Original Article

Clinico-hematological Profile of Pancytopenia in Manipur, India

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ABSTRACT

Objectives: To determine the etiology and clinical profile of pancytopenia in Manipur, India
Design: Prospective study
Setting: Department of Pathology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, a renowned referral hospital in north-east India
Subjects: Fifty cases of pancytopenia were examined in the department of Pathology, RIMS hospital, Imphal, Manipur,India, during a two year period from November 1999 to October 2001.
Interventions: Bone marrow aspiration and examination
Main Outcome Measures: Correlation between pancytopenia and clinico-hematological diagnosis
Results: Hypoplastic anemia was the commonest cause of pancytopenia (22%) followed by megaloblastic anemia and myelodysplastic syndrome (18% each). The other causes include subleukemic / aleukaemic leukemia (14%), iron deficiency anemia (8%), HIV infection (6%), congenital dyserythropoietic anemia (CDA, 4%), pyrexia of unknown origin (PUO) with hepatosplenomegaly (4%), congenital hepatic fibrosis (2%) and systemic lupus erythomatosus (SLE, 2%).
Conclusion: Rare causes of pancytopenia including iron deficiency anemia, HIV infection and CDA have to be kept in mind as possible disorders manifesting as pancytopenia.

KEY WORDS: hypoplastic anemia, myelodysplastic syndrome, pancytopenia

INTRODUCTION

The term pancytopenia denotes simultaneous reduction in all the formed elements of the blood *i.e.,* erythrocytes, leukocytes and platelets. Pancytopenia is not a disease entity but a triad of findings that may arise from a number of disease processes[1]. Pancytopenia, therefore exists when hemoglobin level is below 13.5 g/dl in males or 11.5 g/dl in females, leukocyte count below 4 x 10^9 /l and platelet count below 150 x 10^9/l[2]. A number of bone marrow disorders like aplastic anemia, myelodysplastic disorders, acute leukemias, myelosclerosis and infiltration of bone marrow by lymphoma, myeloma, carcinoma, hairy cell leukemia, infiltrative disorders like Gauchers' disease, Niemman Pick disease, Lietterer Siwe disease may produce pancytopenia[1].

The presenting clinical symptoms are usually due to anemia, leukopenia and thrombocytopenia. Fatigue and weakness due to anemia, increased susceptibility to infections because of leukopenia and bleeding tendency due to thrombocytopenia are the usual presenting symptoms[2].

Fifty cases of pancytopenia diagnosed at Regional Institute of Medical Sciences (RIMS) hospital during a period of two years were analysed. The present study was carried out to find the different causes or disorders among the patients with pancytopenia and their clinical correlation.

SUBJECTS AND METHODS

The present study was conducted in the Department of Pathology, Hematology section, RIMS hospital, Imphal over a period of two years from November 1999 to October 2001. Approval of local ethical committee was obtained to conduct this study. A total of 50 patients who fulfilled the criteria for pancytopenia were taken up for the study. All the 50 cases were subjected to bone marrow aspiration and examination. Consent was taken from all patients. Inclusion criteria for analysis were hemoglobin concentration less than 10 g/dl, total leukocyte count less than 4 X 10^9/l and total platelet count less than 100 X 10^9 /l. Bone marrow aspirations were done in all the cases. A detailed clinical history and physical examination

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were also performed for each case. Clinical details regarding age, sex, exposure to chemicals or drugs, bone pain, fever, night sweats, malaise and weight loss were inquired. Physical examination was done to detect presence of hepatomegaly, splenomegaly, lymphadenopathy, sternal tenderness, gum hypertrophy and primary malignancy. Peripheral blood smears were examined for the presence of anisopoikilocytosis, circulating erythroblast, hypo or hypersegmented neutrophils, abnormal granulations in neutrophils, lymphocytosis and immature WBC. Reticulocyte count was also done for all cases. However, the cytogenetic studies were not done due to lack of facilities in our institution.

RESULTS

A total of 23,335 cases were received for hematological examination during the study period. Out of these, 50 cases (0.2%) showed features of pancytopenia. The male to female ratio in the study was 1.5:1. The age ranged from 3 to 80 years. Maximum number of cases was observed in the 21 to 40 years age group with a slight male preponderance.

The commonest cause of pancytopenia was found to be hypoplastic anemia (22%), followed by megaloblastic anemia and myelodysplastic syndrome (MDS) (Fig. 1) with 18% each. The other causes include subleukemic / aleukaemic leukemia (14%), iron deficiency anemia (8%), HIV infection (6%), congenital dyserythropoietic anemia (CDA, 4%), PUO with hepatosplenomegaly (4%), congenital hepatic fibrosis (2%) and systemic lupus erythomatosus (SLE 2%, Table 1). Splenomegaly was observed in one patient of MDS. The patient incidentally had chronic liver disease. Out of the 11 cases of hypoplastic anemia three cases had history of analgesic intake or some unknown medicine off and on. One patient gave history of jaundice and another presented with alcoholism. Hepato-splenomegaly was seen in six cases of megaloblastic anemia out of which one gave history of taking carbamazepine for seven years. Out of the seven cases of acute leukemia, four cases had hepatosplenomegaly and three cases had lymphadenopathy. The two cases of congenital dyserythropoietic anemia had symptoms of anemia and bleeding. Foetal hemoglobin (Hb F) was slightly increased in both cases and Ham's acidified serum test was negative. The signs and symptoms of the various cases of pancytopenia are shown in Table 2. The age and etiology distribution is shown in Table 3.

Detailed peripheral blood smear examination done in all patients revealed microcytic hypochromic red blood cells in two cases of MDS and macrocytes with anisocytosis in one patient. All the other cases had normocytic and normochromic

Table 1: Causes of pancytopenia as seen in the 50 cases

Hematological Diagnosis	n	Percentage
Hypoplastic anemia	11	22
Myelodysplastic syndrome (MDS)	9	18
Megaloblastic anemia	9	18
Subleukaemic leukemia	7	14
Iron deficiency anemia	4	8
HIV infection	3	6
Congenital dyserythropoitic anemia (CDA)	2	4
PUO with hepatosplenomegaly	2	4
Congenital Hepatic fibrosis with PH	1	2
Squamous cell Ca (N.S)	1	2
SLE	1	2
Total	50	100

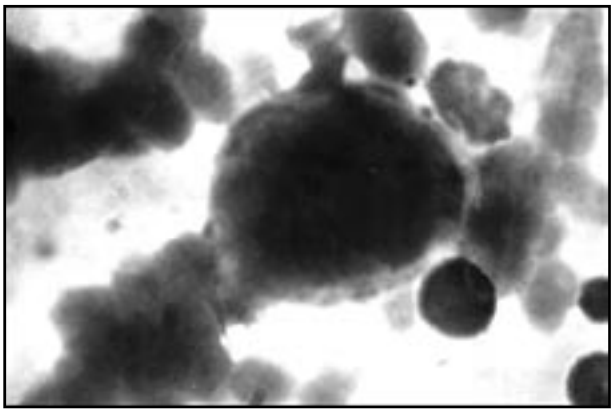

Fig. 1: Photomicrograph of bone marrow smear from a MDS patient showing monolobed megakaryocyte (Leishman's stain, X1000)

Table 2: Sign and symptoms of pancytopenia

Signs and Symptoms	n	Percentage
General Weakness	32	64
Fever	15	30
Bleeding	13	26
Loss of appetite	9	18
Hepatomegaly with splenomegaly	7	14
Hepatomegaly	5	10
Splenomegaly	5	10
Infection	3	6
Pain abdomen	2	4
Palpitation	2	4
Edema	2	4
Headache	1	2
Difficulty in breathing	1	2
Mouth ulceration	1	2
Menorrhagia	1	2

Table 3: Age and etiology wise distribution

Age in yrs	HA	MDS	Megaloblastic anemia	Acute leukemia	SLE	Hypersplenism	PUO	HIV-infection	Misc. (IDA, CDA-I SCC)
0-15	2	0	1	2	0	1	0	0	2
16-30	4	3	2	2	1	-	2	1	1
31-45	-	2	2	1	-	-	-	2	2
46-60	2	2	-	1	-	-	-	-	2
61-75	2	1	4	1	-	-	-	-	-
76-90	1	1	-	-	-	-	-	-	-
	11	9	9	7	1	1	2	3	7

HA-Hemolytic anemia; MDS- Myelodysplastic syndrome; SLE-Systemic lupus erythematosus; PUO- Pyrexia of unknown origin; HIV-Human immunodeficiency virus; IDA- Iron deficiency anemia; CDA- Congenital dyserythropoeitic anemia

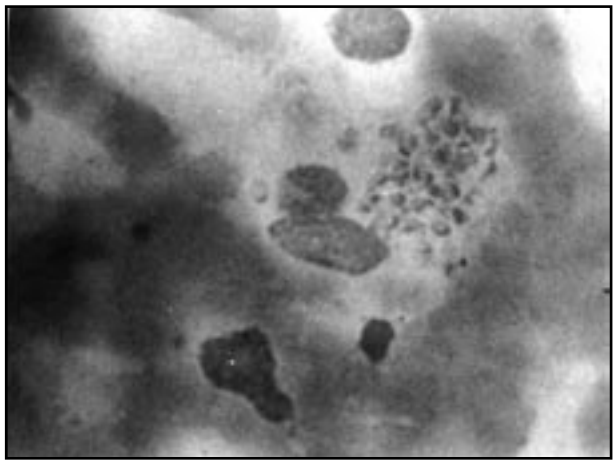

Fig. 2: Photomicrograph of bone marrow smear from an AIDS patient showing *Histoplasma capsulatum* in macrophage (Leishman's stain, X1000)

red blood cells. Lymphocytosis was noted among cases of hypoplastic anemia. Immature white blood cells were noted in five out of seven cases of acute leukemia and in all cases of MDS. Histoplasma capsulatum was present in the bone marrow of one case of HIV infected patient (Fig. 2).

DISCUSSION

The pathophysiology of aplastic/hypoplastic anemia is now believed to be immune mediated. The aberrant immune response may be triggered by viral infections, exposure to chemicals and drugs or endogenous antigens[2]. The mechanism is similar to tissue specific organ destruction mediated by lymphocytes seen in diabetes, multiple sclerosis, uveitis and colitis[3,4]. Incidence of aplastic/hypoplastic anemia as a cause of pancytopenia varies from 10 to 52.7%[2]. In our study, aplastic/hypoplastic anemia was the predominant cause (22%) of pancytopenia similar to a study conducted by Kumar[5]*et al*. The incidence of MDS as a cause of pancytopenia was 2% in a study conducted by Khungar[6]*et al*. In our study MDS was the cause in 18% of the cases. The incidence of megaloblastic anemia as a cause of pancytopenia varies from 0.8 to 32.26%[7]. The incidence was 18% in the present study. In seven out of nine cases of megaloblastic anemia, there was association with cirrhosis/alcoholism/abnormal liver function. One patient was on carbamazepine for the last seven years. Only one patient was a pure case of megaloblastic anemia that had no associated disease or exposure to medicine. In the present study chronic liver disease or cirrhosis seemed to be the main cause of megaloblastic bone marrow, most likely to be due to folate deficiency.

Aleukaemic leukemia was noted in seven cases (14%) of pancytopenia. In the present study, four out of seven cases were of acute lymphoblastic leukemia and three were of acute myeloblastic leukemia. In about 25% of the patients with acute leukemia the total white cell count at the onset is reduced, ranging from 1 to 4 X 10^9/l. Occasionally, blast cells may be present in very small numbers[8]. The symptoms of early acute leukemia are quite varied[9]. General weakness, fever and bleeding were the common symptoms in a few cases of acute leukemia included in the present study. Other symptoms like swelling of the face, ascites, backache, anorexia, headache and loss of consciousness were also observed in a few patients.

Congenital dyserythropoietic anemia (CDA) type-1 producing pancytopenia was seen in two cases (4%) in the present study. The bone marrow showed features of dyserythropoiesis with normal leucopoiesis and megakaryopoiesis. CDA must be considered in the differential diagnosis of MDS especially in young patients[10]. In the two cases, MDS had been ruled out by the presence of normal leucopoiesis and megakaryopoiesis. Maeda *et al* described a case of CDA type-1 developing pancytopenia possibly due to enlarged spleen[11]. One case of CDA type-1 in the present study also had massively enlarged spleen and pancytopenia. Hypersplenism and splenic pooling may contribute to the pancytopenia. The other case had bone marrow hypoplasia along with features of dyserythropoiesis. Hypoplasia of the marrow may be the cause of pancytopenia. Patients infected

with HIV had uni or multi lineage suppression of the bone marrow hematopoiesis along with decrease of CD4+ peripheral blood lymphocytes[12]. All the three patients with HIV in the present study had pancytopenia due to bone marrow suppression. Some patients with severe iron deficiency anemia or long standing iron deficiency may have mild thrombocytopenia possibly due to complicating factors like folate deficiency or splenic sequestration[13]. Mild granulocytopenia may occur in long standing cases of iron deficiency[14]. An association between severe iron deficiency and thrombocytopenia has been observed probably due to an essential role of iron in a late stage of thrombopoiesis[15]. Increase in platelet counts following packed red blood cells transfusion have been observed in some studies[16]. Anemia and associated neutropenia may be due to associated copper deficiency possibly because of the decrease activity of enzymes containing copper[17]. Four cases (8%) of iron deficiency anemia in the present study had prolonged bleeding. Pancytopenia with marrow failure had been observed in patients with malignant ovarian tumours[18]. One case of squamous cell carcinoma of the nasal septum without history of prior chemotherapy has been included in the present study. One case of congenital hepatic fibrosis with portal hypertension was also observed in the study. Hypersplenism may be the possible cause of pancytopenia. Malaria related cytopenia was noted in studies done by Cannard and Aouba *et al*[19,20]. One case of malaria was seen in the present study. In SLE pancytopenia occurs when there is simultaneous depression of erythrocytes, platelets and leukocytes. The bone marrow is usually cellular and rarely hypocellular[21]. One case of SLE was noted in the present study. Bone marrow was normocellular and peripheral blood smear showed pancytopenia. Among the pediatric age group, Bhatnagar *et al* observed acute leukemia (ALL, AML and MDS) and aplastic anemia in 21% and 20 % respectively, megaloblastic anemia in 31 (28.4%) patients and infections in 23 (21%) out of 109 patients presenting with pancytopenia. In our study, out of the 50 cases, there were eight pediatric cases. Acute leukemia and hypoplastic leukemia accounted for two cases each and one case (2%) each of megaloblastic anemia, infantile hepatic fibrosis with splenomegaly, CDA type - 1 and squamous cell carcinoma[22].

CONCLUSION

In our study, pancytopenia has been observed in association with iron deficiency anemia, HIV infection, CDA and carcinomas (squamous cell carcinoma). It is necessary to be aware of these disorders manifesting as pancytopenia.

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