The etiological spectrum of pancytopenia diagnosed from blood smears examined in the pathology department of a rural tertiary care centre in South India

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ABSTRACT

Background: Pancytopenia is a reduction in all three formed elements of blood, namely - erythrocytes, leukocytes, and platelets. This triad of findings occurs in a number of clinical conditions. The underlying pathology determines the management and prognosis of the patients. Identification of the precise cause is exceptionally challenging and requires a systematic study on the detailed clinical history, drug history, and comorbidities of the patients. Early diagnosis and initiation of prompt therapy will be lifesaving. The causes of pancytopenia vary in different populations and this study will document the etiology of pancytopenia in this region. **Objectives:** The objectives of this study were to find out the prevalence and etiological spectrum of pancytopenia in patients diagnosed to have pancytopenia from blood smears done in this institution. **Materials and Methods:** This is a cross-sectional, medical record-based study of patients diagnosed to have pancytopenia from peripheral blood smears to find the prevalence of pancytopenia in patients coming to this rural teaching hospital during a 7 months period in 2015. **Results:** Of the 2813 blood smears examined in the pathology department of this rural medical college, 61 (2.16%) were diagnosed to have pancytopenia. Of these, 46 patients who fulfilled the selection criteria were recruited to the study. The most common causes of pancytopenia were chronic liver disease (17, 37%), followed by dengue fever (9, 19.6%) and hematological malignancies (4, 8.7%). The common presenting symptoms were fatigue and weakness (36, 76.1%) and fever (26, 56.6%). The most common presenting signs were pallor (9, 19.6), splenomegaly (7, 15.2%), and hepatomegaly (6, 13%). **Conclusion:** Chronic liver disease related to alcoholism and dengue fever is the most common causes of pancytopenia in this clinical setting. The common presenting symptoms include fever and fatigue.

KEY WORDS: Pancytopenia; Blood Smear; Hepatomegaly; Splenomegaly

INTRODUCTION

Pancytopenia is an important clinicohematological entity that is encountered by physicians in their daily practice.

Pancytopenia is defined as the reduction of all three major formed elements of blood; erythrocytes, leukocytes, and platelets. It is not a disease entity, but a triad of findings that may result from a number of disease processes. The onset of pancytopenia often is insidious, and the manifestations depend on the severity of anemia, leukopenia, and thrombocytopenia.[1] Pancytopenia is a common hematological finding with a vast spectrum of differential diagnoses. The causes of pancytopenia can be due to decreased hematopoietic cell production, increased destruction of marrow tissue or increased peripheral destruction of blood

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cells, infiltration of marrow by abnormal or malignant tissue, and ineffective hematopoiesis. If not diagnosed at an early stage, it may be fatal.[2]

Pancytopenia results from a multitude of conditions that result in ineffective hematopoiesis with cell death in the marrow, formation of defective cells that are rapidly removed from the circulation, sequestration, or destruction of cells by the action of antibodies, and trapping of normal cells in a hypertrophied and overactive reticuloendothelial system.[1] Identification of the precise cause is exceptionally challenging and requires a systematic study on the detailed clinical history, drug history, and comorbidities of the patients. Along with this, proper diagnostic methods and clinical correlation are important and will help in implantation of relevant and prompt therapy which could be lifesaving. The criteria for diagnosis of pancytopenia were hemoglobin <10 g/dl, leukocyte <3500/cumm, and platelet count <1,00,000/cumm.[3]

The underlying pathology determines the management and prognosis of the patients.[1-3] The etiology of pancytopenia varies in different populations depending on the nutritional status, climate, age patterns and prevalence, and pattern of infections.[4] Hence, it is very important to conduct studies to determine the common causes in a clinical setting so that appropriate investigations and treatment can be implemented.

Few studies have determined the prevalence of pancytopenia as a peripheral smear finding. In the study by Khunger *et al.*, the prevalence of pancytopenia was found to be 1.7% and in the study by Devi *et al.*, the prevalence was 0.2%.[5,6]

The etiology of pancytopenia varies in different populations depending on the differences in nutritional status, climate, age patterns and prevalence, and pattern of infections.[4] The varied causes of pancytopenia can be attributed to the geographic area, genetic differences, stringency of diagnostic criteria, and differences in methodology used. It could be stressed here that a careful examination of the blood film is often helpful in giving a lead to the diagnosis and a marrow examination usually establishes the diagnosis.[7] The major causes of pancytopenia include megaloblastic anemia,[3,5,8-10] aplastic anemia,[11-13] hypersplenism,[13-17] sub-leukemic leukemia,[5,9] and infections.[8,17]

The clinical triad of anemia, leukopenia, and thrombocytopenia in peripheral blood seen in pancytopenia may be due to bone marrow failure or infiltration, pooling and destruction of blood cells in the reticuloendothelial system, ineffective hematopoiesis or very often due to suppression of marrow by cytotoxic drug therapy.[11] The presenting symptoms are attributable to the anemia or the thrombocytopenia. Leukopenia can become the most serious threat to life during the subsequent course of the disorder.[18]

The major etiological factors can be classified into:
Disorders due to infiltration of the bone marrow including subleukemic/aleukemic leukemia, multiple myeloma, myelofibrosis, lymphoma, and metastatic carcinoma.[8]

Disorders involving the spleen include congestive splenomegaly associated with chronic active hepatitis, portal hypertension due to various causes, the most common being cirrhosis of the liver, lymphomas, and metabolic disorders that cause accumulation of substrates in the spleen such as Gaucher's disease, Niemann–Pick disease.[8] Infectious diseases such as miliary tuberculosis and kala azar. Suppress the marrow by toxins and cause splenomegaly. In disseminated lupus erythematosus, the pancytopenia may be due to moderate splenomegaly and/or autoimmune destruction of blood cells.[19]

Deficiency of Vitamin B12 or folic acid can lead to megaloblastic anemia due to impaired DNA synthesis due to Vitamin B12 and/or folic acid.[6]

Miscellaneous disorders include overwhelming infections, mycobacterial infections, brucellosis, sarcoidosis, some refractory anemias, sideroblastic anemia, and drug sensitivity.

Pancytopenia is a diagnostic dilemma that can be caused in several conditions. While the above are the common causes of pancytopenia, bone marrow space-occupying lesions and chronic myeloid leukemia, Sheehan's syndrome, and filariasis are rare causes that have been reported.[9,20,21]

Numerous studies conducted have shown that the frequency of each condition differs considerably depending on the differences in methodology, stringency of diagnostic criteria, period of observation, geographic area, age pattern, nutritional status, prevalence of infectious diseases, genetic differences, and varying exposure to myelotoxic agents among other factors.[11] Hence, the need for this study to establish the etiological spectrum of patients with pancytopenia in this region.

In our clinical setting, the causes of pancytopenia are not well defined, especially because alcohol consumption is on the rise and there are a greater number of people who are dependent on alcohol and presenting with liver disease. There is a need to identify the clinical features and causes of pancytopenia to help clinicians to make an early diagnosis and initiate treatment. There have also been reports of pancytopenia caused by rare conditions.[9,20,21] Thus, there is a need to document the common causes and clinical manifestations of pancytopenia in patients attending this institution from the surrounding rural areas.

Thus, this cross-sectional study was undertaken to find the prevalence of pancytopenia from peripheral blood smears examined in the clinical pathology laboratory in this rural teaching hospital and to determine the common causes of pancytopenia in the age group of 12–80 years.

MATERIALS AND METHODS

Permission to conduct this study and to access the medical records was obtained from the Medical Superintendent of this Medical College. Approval was received from the institutional review board and ethical committee before starting the study.

This is a cross-sectional study on blood smears sent to the pathology department of this rural teaching hospital during January 2015 to August 2015. All blood smears examined in the pathology department showing pancytopenia were eligible for being included on the study.

Blood smears from patients between ages of 12 and 80 years diagnosed to have pancytopenia by the criteria hemoglobin <10 gm/dl, total leukocyte count <3500/cumm, and platelet count <100,000/cumm were serially recruited to the study. Patients who had a blood transfusion before taking blood smear were excluded from the study.

The sample size was measured using nMaster Sample Size Computer Software[22] for single proportion using the prevalence from a study from South India,[3] where pancytopenia was found in 3% of blood smears examined. Sample size was calculated for single proportion for a confidence level of 95% and a precision of 5% for the expected proportion of 0.03. The sample size needed will be 45 samples of pancytopenia.

All data have been stored anonymously using code numbers and were handled only by the investigator and authorized investigators of this study.

The prevalence of pancytopenia in peripheral blood smears examined in the pathology department was found, and the proportions for the clinical features and causes of pancytopenia were found using SPSS computer software. The study flow diagram is given in Figure 1.

RESULTS

A total of 2813 peripheral smears were examined for hematological studies between January 2015 and August 2015. Of these, 61 showed evidence of pancytopenia. The study sample of 46 patients consisting of an equal number (23) of males and females was recruited serially from the above. The age of patients ranged from 12 years to 80 years with a mean age of 48 years. The baseline characteristics are given in Table 1.

61 of the 2813 blood smears (2.16%) collected during the period showed pancytopenia. The prevalence of pancytopenia in the blood smears examined is given in Figure 2.

The etiological spectrum of pancytopenia is shown in Figure 3.

The common symptoms were generalized weakness and fatigue in 36 (76.1%) patients, followed by fever 26 (56.6%), vomiting

Table 1: Baseline characteristics of patients

| Characteristics	Value (%)
Age (*n*=46) (years)	
12–40	10 (21.7)
41–50	12 (26.1)
51–60	10 (21.7)
Over 60	14 (30.4)
Gender (*n*=46)	
Male	23 (50)
Female	23 (50)
Symptoms (*n*=46)	
Generalized weakness	35 (76.10)
Fever	26 (56.55)
Myalgia	13 (28.3)
Vomiting	13 (28.3)
GI bleeding	8 (17.4)
Abdominal pain	6 (13)
Signs	
Pallor	9 (19.6)
Splenomegaly	7 (15.2)
Hepatomegaly	6 (13)
Ascites	3 (6.5)

GI: Gastrointestinal
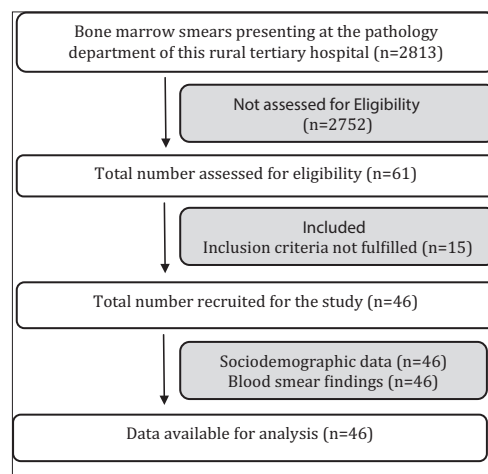
**Figure 1:** Study flow diagram for observational studies

13 (28.3%), myalgia 13 (28.3%), gastrointestinal bleed 8 (17.4%), and abdominal pain 6 (13%). Pallor was the predominant presenting sign 9 (19.6%), followed by splenomegaly 7 (15.2%), hepatomegaly 6 (13%), and ascites 3 (6.5%).

Chronic liver disease was the most common etiology among the 23 male patients (14 [60.1%]) while dengue was the most common cause of pancytopenia in female patients (9 [39.1%]) only two female patients had chronic liver disease while only one male patient had dengue.

Chronic liver disease and hematologic malignancies were more common in the 51–60 year age group while dengue and other causes were more likely in patients over 40 years [Figure 4].
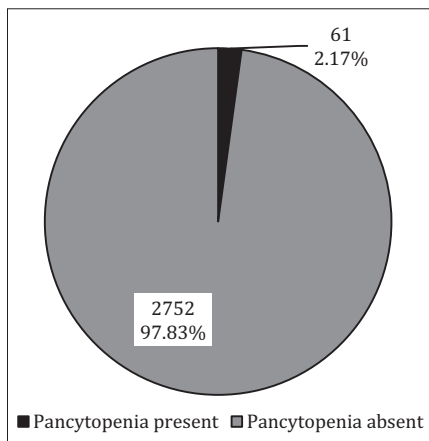
Figure 2: Prevalence of pancytopenia
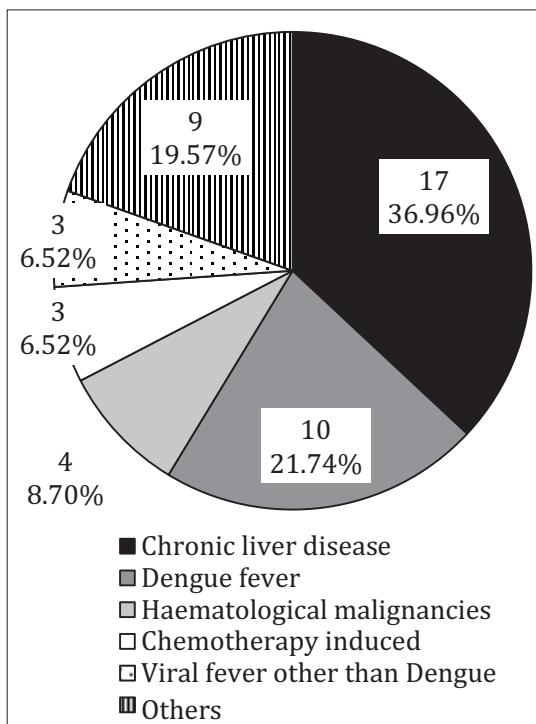
Figure 3: Etiological spectrum of pancytopenia

DISCUSSION

Of the total of 2813 blood smear samples examined 61 showed pancytopenia giving the prevalence of pancytopenia in this institution of 2.16%.

The most common cause of pancytopenia in the present study was chronic liver disease 17 (37%), followed by dengue fever 10 (21.7%). Hematological malignancies accounted for 4 (8.7%) patients while chemotherapy-induced pancytopenia and viral fever other than dengue accounted for 3 (6.5%) each. Other conditions causing pancytopenia 9 (19.6%), included two cases of megaloblastic anemia and one each of myelodysplastic syndrome, aplastic anemia, systemic lupus erythematosus, Rosai-Dorfman syndrome, malaria, toxoplasmosis, and sickle cell anemia.

The most common cause for pancytopenia among males was chronic liver disease while in females it was dengue fever. This may be a reflection of the large number of males who are alcohol dependent in this part of the country.

In the present study, the most common cause of pancytopenia was chronic liver disease secondary to alcoholic cirrhosis (37%) whereas, in other similar studies, the chronic liver disease as a cause for pancytopenia varied from 3% to 68% [Table 2]. This may be due to the current increasing trend of alcohol dependence in this part of the country; leading to an alarmingly large number of patients presenting with chronic liver disease and decompensated liver cirrhosis, hypersplenism being one of its consequences. Similar results were also obtained in the study by Kale *et al*. and Jain and Naniwadekar.[14,17]

Pancytopenia in chronic liver disease can be due to hypersplenism, megaloblastic anemia, and primary marrow suppression. Hypersplenism is the most common cause of pancytopenia in chronic liver disease. Hypersplenism is a clinical syndrome characterized by enlargement of spleen, reduction of at least one cell line in the blood in the presence of normal marrow function, and evidence of increased release of premature cells such as reticulocytes or immature platelets from the bone marrow into the blood. Hypersplenism is a treatable cause of pancytopenia, and hence, timely intervention can reduce patient morbidity and mortality to a great extent.[16]

The next common cause in this study was found to be dengue fever (21.7%) which may be due again to hypersplenism, hemophagocytosis, or immune hemolysis. Although dengue fever per se has not been implicated as a cause of pancytopenia in similar studies, infections and post-viral illness have been reported to be responsible for pancytopenia.[2,17] With dengue assuming epidemic proportions in this region during the summer months, this is a very important finding to enable clinicians to increase suspicion of pancytopenia, early diagnosis and treatment.

The third common causes were hematological malignancies (8.7%). Four patients presented with hematological malignancies which included acute myeloid leukemia, multiple myeloma, myeloproliferative disorder, and non-Hodgkin's lymphoma (all four were the first time diagnoses and were not on any treatment). The frequency of hematological malignancies causing pancytopenia from our study is comparable to that obtained in similar studies where it ranges from 3.8% to 14.5% [Table 2].

Table 2 is taken from Jain and Naniwadekar and gives a comparison of the three most common causes of pancytopenia in different studies conducted in different countries.[17] Chemotherapy-induced pancytopenia (6.5%) and viral fever other than dengue (6.5%) were the next most common causes of pancytopenia. However, there are significant differences in the frequency of certain diseases obtained in this study and other similar studies.
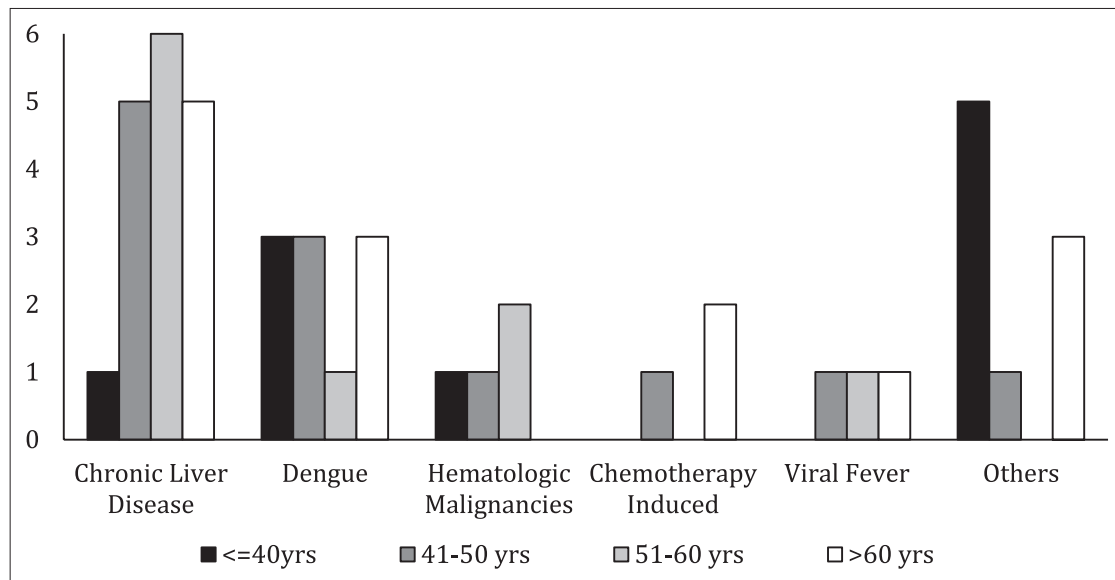
Figure 4: Age distribution of causes of pancytopenia

Table 2: Comparison of number of cases and three most common causes of pancytopenia in different studies conducted in different countries

Study	Country	Year	Number of cases	Common cause (%)	2nd common cause (%)	3rd common cause (%)
Kale *et al.*[14]	India	1991	70	HS (47.6)	MA (25.4)	AL (14.5)
Tilak and Jain *et al.*[3]	India	1999	77	MA (68)	AA (7.7)	Other causes (24.3)
Savage *et al.*[8]	Zimbabwe	1999	134	MA	AA	AL
Kumar *et al.*[11]	India	2001	166	AA (29.5)	MA (22.3)	Aleukemic leukemia (12)
Iqbal *et al.*[23]	Pakistan	2001	208	MA (28.3)	AA (22.1)	HS (14.4)
Khunger *et al.*[5]	India	2002	200	MA (72)	AA (28)	Subleukemic leukemia (5)
Niazi and Raziq.[18]	Pakistan	2004	89	BM aplasia (38.3)	MA (24.7)	HS (18.4)
Ishtiaq *et al.*[24]	Pakistan	2004	100	MA (39)	HS (19)	AA and HA (10)
Hamid and Shukry[15]	Yemen	2008	75	HS (45.3)	MA (14.7)	AA (13.3)
Devi *et al.*[6]	India	2008	50	HA (22)	MA (18)	MDS (18)
Tariq *et al.*[12]	Pakistan	2010	50	AA (36)	MA (16)	MDS (14)
Santra and Das[13]	India	2010	111	AA (22.72)	HS (15)	DI (13)
Aziz *et al.*[25]	Pakistan	2010	88	MA (40.9)	AA (31.9)	HS and CM (11.4)
Ashraf and Naeem[16]	Pakistan	2010	150	HS (68)	MA (25.4)	HM (6.6)
Gayathri and Rao[9]	India	2011	104	MA (74.04)	AA (18.3)	Sub leukemic leukemia (3.8)
Raphael *et al.*[19]	India	2012	80	MA (41.2)	DA (8.7)	AA/HA (8.7)
Jain and Naniwadekar[17]	India	2013	250	HS (29.2)	Infections (25.6)	Myelosuppressants (16.8)
Present study	India	2015	46	CLD (37)	Dengue fever (21.7)	Hematological malignancies and chemotherapy-induced and viral fever other than dengue (6.5 each)

HS - Hypersplenism, MA - Megaloblastic anemia, AA - Aplastic anemia, AL - Acute leukemia, HA - Hypoplastic anemia, BM - Bone marrow, DI - Drug induced, HM - Hypoplastic marrow, MDS - Myelodysplastic syndrome, CM - Chronic malaria, DA - Dimorphic anemia. Table courtesy - Jain and Naniwadekar[17]. CLD: Chronic liver disease

The prevalence of megaloblastic anemia varies from 74% to 13% in similar studies [Table 2], whereas it is only 4.3% in the present study and this could probably be an underestimation due to lack of investigations or reporting. Furthermore, the frequency of aplastic anemia in similar studies ranges from 7.7% to 36% [Table 2] while it is only 2.17% in the present study.

The prevalence of pancytopenia in this rural area is not known and this study may give us a rough estimate following which more elaborate studies may be undertaken by the department.

Pancytopenia is a treatable condition and this information will be made available to the clinicians to enable early

diagnosis and relevant management of patients with pancytopenia.

This study will help the clinicians to raise the level of suspicion for diagnosing pancytopenia in chronic liver disease which is highly prevalent in this region due to increase in alcohol consumption.

The limitation of this study is the small number of patients included. Larger prospective epidemiological studies may enable more evidence-based institutional guidelines for the management of pancytopenia.

CONCLUSION

The prevalence of pancytopenia diagnosed from blood smears examined in this rural setting was 2.16%. The most common cause of pancytopenia was found to be chronic liver disease followed by dengue fever and hematologic malignancies. Fever, fatigue, and generalized weakness were the most common symptoms, and pallor, splenomegaly, and hepatomegaly were the most common signs.

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