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Original Article

Pancytopenia: A Clinico Hematological Study

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ABSTRACT

Background: Pancytopenia is a relatively common hematological entity. It is a striking feature of many serious and life-threatening illnesses, ranging from simple drug-induced bone marrow hypoplasia, megaloblastic anemia to fatal bone marrow aplasias and leukemias. The severity of pancytopenia and the underlying pathology determine the management and prognosis. Thus, identification of the correct cause will help in implementing appropriate therapy.

Objectives: To study the clinical presentations in pancytopenia due to various causes; and to evaluate hematological parameters, including bone marrow aspiration.

Materials and Methods: It was a prospective study, and 104 pancytopenic patients were evaluated clinically, along with hematological parameters and bone marrow aspiration in Hematology Unit, Department of Pathology, JJMMC, Davanagere, during the period of September 2005 to September 2007.

Results: Among 104 cases studied, age of patients ranged from 2 to 80 years with a mean age of 41 years, and male predominance. 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 hypercellularity with megaloblastic erythropoiesis. The commonest cause for pancytopenia was megaloblastic anemia (74.04%), followed by aplastic anemia (18.26%).

Conclusion: The present study concludes that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients are helpful for understanding disease process and to diagnose or to rule out the causes of cytopenia. These are also helpful in planning further investigations and management.

Keywords: Bone marrow aspiration, megaloblastic anemia, pancytopenia

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 disorder in which all three major formed elements of blood (red blood cells, white blood cells and platelets) are decreased in number.[2] It is not a disease entity but a triad of findings that may result from a number of disease processes – primarily or secondarily involving the bone marrow.[3]

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The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patients.[4] In India, the causes of pancytopenia are not well defined, so the present study has been undertaken to evaluate the various causes and to correlate the peripheral blood findings with bone marrow aspirate.[4,5] Thereby, this data would help in planning the diagnostic and therapeutic approach in patients with pancytopenia.

MATERIALS AND METHODS

The present prospective study was undertaken for a period of 2 years, from September 2005 to September 2007, at Hematology Unit, Department of Pathology, J.J.M. Medical College, Davanagere. Patients of all age groups and both sexes were included. Case selection was based on clinical features and supported by laboratory evidence, which included peripheral blood

counts for hemoglobin, leukocytes and platelets. Inclusion criteria were presence of all 3 of the following: hemoglobin, <9 g/dL; total leukocyte count (TLC), <4,000 / μL ; platelet count, <100,000/ μL.[5]

Patients on myelotoxic chemotherapy were excluded. Two milliliters of EDTA (ethylene diamine tetra-acetic acid) anticoagulated blood was collected and processed through ABX MICROS 60 automated hematology analyzer; and 9 hematological parameters were obtained, which included hemoglobin, red blood cell count, total leukocyte count, differential leukocyte count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), packed cell volume (PCV). Erythrocyte sedimentation rate (ESR) was estimated in all cases by Westergren's method. Peripheral smear was stained by Leishman stain for all the cases and examined in detail. Bone marrow aspiration was subsequently carried out under aseptic precaution after obtaining written consent from the patient or guardian.

RESULTS

A total of 104 patients who presented with pancytopenia were studied. They consisted of 57 males and 47 females with a male-to-female ratio of 1.2:1. The age of patients ranged from 2 to 80 years (mean age, 41 years). Out of 104 cases, pancytopenia was observed in 31 pediatric patients (2-18 years); they consisted of 13 males and 18 females. No familial disease was observed in association with pancytopenia. Presenting complaints and physical findings are shown in Table 1.

The commonest mode of presentation was generalized weakness; other main symptoms were dyspnea, fever, weight loss. Pallor was noted in all cases.

Splenomegaly and hepatomegaly were seen in cases of megaloblastic anemia, followed by subleukemic leukemia and malaria. Bony tenderness was seen in multiple myeloma. Lymphadenopathy was noted in subleukemic leukemia – lymphoblast type.

Hematological parameters in the 3 subgroups of pancytopenia are shown in Table 2.

The predominant blood picture was dimorphic anemia (37.5%), followed by macrocytic anemia (31.7%); peripheral smear showed macro-ovalocytes with hypersegmented neutrophils [Figure 1]. Normocytic normochromic anemia constituted 15.3% of the cases; and normocytic hypochromic anemia, 15.3%. Leucopenia and thrombocytopenia were seen in all cases.

The causes of pancytopenia and case distribution are shown in Table 3.

Megaloblastic anemia was observed in 43 males and 34 females, their age ranging from 4 to 80 years, with a mean age of 42 years. Four patients had evidence of malabsorption syndrome. Six patients had clinical neurological deficits: subacute combined degeneration (SACD) of spinal cord in 4 and sensory ataxia in 2 patients. In the remaining 67 cases, the underlying disorder could not be established. Since B_{12} and folate levels could not be estimated as a routine, both folic acid and parenteral hydroxycobalamine therapies were administered to all, and they showed complete clinical and hematological remission. Bone marrow aspiration showed megaloblastic erythroid hyperplasia. Megaloblasts had the characteristic feature of

Table 1: Presenting complaints and physical findings in pancytopenia

S. no.	Presenting complaints and physical findings	No. of cases	Percentage
1	Generalized weakness	104	100
2	Dyspnea	45	43.26
3	Fever	40	38.46
4	Bleeding manifestation	4	3.84
5	Weight loss	4	3.84
6	Chills and rigor	3	2.80
7	Pallor	104	100
8	Splenomegaly	37	35.57
9	Hepatomegaly	29	26.92
10	Jaundice	4	3.82
11	Bony tenderness	1	0.96
12	Lymphadenopathy	1	0.96

Table 2: Hematological parameters in three subgroups of pancytopenia

Parameters	Megaloblastic anemia	Aplastic anemia	Subleukemic leukemia
Hb (g/dL)	1.8-9.2	2-8.6	2.8-6
TLC (μL)	500-3,900	700-3,800	600-3,200
Platelets (μL)	12,000-95,000	10,000-92,000	15,000-85,000

Table 3: Distribution of various causes of pancytopenia

S. no.	Causes	No. of cases	Percentage
1	Megaloblastic anemia	77	74.04
2	Aplastic anemia	19	18.26
3	Subleukemic leukemia	4	3.85
4	Malaria	2	1.93
5	Multiple myeloma	1	0.96
6	Storage disorder	1	0.96
	Total	104	100

sieved nuclear chromatin, asynchronous nuclear maturation and bluish cytoplasm with cytoplasmic blebs [Figure 2]. Giant metamyelocytes and band forms were predominant in granulocyte series.

Aplastic anemia was seen in 10 males and 9 females; their age ranged from 2 to 50 years, with a mean age of 26 years. In the present study, out of 19 cases of bone marrow hypoplasia, cause was not known in 16 cases and was grouped under idiopathic bone marrow hypoplasia. One patient had history of hepatitis infection. Another patient gave history of reatment with carbamazepine for epilepsy. One patient, a known case of hyperthyroidism, was on antithyroid medication. Bone marrow (BM) showed hypocellularity with suppression of erythropoiesis, myelopoiesis and megakaryopoiesis with relative lymphoplasmacytosis [Figure 3].

We encountered 4 patients of subleukemic leukemia; their age ranged from 4 to 30 years. Three cases were of AML-M2 (acute myeloblastic leukemia) and 1 case was of ALL-L2 (acute lymphoblastic leukemia). Bone marrow was hypercellular in all cases. Erythroid and megakaryocytic series were reduced. Majority of cells were myeloblasts and lymphoblasts, constituting more than 40% and 30% of cells in marrow, respectively. Bone marrow aspirate showed myeloblasts with Auer rods [Figure 4]. Malarial infestation was seen in 2 male patients aged 5 years and 25 years. Peripheral blood picture showed pancytopenia, and gametocytes of plasmodium falciparum were seen in blood smear in both cases [Figure 5]. BM was hypercellular with megaloblastic change. No malarial parasites were seen on bone marrow smears. The patients recovered after antimalarial treatment and folic acid therapy. Multiple myeloma was diagnosed in a 41-year-old female, who presented with weakness and bony tenderness. BM showed abnormal proliferation of plasma cells, constituting >40% of marrow cells, including good number of binucleate and trinucleate forms [Figure 6].

We encountered 1 case of storage disorder in a 15-year-old male, who presented with fever, pallor, hepatosplenomegaly. BM showed good number of large cells with peripherally placed relatively small nucleus and abundant multivacuolated foamy cytoplasm and was PAS (periodic acid Schiff) negative. Hence diagnosis of Niemann-pick disease was considered.

DISCUSSION

A total of 104 cases of pancytopenia were studied. Age, gender-wise incidence, presenting complaints, peripheral blood picture, bone marrow aspiration smears and various causes of pancytopenia were studied in all cases, and observations were compared with those in studies published in the literature.

The age of the patients ranged from 2 to 80 years, with a mean age of 42 years. Cytopenias were observed more in males (54.81%) than females (45.19%), with male-to-female (M: F) ratio of 1.2: 1. Age and sex distribution was compared with other studies as shown in Table 4.

Chronic lymphocytic leukemia/Small lymphocytic lymphoma

The most common presenting complaint in our study was generalized weakness (100%), followed by dyspnea (43.26%). The most common physical finding was pallor (100%), followed by splenomegaly (35.57%) and hepatomegaly (26.92%).

The presenting symptoms were usually attributed to anemia or thrombocytopenia. Leucopenia was an uncommon cause of the initial presentation of the patient but can become the most serious threat to life during the course of the disorder. Physical findings were comparable with those in other studies as shown in Table 5.

Hemoglobin, total leucocyte count and platelet count were comparable with those in other studies as shown in Table 6.

Hypersegmented neutrophils were noted in 51.35% of cases compared to 84.9% in Tilak V *et al.* study, and Khunger JM *et al.* demonstrated no hypersegmented neutrophils in megaloblastic anemia. Also, relative lymphocytosis in aplastic anemia was noted in 52.63% of the cases in our study compared to 50% in Tilak V *et al.* study and 85.71% in Khunger JM *et al.* study.[4,6] Table 7 shows comparision of peripheral blood findings with other studies.

In our study, we came across 31 pediatric pancytopenic cases; again megaloblastic anemia was the common cause for pancytopenia, followed by aplastic anemia. Similar results were reported by Bhatnagar *et al.*[8] However, in a study by Gupta and colleagues, 105 patients aged 1.5 to 18 years, with a mean age of 8.6 years, were included in the 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% of the patients.[9] In another study, 64 children were identified with diagnosis

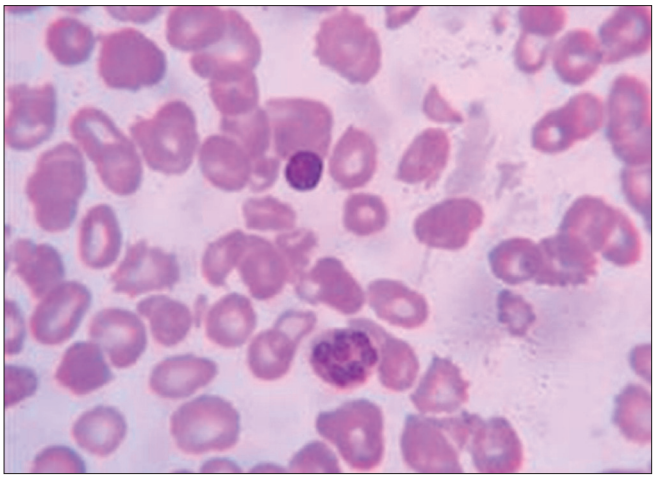

Figure 1: Peripheral smear showing macrocytic anemia with hypersegmented neutrophils (Leishman, ×1000)

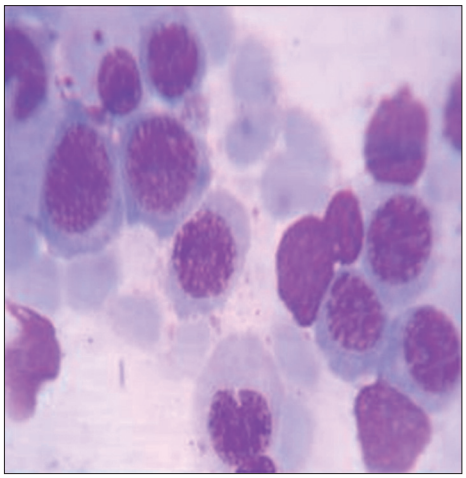

Figure 2: Bone marrow showing megaloblasts, with royal blue cytoplasm and sieve-like chromatin (Leishman, ×1000)

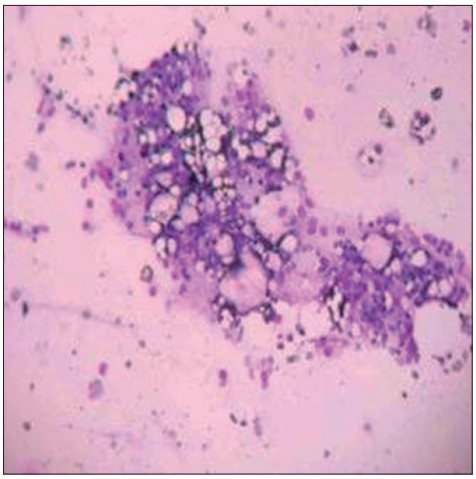

Figure 3: Bone marrow showing hypocellularity with increased fat and reactive lymphoplasmacytosis (Leishman, ×100)

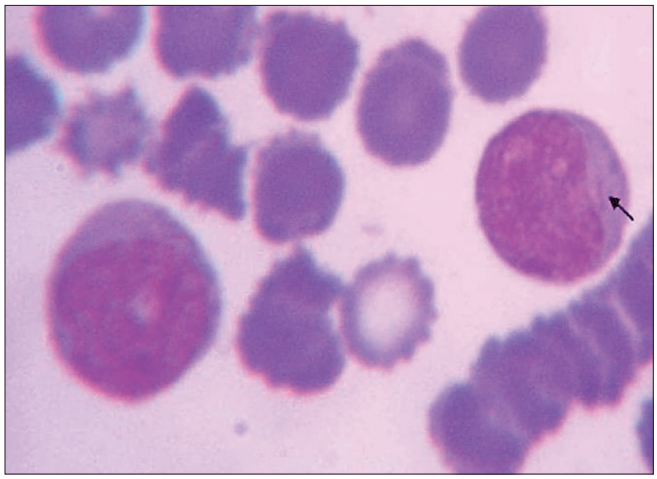

Figure 4: Bone marrow showing myeloblasts with Auer rod (arrow) (Leishman, ×1000)

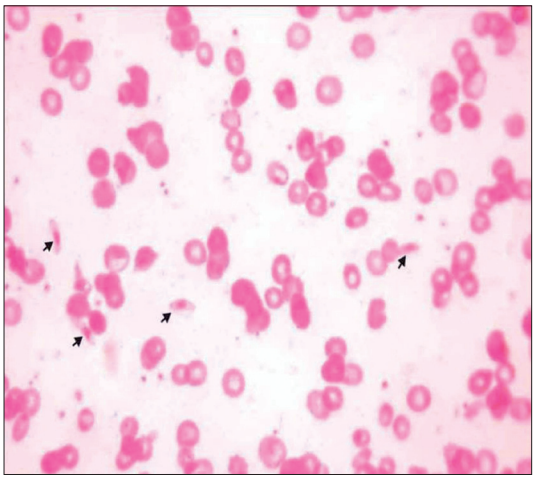

Figure 5: Pancytopenic smear showing gametocytes of plasmodium falciparum (arrows) (Leishman, ×400)

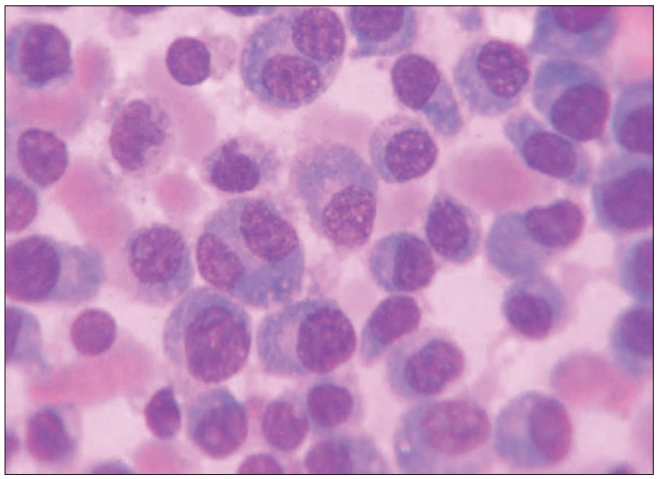

Figure 6: Bone marrow showing increased plasma cells with binucleate forms (Leishman, ×1000)

of pancytopenia. The most common cases were infectious in origin (64%), followed by hematological (28%) and miscellaneous (8%) etiologies.[10]

Variations in the frequency of various diagnostic entities causing pancytopenia have been attributed to difference in methodology and stringency of diagnostic criteria,

geographic area, period of observation, genetic differences and varying exposure to myelotoxic agents, etc.[4]

The commonest cause of pancytopenia, reported in various studies throughout the world has been aplastic anemia.[4]

Table 4: Age, sex distribution compared to those in other studies of pancytopenia

S. no.	Authors	No. of cases	Age range (y)	M : F
1	Khunger JM *et al.*[6] (2002)	200	2-70	1.2: 1
2	Kumar R *et al.*[5] (2001)	166	12-73	2.1: 1
3	Khodke K *et al.*[7] (2001)	50	3-69	1.3: 1
4	Tilak V *et al.*[4] (1999)	77	5-70	1.14: 1
5	Present study	104	2-80	1.2: 1

Table 5: Physical findings compared to those in other studies

Diseases	Physical findings								
	Splenomegaly			Hepatomegaly			Lymphadenopathy		
	A	B	C	A	B	C	A	B	C
Megaloblastic anemia	40	22	31	42	23	23	1	3	-
Aplastic anemia	-	4	-	1	3	-	-	1	-
Subleukemic leukemia	8	1	4	10	1	4	6	-	1
MDS	4	-	-	4	-	-	-	-	-
Hypersplenism	6	-	-	4	-	-	-	-	-
Malaria	2	2	2	-	-	2	-	-	-
Multiple myeloma	1	1	-	-	-	-	-	-	-
Disseminated tuberculosis	1	1	-	-	1	-	1	1	-
Storage disease	-	-	1	-	-	1	-	-	-
CLL/ SLL	2	1	-	2	1	-	2	1	-

Table 6: Comparison of hematological parameters between major subgroups of cytopenias

Parameters	Aplastic anemia		Megaloblastic anemia	
	A	B	A	B
Hb (g/dL)	1.3-8	2-8.6	2.4-7	1.8-9.2
TLC × 10^3/ µL	0.2-3.0	1.0-3.8	0.7-3.6	0.5-3.9
Platelets (µL)	8,000-86,000	10,000-92,000	10,000-1,30,000	12,000-95,000

Hb: Hemoglobin; TLC: Total leukocyte count

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.[5-7] This seems to reflect the higher prevalence of nutritional anemia in Indian subjects. Table 8 shows causes of pancytopenia compared to other studies.

Incidence of megaloblastic anemia was 74.04% in our study. Incidence of 72% was reported by Khunger JM *et al.;* and 68%, by Tilak V *et al.*[4,6] 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.[6] 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 B_{12} levels are not routinely available in most centers in India, the exact deficiency is usually not identified.[5]

Incidence of aplastic anemia varies from 10% to 52% among pancytopenic patients.[7] The incidence of hypoplastic anemia in our study was 19%, which correlated with the corresponding figures in studies done by Khodke K *et al.* and Khunger JM *et al.,*Both observed an incidence of 14%.[6,7] A higher incidence, viz., 29.5%, was reported by Kumar R *et al.*[5]

We encountered 3.85% incidence of subleukemic leukemia, compared to 5% reported by Khunger JM *et al.* Kumar R *et al.* reported 12% incidence of aleukemic leukemia. Pancytopenia was the common feature in our study; this correlated with the corresponding finding in the studies by Kumar R *et al.* and Khunger JM *et al.*[5,6] The diagnosis of AML was based on bone marrow aspiration study, and

Table 7: Comparison of peripheral blood findings with those in other studies

Diseases	Total no. of cases			Anisopoikilocytosis			Nucleated RBC			Hypersegmented neutrophils			Immature WBC			Relative lymphocytosis			Reticulocytosis		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Megaloblastic anemia	77	144	53	68	140	51	-	18	13	38	-	45	20	18	-	6	14	7	5	-	5
Aplastic/Hypoplastic anemia	19	28	6	17	2	2	-	-	-	5	-	-	-	-	-	10	24	3	-	-	-
Hypersplenism	-	6	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MDS	-	4	-	-	-	-	-	2	-	-	1	-	-	3	-	-	-	-	-	-	-
Subleukemic leukemia	4	10	1	1	1	1	1	4	1	-	-	-	2	10	1	-	-	-	-	-	-
Malaria	2	-	3	2	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Multiple myeloma	1	2	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Disseminated tuberculosis	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Storage disease	1	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CLL/ SLL	-	2	2	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

CLL/ SLL: Chronic lymphocytic leukemia/Small lymphocytic lymphoma; MDS: Myelodysplastic syndrome

Table 8: Various causes of pancytopenia compared to those in other studies

Causes	Khunger JM *et al.*[6] (2002)	Kumar R *et al.*[5] (2001)	Khodke *et al.*[7] (2001)	Tilak V *et al.*[4] (1999)	Present study
Aplastic anemia	28	49	7	6	19
Megaloblastic anemia	144	37	22	53	77
Hypersplenism	4	19	-	-	-
Subleukemic leukemia	10	20	1	1	4
Lymphoma	2	10	-	2	-
MDS	4	6	1	-	-
Marrow metastasis	-	2	-	-	-
Myelofibrosis	2	2	-	1	-
Malaria	2	5	-	3	2
Enteric fever	-	2	-	-	-
Malignant histiocytosis	-	1	-	-	-
Disseminated TB	1	1	1	1	-
Multiple myeloma	2	-	2	1	1
Waldenstrom's macroglobulinemia	1	-	-	1	-
AIDS	-	-	1	-	-
Storage disorder	-	-	-	-	1

we reported 3 cases of AML-M2 and 1 case of ALL-L2. Khodke K *et al.* reported a single case of AML-M2 out of 50 cases of pancytopenia. Kumar R *et al.* 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.[5]

We encountered 2 cases of malaria in our study, constituting 1.93% of total cases – compared to Khunger JM *et al.,* who have reported an incidence of 1%; Tilak V *et al.,* who have reported an incidence of 3.9%; and Kumar R *et al.,* who have reported an incidence of 3% of the total cases.[4-6]

We encountered 1 case of multiple myeloma, constituting 0.96% of total cases – compared to Khodke K *et al.,* who have reported an incidence of 4%; Tilak V *et al.,* who have reported an incidence of 1.3%; and Khunger JM *et al.,* who have reported an incidence of 1% in their studies.[4,6,7] Patients present study presented with generalized weakness, fever and bony tenderness. ESR was 92 mm at the end of 1 hour by Westergren's method. Plasmablasts with increased N:C (nuclear- cytoplasmic) ratio, multinuclearity and nuclear lobulation were seen. Terpstra *et al.* reported >50% of plasma cells in the bone marrow in 12 of 54 patients with multiple myeloma in their study.[11]

We have reported a single case of storage disorder (Niemann-pick disease), in a 15-year-old boy, who presented with hepatomegaly, splenomegaly and pancytopenia. BM was normocellular with normoblastic erythropoiesis. Aspirated smears showed collection of large foamy histiocytes (Niemann-pick cells) dispersed throughout the smear. Kumar R *et al.,* Khunger JM *et al.* and Khodke K *et al.* have not reported any case of storage disorder as a cause of pancytopenia in their studies.[5-7]

The causes of pancytopenia were treatable in 70% of the patients, who fully recovered from cytopenia. Death occurred in 20% of the cases, which was due to severe pancytopenia and overwhelming infections.

CONCLUSION

Pancytopenia is not an uncommon hematological 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 present study concludes that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients are helpful for understanding the disease process; to diagnose, or to rule out the causes of, cytopenia; and in planning further investigations and management of cytopenic patients. Severe pancytopenia has significant relation with the clinical outcome and can be used as a prognostic indicator.

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