Research Article

Etiological diversities in abnormal reduction of all blood cells: An institutional experience

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Abstract

Introduction: Pancytopenia is not an uncommon haematological entity and is encountered in our day to day clinical practice. It is referred to as reduction in all the three formed elements of blood: red blood cells, white blood cells and platelets. The aetiology of pancytopenia varies in different populations depending on the differences in age patterns, nutritional status, climate and the prevalence of infections. The causes can also range from transient viral marrow suppression to marrow infiltration by life threatening malignancies. Not many studies are available enumerating the various causes of pancytopenia. The main purpose of this study was to determine the spectrum of causes of pancytopenia and to determine their frequencies. **Materials and Methods:** 223 patients who aged between 18-75 years were analysed through primary investigations like peripheral smear examinations and complete blood hemogram along with history and general physical examination. Bone marrow studies were performed only when clinically indicated. Other investigations were also performed to confirm the diagnosis. **Results:** This study included a total 223 patients with pancytopenia. The age of the patients in the study ranged from 18 years to 75 years, with a mean age of 43.7 years. Most common cause for pancytopenia was malaria (31.8%). Commonest presenting symptom was fever (62.7%) and the most common physical finding was pallor (32.7%). **Conclusion:** A Panel of primary investigations coupled with detailed history and general physical examination helps to diagnose or rule out various causes of pancytopenia. Invasive procedures like bone marrow aspiration or biopsy are not mandatory for diagnostic purpose in every case of pancytopenia.
Keywords: Pancytopenia, Malaria, Fever, Pallor.

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INTRODUCTION

Pancytopenia is an important clinico hematological entity encountered in our day to day clinical practice. There are varying trends in its clinical pattern, treatment modalities and outcome.[1] It is a reduction in all the three cellular elements of blood and results in anemia, leucopenia and thrombocytopenia. The causes of pancytopenia can be due to ineffective hematopoiesis with cell death in the marrow; formation of defective cells which are rapidly removed from circulation, sequestration and or destruction of cells by the action of antibodies or trapping of normal cells in a hypertrophied and over-reactive reticulo endothelial system.[2] Few of the secondary causes are drugs, viral infections, mycobacterial infections, autoimmune disorders, chemicals like benzene, cytotoxics, malignant infiltration and paroxysmal nocturnal hemoglobinuria. Primary causes are further divided into idiopathic and congenital/familial.[1] It presents with symptoms of marrow failure such as pallor, dyspnea, bleeding, bruising and increased propensity to infections. A wide variety of disorders can cause pancytopenia although the frequency with which each condition is associated with pancytopenia differs considerably. The prognosis depends on the severity of the pancytopenia and on the nature of the underlying condition. The incidence of various disorders causing pancytopenia varies due to geographical distribution and genetic disturbances. The management and prognosis of pancytopenia depends on the underlying pathology.[3] Marrow aspirate has been primarily utilized for

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cytological assessment. Trephine biopsy on the other hand allow for studies of the marrow's overall cellularity, detection of focal lesions and extent of infiltration by various pathologic entities.[4] The spectrum of primary and secondary disorder that affect the bone marrow may manifest with pancytopenia.[5] Hypersplenism due to decompensated alcoholic liver cirrhosis and infections like HIV and tuberculosis are on rise in today's society more so in this part of the world and hence should be kept in mind as causes for pancytopenic presentation. Anti-neoplastic therapy cycles are known to cause pancytopenia due to myelosuppression and so these hazardous therapies should not be used without facility for regular follow-up and supervision. Although pancytopenias are a relatively common hematological entity and a serious clinical problem with exhaustive differential diagnoses, there is relatively little discussion on this abnormality in major textbooks of hematology and internal medicine. A look at literature shows that there aren't many comprehensive studies on this subject from developed world, though extensive studies have been done for its individual etiological factors like aplastic anemia, megaloblastic anemia, leukemia, myelodysplastic syndrome, etc. As the severity of pancytopenia and the underlying pathology determines the management and prognosis of these patients, identifying the correct etiopathology in a given case is crucial and helps in implementing timely and appropriate treatment.[6] Initially, mild impairment in marrow function may go undetected and Pancytopenia may become apparent only during times of stress or increased demand (e.g., bleeding or infection).[7] Detailed clinical history and meticulous physical examination along with baseline hematological investigations provide invaluable information in the evaluation of pancytopenic patients, helping in systematic planning of further investigations to diagnose and ascertain the cause, avoiding unnecessary tests which not only add to the expense of treatment but sometimes also may result in delayed diagnoses and treatment. A systematic evaluation of pancytopenia needs clinical findings, Peripheral blood, Additional blood tests, Imaging (radiographic), Bone marrow examination, Integrated diagnosis and follow up (as part of evaluation).[6]

OBJECTIVES

- To determine the various causes of pancytopenia in adults encountered in our institution.
- To determine the common clinical presentations of pancytopenia seen in our set up.

MATERIALS AND METHODS

The present study was conducted in the Department of pathology of Father Muller Medical College.

Study Period: January 2011 to January 2014.A one year retrospective and 2 year prospective study.

Inclusion Criteria for Analysis

Patients belonging to the age group of 18 to 75 years with pancytopenic features was included in this study i.e.)hemoglobin level below 13.5gm/dl in men and 11.5gm/dl in females, total white blood cell count < 4000 per cu mm and platelet count < 1,50,000 per cu mm.[8]

Exclusion Criteria for Analysis

Patients undergoing treatment (radio or chemotherapy) was excluded from the study.

Sample Size: 223

METHODOLOGY

All the patients referred to the central clinical laboratory of the hospital for routine complete blood count (CBC) and peripheral smear (PS) from the outpatient and inpatient departments were screened for pancytopenia and the cases were selected based on criterias defined by deGruchy.[6, 8] In all patients, a complete relevant medical history including age, sex, smoking status, alcohol intake, history of any treatment, intake of or exposure to potentially toxic chemicals, agents or drugs, radiation exposure, history of symptoms such as bone pains, fever, weakness, weight loss, bone pain, dyspnoea, pain abdomen and bleeding was taken. A detailed meticulous physical examination of every patient was done for pallor, jaundice and hepatomegaly was done. Evidence of hypersplenism and primary malignancy was searched for whenever necessary. Informed consent was obtained from every patient before taking their blood for examination. Under strict aseptic precautions venepuncture was performed and blood was taken into ethylenediaminetetra-acetic acid (EDTA) vaccutainer. The collected samples were subjected to complete hemogram evaluation (hemoglobin, RBC count, hematocrit, red blood cell indices, platelet count, total and differential white blood cell count) by an automated analyzer (Beckman Coulter LH500), after which peripheral blood smears were prepared on glass slides and stained with Leishman stain. The peripheral smears were then examined for features of pancytopenia and proceded with bone marrow aspiration and or biopsy when indicated.

RESULTS

The present study evaluated 223 patients with pancytopenia who fulfilled the inclusion criteria. Data obtained were entered into the Microsoft excel spread sheet and analyzed. Complete blood count and peripheral smear examination was done in all patients. Bone marrow aspiration and biopsy was done when clinically indicated which accounted for 67 patients.

Table 1: Age and gender wise distribution of pancytopenia cases studied

Age group (years)	Male (Number)	Male (Percent)	Female (Number)	Female (Percent)	Total (Number)	Total (Percent)
≥18	27	12.1%	27	12.1%	54	24.2%
31-40	25	11.2%	25	11.2%	50	22.4%
41-50	26	11.7%	13	5.8%	39	17.4%
51-60	22	9.8%	18	08%	40	17.9%
61-70	16	7.1%	14	6.2%	30	13.4%
≤75	04	1.7%	06	2.6%	10	4.4%
TOTAL	**120**	**53.8%**	**103**	**46.2%**	**223**	**100%**

The age range of 223 pancytopenic cases studied ranged from 18-75 years, with a mean age of 43.7 years. Maximum numbers of cases were seen in the age group of 18-30 years (24.2%) and the least were seen in the age group of 70-75 years (4.4%).

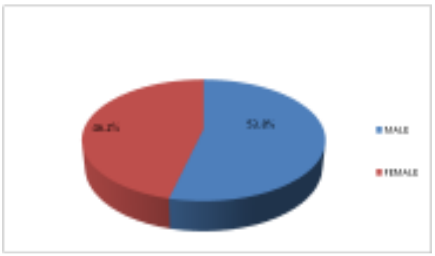

Figure 1: Pie chart showing gender distribution of pancytopenia cases

Of the 223 patients studied 120 patients were male (53.8%) and 103 patients were female (46.2%), with an overall approximate male to female ratio of 1.2:1. Maximum male and female patients belonged to the age group of 18-30 years. In the present study the overall hemoglobin percentage ranged from 1.8% to 11.6%(median-8.4gm%), total leukocyte count ranged from 300 to3800 cells/mm^3(median-2900 cells/mm^3) and platelet count ranged from 1000 to 1,43,000 cells/mm^3(median-51,000 cells/mm^3).

Table 2: Etiological break up of pancytopenia

	Cause	Number	Percent
❖	Infections		
•	Malaria	71	31.8%
•	Sepsis	12	5.3%
•	Viral hepatitis	03	1.3%
•	Viral fever	06	2.6%
•	Enteric fever	03	1.3%
•	Aids	09	04%
•	Herpes zoster	01	0.4%
•	Tuberculosis	03	1.3%
•	Dengue	02	0.8%
❖	Chronic liver disease	33	14.7%
❖	Neoplasms		
•	All	04	1.8%
•	Aml	08	3.5%
•	Mds	04	1.8%
•	Nhl	01	0.4%
•	Multiple myeloma	01	0.4%
•	Myelofibrosis	03	1.3%
•	Disseminated malignancies	03	1.3%
❖	Megaloblastic anemia	18	8%
❖	Aplastic anemia	12	5.3%
❖	Sle	04	1.8%
❖	Drug induced	03	1.3%
❖	Hypothyroidism	02	0.8%
❖	Unknown		
•	With Hypersplenism	03	1.3%
•	Without Hypersplenism	07	3.1%
❖	Miscellaneous	07	3.1%
	TOTAL	**223**	**100%**

Malaria (Table: 3) was the commonest underlying etiology for pancytopenia in 31.8% cases.

Table 3: Distribution of types (parasite) of malaria

Cause	Number	Percent
Vivax	51	71.8 %
Falciparum	5	7 %
Mixed	15	21.1 %
Total	**71**	**100 %**

Chronic liver disease with portal hypertension was the second most common cause and included 14.7% cases. The third most common cause was megaloblastic anemia in 8% of cases followed by sepsis and aplastic anemia in 5.3% cases each. AIDS (Table: 4) were diagnosed in 4% of the cases in which four cases were associated with secondary infections.

Table 4: AIDS and associated infections

Cause	Number	Percent
AIDS	5	55.5%
AIDS with Tuberculosis	2	22.2%
AIDS with mixed malaria	1	11.1%
AIDS with histoplasmosis	1	11.1%
Total	**9**	**100%**

AML was the cause in 3.5% of the cases. Myelofibrosis, disseminated malignancies, unknown causes without hypersplenism and miscellaneous causes (3 cases of chronic kidney disease, 3 cases of cor pulmonale with COPD and 1 case of pneumonia) accounted for 3.1%

each. While viral fever was seen in 2.6% of pancytopenic cases, SLE, ALL and MDS were seen in 1.8% of cases each. Viral hepatitis, enteric fever, tuberculosis, drug induced and unknown causes with hypersplenism in 1.3% of cases each. Dengue and hypothyroidism was seen in 0.8% of cases. NHL and multiple myeloma in 0.4% of cases each. Fever was the commonest presenting complaint in 62.7% of the cases, followed by weakness in 32.2%, pain abdomen in 18.8%, bleeding in 14.3%, dyspnea in 13.4%, bone pain in 3.5% and weight loss in 3.1%. Pallor was the commonest physical finding detected in 34% of the cases followed by spleenomegaly in 29.1%, hepatomegaly in 18.8%, icterus in 8% and lymphadenopathy in 4% of the pancytopenic patients.

DISCUSSION

In the present study malaria constituted the most frequently encountered underlying etiology in 31.8% of pancytopenia patients. This correlated with other studies that showed malaria as the most common cause in 45% and 29.4% of patients with pancytopenia done in 2012 and 2008 respectively.[9,10] Few other studies also showed incidence of malaria as the second and fourth common cause.[6, 11,12,13] The high incidence of malaria is mainly attributed to its endemicity in Mangalore. Plasmodium vivax was found to be the major parasite type in 71.8%, mixed in 21.1% and falciparum in 7%.Of all the patients with malaria, hypersplenism was found only in 36.6% of cases and the rest of the cases presented with pancytopenia without hypersplenism. Similar findings were encountered in a study done by Hamid *et al*.[10] It has been stated that Malaria may cause pancytopenia as a result of direct bone marrow invasion by a parasite, immune haemolysis, disseminated intravascular coagulation, hypersplenism, bone marrow necrosis or haemophagocytosis.[14] The second most common cause for pancytopenia in the present study was chronic liver disease in 14.7% cases. Most of the patients were being treated for ADS (alcohol dependence syndrome) at the Father Muller De addiction and Rehabilitation facility centre. These patients had presented with liver cirrhosis associated with portal hypertension (66.6%), variceal bleeding (51.1%) and hepatic encephalopathy (15%). Hypersplenism was noted in 39% of CLD cases. Similar findings were found in a study done by Jain *et al* in 2013 in which out of 73 cases of hypersplenism, 36 cases presented with portal hypertension with a known history of alcoholism in 27 cases.[6] Pancytopenia due to megaloblastic anemia was the third most common cause accounting for 18% of the cases. Similar results were observed in a study done by Kumar *et al* in 2012 and Hamid *et al* in 2008, where megaloblastic anemia was the third most common cause of pancytopenia in 18.7% and 14.7% of cases respectively.[2,10] We diagnosed acute leukemias in 5.3% of cases presenting with pancytopenia, which was comparable to 8%, 2.8% and 1% incidence of acute leukemias reported in study done from Nepal in 2012 and two Indian studies done in 2013 respectively.[6,7,11] In our study sepsis was seen in 5.3% cases of pancytopenia. In the study done by Jain *et al* in India, 5.6% of pancytopenic patients showed features of sepsis which correlated well with our study.[6] There were totally 12 patients who presented with signs of sepsis, out of which 10 of them succumbed to the illness. In the present study AIDS was seen in 4% of cases. Two studies done in India by Jain *et al* and Thakkar *et al* had shown an incidence of 12% and 1% of patients with AIDS related pancytopenia.[6,11] In the present study 5.3 % of patients were diagnosed with aplastic anemia as a cause of pancytopenia. Similar findings were observed in 2 Indian studies done by Jain *et al* and Thakkar *et al* with an incidence of 3.2% and 6% respectively.[6,11] Viral fever was noted in 2.6% of cases presenting with pancytopenia. Our finding correlated well with a study done in India in 2013 which had 1% of pancytopenic cases that were diagnosed to have fever due to viral infection.[11] In the present study, SLE was a common cause for pancytopenia in1.8% cases. In a study done by Santra *et al*, 4.5% of pancytopenic patients were diagnosed with SLE.[14] Drug induced pancytopenia was seen in 1.3% of cases, which correlated with an Indian study done in 2013 which showed an incidence of 3% drug induced pancytopenic patients. In our study, out of the 3 drug induced pancytopenic cases 2 were caused due to methotrexate and one due to Azathioprine. In the present study tuberculosis was seen in 1.3% of the pancytopenic cases which correlated with studies that showed incidence of 3% and 5% of cases respectively with pancytopenia caused due to tuberculosis.[11, 12] Another cause for pancytopenia noted in the present study was enteric fever in 1.3% of cases. Similar findings were noted in 2 Indian studies done in 2010 and 2013 with an incidence of 1.8% and 3.6% respectively.[6, 14] Myelofibrosis was seen in our study as a cause of pancytopenia in 1.3% of cases which correlated with the study done by Hamid *et al* in 2008 who reported an incidence of 4%.[10] In the present study disseminated malignancies were seen in 1.3% of pancytopenic cases. In a study done by Ishtiaq *et al* in 2004, pancytopenic cases with disseminated malignancies were seen in 2% of cases.[12]

CONCLUSION

Pancytopenia in not an uncommon haematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever and tendency

to bleed. The etiological spectrum of pancytopenia is diverse which is ranging from infections, alcohol consumption, radiation exposure, nutritional deficiencies, autoimmune disorders and malignancies. A detailed history with thorough physical examination is mandatory along with routine blood investigations and peripheral blood smear examination. Most of the studies done on patients presenting with pancytopenia have reported megaloblastic anemia and aplastic anemia as the two most frequently diagnosed underlying cause. In places like Mangalore, where infectious conditions like malaria, dengue etc. are endemic, it's necessary to evaluate and rule out infections as primary cause if no other obvious findings are noted.

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