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CLINICAL PROFILE OF PANCYTOPENIA: A TERTIARY CARE EXPERIENCE

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Abstract: This study was done to document the clinico-hematological profile of pancytopenia in adult patients. A total of 53 cases of pancytopenia were diagnosed during the period of Jan 2012 to Dec 2012. Full blood count was performed in all the cases. Clinical variables were recorded for each patient. Out of 53 cases 29 were male. The mean age of patients was 35.15±12.6 years. Pallor and fever were the main presenting symptoms. The main etiological cause of pancytopenia in our case series was megaloblastic anaemia followed by septicaemia and alcoholic and non-alcoholic liver disease. Early identification of the underlying conditions would help in understanding the disease process, and early planning for further investigations and management will enhance survival rate of a case with pancytopenia.

Key words: Pancytopenia, Megaloblastic anemia, Septicemia, Leukemia, Aplastic anemia

INTRODUCTION

Pancytopenia is an important haematological problem encountered in our day-to-day clinical practice. It is a decrease in all three cellular elements of peripheral blood leading to anemia, leukopenia and thrombocytopenia. Pancytopenia usually presents with symptoms of bone marrow failure such as pallor, dyspnea, and bleeding, bruising and increased tendency to infections. The incidence of various disorders causing pancytopenia varies according to geographical distribution and genetic mutations. It can result either from failure of production of hematopoietic progenitors in bone marrow, malignant cell infiltration, antibody-mediated bone marrow suppression, ineffective hematopoiesis and dysplasia, or peripheral sequestration of blood cells in overactive reticulo endothelial system.

A detailed history, physical examination and complete blood counts with reticulocyte count and peripheral blood smear are essential for diagnosis. Profound neutropenia and thrombocytopenia associated with sepsis and bleeding, more often reflect underlying marrow aplasia or leukemia, while glossitis, diarrhoea and paresthesias are associated with megaloblastic anemia. Blast cells are seen on blood film of most patients having acute leukemia's, whereas hypo granulated and segmented neutrophils often indicate myelodysplastic syndrome. In addition, hyper-segmentation of neutrophils in pancytopenic patients or abnormalities of erythrocyte morphology with low serum vitamin B12 and folate levels confirm megaloblastic anemia. Bone marrow examination is essential to determine the cause of pancytopenia, as it plays a major role in haematological malignancies, unexplained cytopenias and storage disorders (1). Trephine biopsy is mainly undertaken when hypoplasia or aplasia of bone marrow being suspected on aspiration. Furthermore, this study provides a new forum for approaching the patients with pancytopenia. Few studies have analyzed paediatric patients with pancytopenia (2). There is scarcity of such data on adult patients. The aim of this study was to evaluate the clinico-hematological profile of adults with pancytopenia.

MATERIAL AND METHODS

This study was conducted on adults presenting with pancytopenia (Hb < 10g/dl, WBC count 4000cu/mm, platelets < 100,000/cu. mm at admission) in OPD and indoor patients from January 2012 to December 2012 at tertiary care hospital of medical college in Indore, Madhya Pradesh. Patients less than 18 year and/or who had received chemotherapy for neoplasms or already received platelet transfusion prior to admissions were excluded from the study.

Clinical case history was followed by haemogram on five part differential haematology analyzer (Mindray BC 3200), peripheral smear and subsequently urine & stool samples were analysed for occult blood. Platelet counts obtained from hematology analyzer were confirmed by peripheral smear examination and by manual method.

Bone marrow aspiration and trephine biopsies were carried out as per the clinical indications. The bone marrow procedure and staining were carried out by standard methods. All the bone marrow aspirates were stained with May-Grunwald Giemsa and trephine biopsies were stained by hematoxylin and eosin. Special staining of Perl's stain, myeloperoxidase, Sudan Black B, periodic acid Schiff were done on aspirate smears as needed. Reticulin stain was done on biopsy where ever indicated. Statistical analysis was done by chi-square test & unpaired t test. A p value of <0.05 was taken as statistically significant.

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RESULTS

Fifty- three cases, 29 (82.85%) male & 24 (45.28%) female were diagnosed to have pancytopenia during the study period. The mean age of patients was 35.15±12.6 years

In the present study, Megaloblastic anemia (35.84%), Septicaemia (11.32%) and alcoholic & non-alcoholic liver diseases (9.43% each) were found as the most common causes of pancytopenia (Table 1). On the other hand, rheumatoid arthritis, malaria, dimorphic anemia and Idiopathic thrombocytopenic purpura (ITP) were found as least common causes of pancytopenia.

Table 1: Pancytopenia cases distribution as per gender and etiology

S. No	Diagnosis	Case distribution as per gender		Total Cases	%
		Male	Female		
1	Dimorphic Anemia	0	1	1	1.88
2	Megaloblastic Anemia	12	7	19	35.84
3	Aplastic Anemia	3	0	3	5.66
4	Rheumatoid Arthritis	0	1	1	1.88
5	Cancer/Malignancy	2	2	4	7.54
6	disseminated intravascular coagulation	1	1	2	3.77
7	Acute myeloid leukemia	1	1	2	3.77
8	Alcoholic Liver disease	4	1	5	9.43
9	Non-alcoholic Liver disease	1	4	5	9.43
10	Malaria- P. falciparum	1	0	1	1.88
11	Malaria- P. vivax	0	1	1	1.88
12	Septicaemia	2	4	6	11.32
13	ITP	1	0	1	1.88
14	Dengue	1	1	2	3.77
	Total	29	24	53	

Common clinical presentations of pancytopenia cases noted were pallor 60%, fever 41.5%, weakness 34%, splenomegaly 24.5%, hepatomegaly 17%, bleeding 19% and edema 15% (Table 2).

DISCUSSION

There are limited number of studies in the literature evaluating incidence of pancytopenia in adults and children. Most of the studies are on particular iteology. There are very limited broad spectrum studies pertaining to encompassing various etiologies have been done in context of central India. The published studies on pancytopenia have also been limited by the referral nature of patient population. (2)

Despite of invasive nature of bone marrow examination, it is one of the most frequent and relatively safe procedures done routinely in practice. Even it can be performed easily in the presence of severe thrombocytopenia with little or no risk of bleeding. Commonly it is done for the evaluation of unexplained cytopenias and malignant conditions like leukemia. Bone marrow examination is also done for diagnosis or staging of a neoplasm and storage disorders. Trephine biopsy is usually performed in case of hypoplasia or aplasia or dry aspiration, it is also done in cases of lymphomas, granulomatous conditions and malignancies (2).

Table 2: Clinical presentation of pancytopenia patients

S No	Clinical Presentation	Total number(53)	%
1	Pallor	32	60
2	Fever	22	41.5
3	Weakness	18	34
4	Icterus	14	26.4
5	Splenomegaly	13	24.5
6	Hepatomegaly	9	17
7	Bleeding	10	19
8	Edema	8	15

Naseem *et al.*, (2), studied 990 children for different indications and referred for bone marrow examination, it was found that acute leukemia (66.9%) was the most common etiology in bicytopenic children and aplastic anemia (33.8%) in pancytopenic children. It was revealed that children with bicytopenia had a higher incidence of underlying malignancy (69.5% vs. 26.6%), splenomegaly (60.5% vs. 37.4%), lymphadenopathy (41.8% vs. 15.1%) and circulating blasts (64.6% vs. 20.1%) and a lower incidence of bleeding manifestations (12.1% vs. 26.6%) as compared to children with pancytopenia (2).

In the present study, among 53 cases of pancytopenia, 35.84% had Megaloblastic anaemia as a evident etiology followed by Septicemia (11.32%) and alcoholic & non-alcoholic liver diseases (9.43% each) as common causes of pancytopenia. On the other hand, rheumatoid arthritis, malaria, dimorphic anemia and ITP were less common etiology. The most common clinical presentations of these cases were pallor (60%), fever (41.5), and weakness (34%). Whereas hepatosplenomegaly, bleeding manifestations and edema were less common clinical presentations with 25%, 19% and 15% occurrence respectively.

Deficiency (Combined deficiency) anemia was found as the most common cause of pancytopenia. 24.29% micronutrients deficiency anemia like megaloblastic anemia and 15% mixed deficiency anemia was reported by Rahim *et al.*, (3), in a study in Pakistan. In other similar studies its frequency ranges from as low as 24% to as high as 68% (4-6). Folate deficiency is more common in children, while B12 deficiency is more common in adults. (4) It is a common problem in developing countries. The usual presenting age in developed world is in infancy. But in developing countries like ours it can occur at any age.

There are varying reports on the underlying etiology of pancytopenia from various parts of the world. In a study in France by Imbert *et al.,* (5), 213 consecutive adult pancytopenic patients were reviewed and underlying malignant myeloid disorders were found in 42% of their cases and various malignant lymphoid disorders in 18%, followed by aplastic anemia in 10%. In a study from Zimbabwe comprising 134 patients with pancytopenia, megaloblastic anaemia was the most frequent cause, followed by aplastic anemia and acute leukemia in their cohort of pancytopenic patients. (6) Jha *et al.,* from Nepal studied the causes of pancytopenia in 148 patients. The commonest etiology of pancytopenia in their study was hypoplastic bone marrow seen in 43 cases (29%), followed by megaloblastic anemia in 35 cases (23.6%) and hematological malignancy in 32 cases (21.6%). In children, hypoplastic bone marrow (38.1%) and in adults megaloblastic anemia (30.2%) was the commonest etiology reported by them. (7)

A study from Pakistan found megaloblastic anemia as the most prevalent diagnosis and the major cause of bicytopenia and pancytopenia in the bone marrow aspirates performed in their paediatric unit(8). Another study from Pakistan by Memon *et al.,* on 230 pancytopenic children found the most common causes of pancytopenia as aplastic anemia, megaloblastic anemia, leukemia and infections. The common clinical presentations of pancytopenic children in their study were pallor, fever, petechial haemorrhages, visceromegaly and bleeding from nose and gastrointestinal tract. (9)

Studies from India on etiology of pancytopenia are limited and have shown variable causes, depending on the referral population and nutritional status of the study area. Etiological profile of adult pancytopenia patients was studied by Varma *et al.,* , Kumar *et al.,* , Tilak *et al.,* and Khunger *et al.,* (10-13) included children along with adults while doing a clinico-hematological analysis of 202, 166, 77 and 200 pancytopenic patients, respectively. Bhatnagar *et al.,* (14) and Gupta V *et al.,* (15) have also evaluated causes of pancytopenia exclusively in children.

In adults, aplastic anemia was found to be the most common cause of pancytopenia in reports by Varma *et al.,* (10) and Kumar *et al.,* (11). However, studies by Tilak *et al.,* (12) and Khunger et *al.,* (13) found megaloblastic anemia to be the most important cause of pancytopenia in adults.

In our study we found Megaloblastic anemia as the commonest cause of adult pancytopenia followed by sepsis & chronic liver disease. We found that the routine hematological parameters were non-specific and showed a significant overlap among the major causes of cytopenias. However, the peripheral blood films were valuable in pointing toward the cause in patients with megaloblastic anemia and leukemia. Bone marrow aspirate was found to be sufficient for diagnosis in most cases of leukemia and megaloblastic anemia; however, bone marrow biopsy was mandatory for the diagnosis of aplastic anemia.

Bhatnagar *et al.,* (14) retrospectively analyzed 109 pediatric patients presenting with pancytopenia, found megaloblastic anemia as the single most common etiological factor causing pancytopenia in 28.4% children, followed by acute leukemia and infections in 21% patients each, and aplastic anemia in 20% cases. Gupta *et al.,* (15) reviewed 105 children aged 1.5-18 years with pancytopenia. In their study, aplastic anemia was the most common cause of pancytopenia (43%), followed by acute leukemia (25%). Infections were the third most common cause of pancytopenia of which kala-azar was the most common. Megaloblastic anemia was seen in 6.7% children by them. Fever and progressive pallor were the most common presenting complaints in their cohort, being present in 81.4%, followed by bleeding manifestations in 72.9%. In a prospective study, 104 pancytopenic patients were evaluated clinically, along with hematological parameters and bone marrow aspiration (16). Among 104 cases studied, most of the patients presented with generalized weakness and fever. The commonest physical finding was pallor, followed by splenomegaly and hepatomegaly. Dimorphic anemia was the predominant blood picture. Bone marrow aspiration was conclusive in all cases. The commonest marrow finding was hyper cellularity with megaloblastic erythropoiesis. The commonest cause for pancytopenia was megaloblastic anemia (74.04%), followed by aplastic anemia (18.26%). The commonest cause of pancytopenia, reported in various studies throughout the world has been aplastic anemia (12). This is in sharp contrast with the results of our study, where the commonest cause of pancytopenia was found to be megaloblastic anemia. Similar findings were observed in other studies conducted in India (11-13, 17). This seems to reflect the higher prevalence of nutritional anemia in Indian subjects.

Out of 89 cases studied by Mussarrat Niazi, aplastic anemia-38% and Megaloblastic anemia- 24% were commonest cause. The other common causes were hypersplenism & acute leukemia (18). A retrospective study conducted over a 15 month period by Fauzia Shafi Khan *et al.,* (19) included 279 pancytopenic children. Acute leukemia was the commonest etiology 32.2% followed by Aplastic anemia 30.8%, Megaloblastic anemia 13.2% and miscellaneous etiologies. Clinical presentation being pallor (81%), fever

(68%), petechial haemorrhages (51%) bleeding manifestations (21.5%) and other features included hepatomegaly (44.8%), splenomegaly (37.2%) and lymphadenopathy (22.5%). (19)

Incidence of megaloblastic anemia was 35.84% in our study. Incidence of 72% was reported by Khunger *et al.,* (13); and 68%, by Tilak *et al.,* (12). All the above studies have been done in India, and they stress the importance of megaloblastic anemia being the major cause of pancytopenia. It is a rapidly correctable disorder and should be promptly notified (13). Although bone marrow aspiration studies are uncommon in suspected cases of megaloblastic anemia, if the diagnosis does not appear straightforward or if the patient requires urgent treatment and hematological assays are not available, bone marrow aspiration is indicated. As facilities for estimating folic acid and vitamin B12 levels are not routinely available in most centers in India, the exact deficiency is usually not identified (11).

Incidence of aplastic anemia varies from 10% to 52% among pancytopenic patients (17). The incidence of hypoplastic anemia in our study was 5.66%, which correlated with the corresponding figures in studies done by Khodke *et al.,* (17) and Khunger *et al.,* (13). Both observed an incidence of 14%. A higher incidence, viz., 29.5%, was reported by Kumar *et al.,* (11).

The diagnosis of AML was based on bone marrow aspiration study, and we reported 2 cases of AML. Khodke *et al.,* (17) reported a single case of AML out of 50 cases of pancytopenia. Kumar *et al.,* (11) reported 5 cases of ALL, 13 cases of AML, 2 cases of hairy cell leukemia out of 166 cases of pancytopenia, over a 6-year study period (11). We encountered 2 cases of malaria in our study, constituting 2.76% of total cases compared to Khunger *et al.,* (13), who have reported an incidence of 1%; Tilak *et al.,* (12), who have reported an incidence of 3.9%; and Kumar *et al.,* who have reported an incidence of 3% of the total cases (11-13).

In present study pancytopenia cases, 17% had hepatomegaly & 24.52% cases had splenomegaly. Hepatosplenomegaly was commonest in cases with moderate thrombocytopenia group. Hepatomegaly was least in mild thrombocytopenia cases & no splenomegaly was seen in severe thrombocytopenia group.

In Naseem *et al.,* study of 990 cases, Children with bicytopenia had a higher incidence of underlying malignancy (69.5% vs. 26.6%), splenomegaly (60.5% vs. 37.4%), lymphadenopathy (41.8% vs. 15.1%) and circulating blasts (64.6% vs. 20.1%) and a lower incidence of bleeding manifestations (12.1% vs. 26.6%) as compared to children with pancytopenia. (2) The main presenting features in children with pancytopenia were fever (51.8%) and pallor (59%). Other common symptoms consisted of petechial rash, bleeding and bone pains. On clinical examination, hepatomegaly was seen in 51.8% and splenomegaly in 37.4% cases. (2)

CONCLUSION

Pancytopenia is not an uncommon hematological problem encountered in clinical practice. In the present study, megaloblastic anemia (35.84%) was found as the most common cause of pancytopenia followed by septicaemia (11.32%) and alcoholic & non-alcoholic liver diseases (9.43% each). On the other hand, rheumatoid arthritis, malaria, dimorphic anemia and ITP were found as least common causes of pancytopenia. Whereas in terms of clinical presentation, pallor and fever followed by weakness was found as the most common while bleeding and edema were least. Thus, clinical findings along with detailed primary haematological investigations with bone marrow aspiration would be helpful in early identification and early intervention of patient with pancytopenia. Consecutively, early identification of the underlying conditions would help in understanding the disease process, and early planning for further investigations and management will enhance survival rate of a case with pancytopenia. So, when a patient presents with unexplained anemia, prolonged fever and tendency to bleed could be suspected for pancytopenia on clinical grounds, its severity has significant relation with the clinical outcome and can be used as a prognostic indicator.

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