, al.,[26] | 105 | Aplastic anemia (43) | Acute leukemia (25) |
| This Study | 50 | Megaloblastic anemia (34%) | Hypersplenism (14%) |

## 5. CONCLUSION

We conclude that Pancytopenia is relatively a common problem in general medical wards. A thorough assessment is necessary to find out the underlying causes. Bone marrow aspiration and trephine biopsy are found to be useful tools in evaluation of Pancytopenia.

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