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Original Article

A Clinico-Hematological Profile in Pancytopenia, A Cross-Sectional Study, at Tertiary Care Centre.

Dr. Achla Singla[1], Dr. Varun Prasad[2], Dr. Srijan Srivastav[3]

[1]Lab director, medical officer (Specialist), ESI DISPENSARY, Sangrur (Pb). 148001
[2]Assistant Professor, PRSSSGMC, Rudrapur Uttarakhand.
[3]Associate Professor, PRSSSGMC, Rudrapur Uttarakhand.

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Corresponding Author:

Dr. Srijan Srivastav
Associate Professor, PRSSSGMC, Rudrapur.

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ABSTRACT

The present study was a cross-sectional observational study done in the Department of Pathology, IGMC Shimla, over a period of one year. Bone marrow aspiration and biopsy samples were taken from the posterior superior iliac spine on the iliac crest. A total of 122 bone marrow aspirations and 109 bone marrow biopsies were done. Imprint smears were made along with biopsies.
The most important cause of pancytopenia is nutritional deficiency megaloblastic anemia in the Indian population. This is treatable with folic acid and Vitamin B12 therapy; hence a life-threatening condition of pancytopenia becomes curable with the establishment of a correct diagnosis after bone marrow examination. Haematological malignancies are also an important cause of pancytopenia. Aspiration and biopsy are important methods for the diagnosis, staging, and management of patients with various haematological malignancies. Biopsy is essential for diagnosing aplastic anemia, which is another important cause of pancytopenia. Other causes include visceral leishmaniasis and, rarely, metastasis, reactive HLH, and pure red cell aplasia. Aspiration and imprint smears are helpful in earlier diagnosis, and biopsy is beneficial in cases where aspiration is non-contributory. Hence, it is concluded that both aspiration and biopsy are complementary procedures.

Keywords: *Bone marrow, aspiration, biopsy, pancytopenia.*

INTRODUCTION

Pancytopenia is the simultaneous presence of anemia, leucopenia, and thrombocytopenia. It is defined as a hemoglobin level of less than 10 g/dl, a leucocyte count of less than 4x109/l, and a platelet count of less than 150 x10^9/l.[1]

Pancytopenia develops by various mechanisms, such as a decrease in haematopoietic cell production as a result of destruction of marrow by toxins or suppression of normal marrow growth and differentiation. Other mechanisms include ineffective haematopoiesis 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 hypertrophied and overactive reticuloendothelial system. [1]

Pancytopenia is not a disease entity but a triad of findings that may result from several disease processes—primary or secondary—mostly involving the bone marrow. The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patients.

Based on the cellularity of bone marrow, the causes of pancytopenia are divided into three categories, i.e., hypocellular bone marrow, cellular bone marrow with primary marrow disorders, and cellular bone marrow with systemic disorders [2,3]

The causes of hypocellular bone marrow are aplastic anemia, hypoplastic MDS, cytotoxic agents and radiotherapy, acute leukemia, and lymphoma in the hypoplastic bone marrow.[2,3]

Causes of cellular bone marrow with primary bone disorders are acute leukemias, lymphomas, hairy cell leukemia, myelofibrosis, MDS, PNH, and various causes of pancytopenia due to systemic diseases with cellular bone marrow are hypersplenism, deficiency of vitamin B12, folic acid deficiency, tuberculosis, kala-azar, brucellosis and autoimmune diseases like SLE.[2,3]

The hematological profile includes a complete blood count, peripheral blood film, bone marrow aspiration, and bone marrow biopsy. [2] In addition, ultrasound/computed tomography may be required to assess organomegaly.

Complete blood count findings are correlated with peripheral blood findings. Total leucocyte and platelet counts can be significantly low in disease conditions like aplastic anaemia, myelofibrosis, aleukemic leukemia, and subleukemic leukemia.

Peripheral blood smear evaluation reveals important information regarding etiology, e.g., macro-ovalocytes and hypersegmented neutrophils in megaloblastic anemia, occasional blast cells in sub-leukemic leukemia, tear drop cells with leuco-erythroblastic blood picture in myelofibrosis and giant platelets, Pelger–Huet neutrophils in myelodysplastic syndrome. In conditions like hairy-cell leukemia, the peripheral blood film will show lymphocytes having thin hair-like cytoplasmic projections (hairy cells). In paroxysmal nocturnal hemoglobinuria, peripheral blood film will show anemia of varying degrees with moderate macrocytosis, polychromasia, neutropenia, and thrombocytopenia.[4] In storage disorders like Gaucher's disease, there are usually no specific features, although very occasionally, Gaucher's cells may be seen, particularly after splenectomy. Moderate normocytic normochromic anemia is usual; in some cases, anemia is severe, with mild to moderate leucopenia and thrombocytopenia.[5] In aplastic anemia, peripheral smear shows the presence of pancytopenia with a predominance of lymphocytes. In autosomal recessive Fanconi anemia, normocytic normochromic anemia with neutropenia and thrombocytopenia is seen.[6]

Bone marrow aspiration along with biopsy is important to determine the cause of pancytopenia, which is evaluated based on cellularity; the Myeloid: Erythroid ratio; abnormalities in the erythroid, myeloid, or megakaryocytic series; cell distribution; and any infiltration. Depending on the findings, various etiological factors are determined, e.g., nuclear-cytoplasmic asynchrony; erythroid hyperplasia with megaloblasts having open chromatin (maturation arrest at the basophilic erythroblast stage); abnormal mitoses; and large, atypical giant myelocytes and metamyelocytes, which are seen in megaloblastic anemia.

Although bone marrow aspiration is conclusive in many cases, trephine biopsy is essential for diagnosis whenever there is a 'dry tap' as a consequence of the marrow being fibrotic or very densely cellular. Only a biopsy allows a complete assessment of marrow architecture, the pattern of distribution, and the presence of any abnormal infiltrate. This is particularly useful in investigating cases suspected of aplastic or hypoplastic anemia, lymphoma, metastatic carcinoma, myeloproliferative neoplasms, and bone diseases. Bone marrow biopsy can also be used for special stains and immunohistochemistry for further studies and, in some instances, for further typing, especially in Lymphomas. Under specific conditions, e.g., myelofibrosis, bone marrow biopsy provides specific information about the stage of fibrosis. In cases of lymphoma, the pattern of involvement can be studied, which further decides the prognosis of the patients. In myelodysplastic syndrome, abnormal localization of immature precursors can be appreciated. In all the above-mentioned causes of bone marrow aspiration, the aspiration is usually dry, and a bone marrow biopsy is essential to arrive at a diagnosis.[2,7]

MATERIAL AND METHOD

A prospective, cross-sectional study was conducted over one year in the Department of Pathology, IGMC, Shimla.

The study included all the patients who presented with pancytopenia (i.e., anemia, leucopenia, and thrombocytopenia).

Inclusion Criteria for Study

1 Patients willing to give consent.
2 Patients with pancytopenia as per diagnostic criteria[1]
Hemoglobin: < 10g/dl
Platelets: <1,50,000/µl
Total leucocytic count: <4000/µl

Exclusion Criteria for the study:

1 Patients not willing to give consent.
2 Anaemia / Thrombocytopenia / Leucopenia alone.
3 Patients with bicytopenia.
4 Diagnosed cases of malignancy, including leukemia, receiving chemotherapy or radiotherapy.
5 The patients should not have been given any blood transfusions three days before investigations.

6 Patients with any coagulation disorder.

Methodology:
Before various investigations, informed consent, a detailed history, and a clinical examination were conducted according to the attached proforma.

All the patients were subjected to various hematological investigations, as detailed below:
- Complete haemogram with peripheral smear examination.
- Bone marrow aspiration.
- Bone marrow biopsy.

Whenever indicated, special stains like periodic Acid Schiff stain (PAS), myeloperoxidase (MPO), non-specific esterase (NSE), Sudan Black, Ziehl-Neelsen stain, Silver stain, Prussian blue stain, and Reticulin stain were done.

Immunohistochemistry (IHC) was done in selected patients for confirmation and exact characterization.

RESULTS
A total of 122 patients with pancytopenia were included in the study. The age range was 1/2 year to 82 years, and the mean age was 45.55 years. Male: Female ratio was 1.97:1.

The most common presenting complaint was fever, present in 61 (50%) patients, followed by easy fatigability in 53 (43.4%) cases, and shortness of breath in 23 (18.9%) cases. The least common presenting complaint was bleeding, seen in 17 (13.9%) patients. 21(17.2%) patients presented with some other nonspecific complaints only.

The most common clinical finding was pallor, seen in 100% of cases. Splenomegaly was seen in 52(42.6%) patients, whereas isolated splenomegaly was present in 37(30.3%) patients. Hepatomegaly was seen in 22(18.03%) patients, whereas isolated hepatomegaly was seen in 6(4.9%) of patients. Hepatosplenomegaly was observed in 16 patients (13.11%). Lymphadenopathy was present in 19(15.57%) patients.

Table 1 shows hematological findings in patients with pancytopenia. (n=122)

		Number of patients	Percentage
Hb(g/dl)	8.1-10.0	50	41%
	6.0-8.0	44	36.1%
	<6	28	22.9%
TLC(/mm^3)	3000-3999	56	45.9%
	2000-2999	36	29.5%
	1000-1999	24	19.7%
	<1000	6	4.9%
Platelets(/mm^3)	>80,000	48	39.3%
	60,001-80,000	19	15.6%
	40,001-60,000	24	19.7%
	20,000-40,000	21	17.2%
	<20,000	10	8.2%

RBC Morphology
The most common RBC picture was Dimorphic (predominantly Macrocytic and Normocytic) in 56(45.09%) cases. A macrocytic picture was seen in 30(24.6%) patients. A normocytic normochromic picture was seen in 33(27.04%) cases. A microcytic hypochromic picture was seen in 3 patients (2.45%).

Table 2 shows various causes of pancytopenia in the study population(n=122)

		Number of patients	%
Anemia	Megaloblastic anemia	40	32.78%
	Aplastic anemia	4	3.27%
	Hypoplastic Anemia	8	6.5%
Infections	Visceral leishmaniasis	7	5.7%
Myeloid malignancy	AML	10	8.1%
	MDS	1	0.82%
	Myelofibrosis	4	3.2%
Lymphoid malignancy	Primary lymphoma	8	6.5%
	NHL infiltration	4	3.2%
	MM	6	4.9%

Other groups of malignancy	Histiocytic Sarcoma	1	0.82%
	Metastatic Carcinoma	2	1.6%
Others	Reactive HLH	4	3.2%
	Pure Red cell aplasia	1	0.82%
Inconclusive		23	18.9%
Total		122	100%

Bone Marrow aspiration findings

Particulate marrow was seen in 104/122(86.90%) cases. Diluted aparticulate marrow was seen in 11.5% cases. Dry tap was obtained in 3.2% cases.

Erythropoiesis was dimorphic in 53(43.44%) cases. Megaloblastic erythropoiesis was seen in 24(19.67%) cases. Normoblastic erythropoiesis was observed in 44 patients (36.1%). Micronormoblastic erythropoiesis was seen in only one patient (1.8%).

Bone marrow biopsy findings

Cellularity was increased in 56 cases (45.9%). Normal cellularity was seen in 28(22.95%) cases. Decreased cellularity was seen in 18 (14.8%) patients. Cellularity could not be assessed in 20 (16.4%) patients due to inadequate tissue or because a biopsy was not performed.

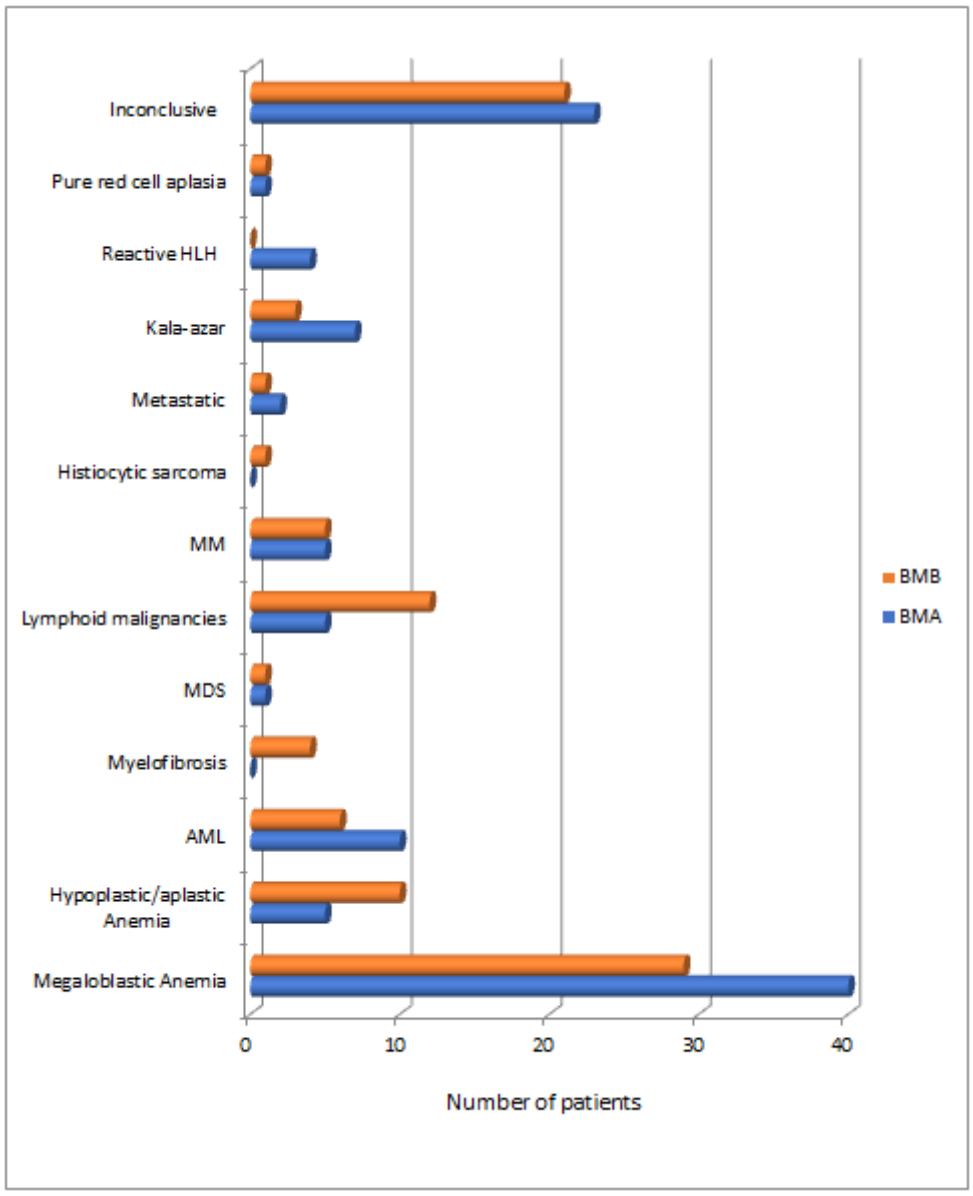

Figure 1 shows the correlation of aspiration and biopsy (n=122)

ANEMIA

- Most common affected age group in megaloblastic anemia was 21-40yrs(40%) followed by 41-60yrs(27.5%). In aplastic/hypoplastic anemia, the majority of patients (58.33%) were aged 21-60 years. In Megaloblastic and hypoplastic/aplastic anemia, fever was the most common symptom in 23 (57.51%) and 6(50%) cases, respectively. Bleeding manifestations were seen in 7 (17.5%) and 4 (33.3%) cases of megaloblastic and hypoplastic/aplastic anemia, respectively.
- Isolated splenomegaly and hepatomegaly was seen in 15/40(45%)cases and 4(17.5%) cases respectively. Organomegaly was absent in 18 cases.
  Lymphadenopathy was seen in 9/40(22.5%) cases of megaloblastic anemia.

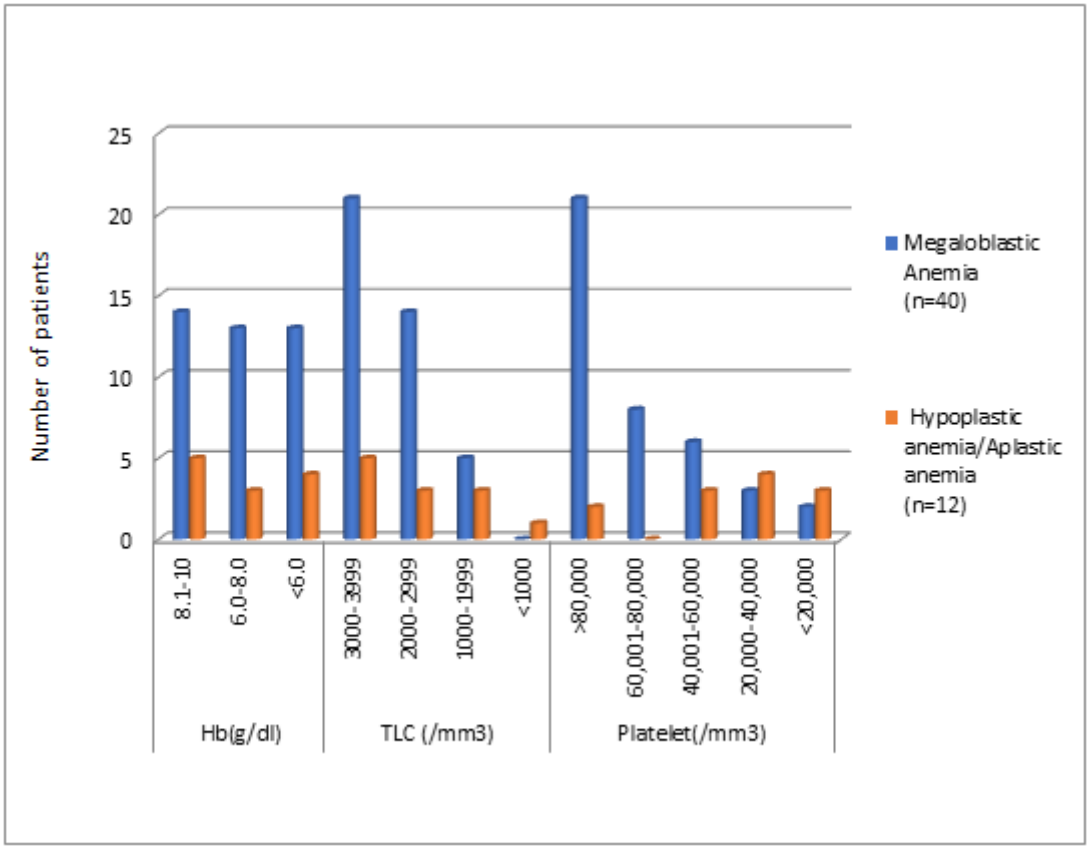

Figure 2 shows hematological findings in various groups of anemia.

- Dimorphic blood picture was seen in 25(62.5%)cases of megaloblastic anemia and 25% cases of aplastic anemia. Macrocytic anemia was seen in 10/40 (25%) cases of megaloblastic anemia and in 33.3% of cases of aplastic anemia. The normocytic normochromic picture was observed in 5/40 (12.5%) cases of megaloblastic anemia and 5/40 (41.67%) cases of aplastic anemia.
- In megaloblastic anemia, the marrow aspirate was particulate in all cases. On aspiration Erythropoiesis was purely megaloblastic in 16(40%)cases and dimorphic (megaloblastic+normoblastic) in 24(60%) cases. On bone marrow biopsy, erythropoiesis was purely megaloblastic in 16(40%) cases, but dimorphic erythropoiesis was seen in 18 (45%)cases. In 6(15%) cases, erythropoiesis could not be commented on biopsy due to inadequate tissue, or a biopsy was not done. Out of 12 cases of aplastic/Hypoplastic anemia, the marrow was diluted in 2(16.7%) cases.
- Hypercellular marrow was seen in 25/40 cases of megaloblastic anemia.
  Normal cellularity was seen in 8/40 cases of megaloblastic anemia. Hypocellular marrow was seen in 10/12 cases of hypoplastic/aplastic anemia and one case of megaloblastic anemia. In 6 cases of megaloblastic anemia and 2 cases of hypoplastic/aplastic anemia, cellularity could not be assessed due to inadequate tissue or the absence of a biopsy.

MYELOID AND LYMPHOID MALIGNANCY

- 10 cases of AML were seen in the age range of 14-77yrs with M: F::1:1. 4 cases of myelofibrosis were seen in the age range of 42-82 yrs with M: F::3:1. There was only one case of MDS, 60 yrs 60-year-old male patient. The most commonly affected age group for lymphoid malignancies was 61-80 years, with an M: F ratio of 11:1
- In AML, the marrow aspirate was particulate in all cases. On aspiration, erythropoiesis was dimorphic in 5/10 cases, megaloblastic in 2 cases, and normoblastic in 3 cases of AML. In myelofibrosis, bone marrow aspiration

was a dry tap in all cases, and the diagnosis was made only on bone marrow biopsy. Erythropoiesis on bone marrow biopsy was dimorphic in 2 cases, megaloblastic and normoblastic in 1 case each of myelofibrosis. Erythropoiesis was dimorphic on aspiration and biopsy in MDS. In lymphoid malignancies, a diluted aspirate was obtained in 4/12 (33.33%) cases. Out of 12 cases of lymphoid malignancies, erythropoiesis on aspiration was dimorphic in 3(25%) cases, normoblastic in 3(25%) cases, and megaloblastic in 2/12(16.7%) cases. On biopsy, dimorphic, normoblastic, and megaloblastic erythropoiesis were seen in 6,4, and 2 lymphoid malignancies, respectively.

- In AML, bone marrow was hypercellular in 5/10 cases and normal in one case. Cellularity could not be assessed in 4 cases due to inadequate tissue or no biopsy performed. Increased cellularity was observed in all cases of myelofibrosis and MDS. In lymphoid malignancies, cellularity was increased in 10/12 cases, marrow was hypocellular in 1 case, and tissue was inadequate in one case.

OTHER GROUP OF MALIGNANCIES

- 5 (83.3%) cases of Multiple myeloma (MM) were seen in the 61-80 years of age group. M: F was 5:1. One case of histiocytic sarcoma was seen in the 21-40-year age group. There were two female patients with metastatic malignancies. One patient was 70 years old, and the second patient was 45 years old.

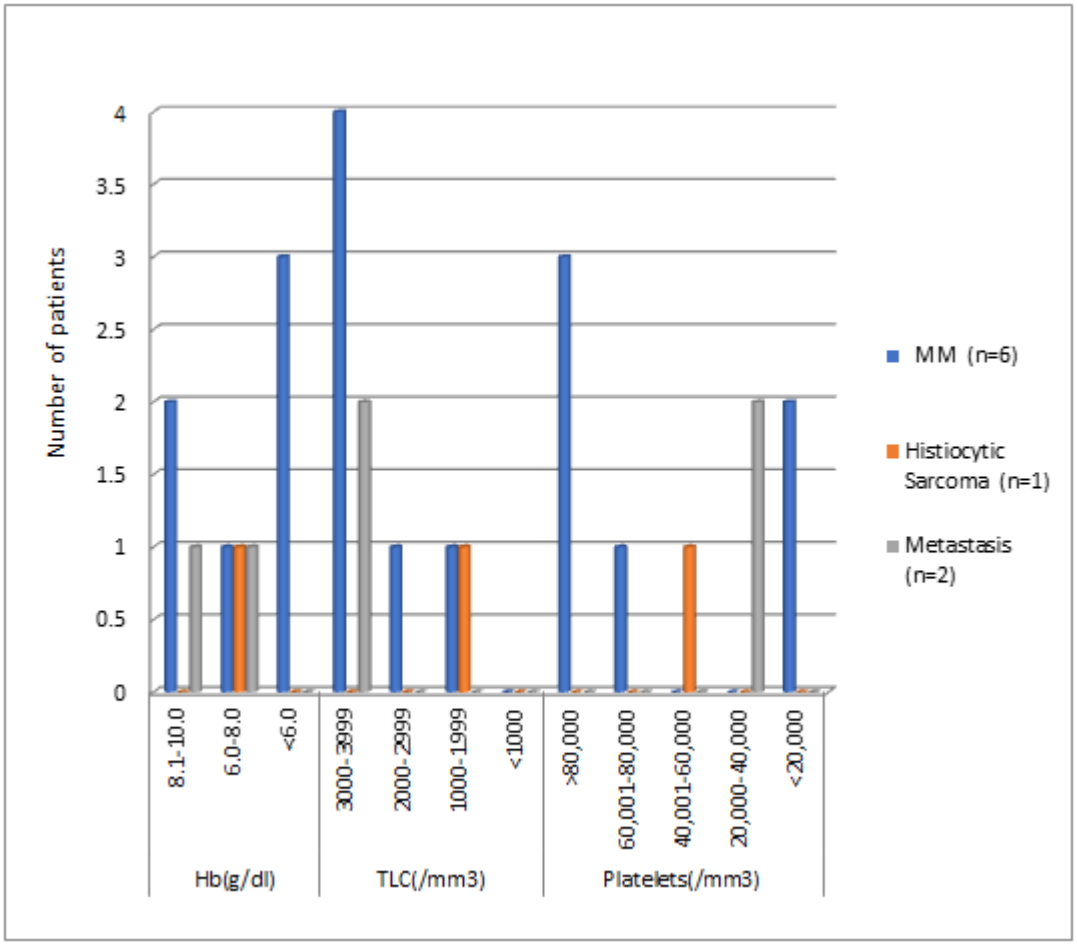

Figure 3 shows hematological findings in other malignancy groups.

- In MM, diluted marrow was obtained in one case only. Erythropoiesis was normoblastic in 4 (83.3%) cases and dimorphic in 1 (16.7%) case on aspiration and biopsy in MM. Erythropoiesis could not be assessed on biopsy in one case because the tissue was inadequate. Bone marrow aspirate was diluted in Histiocytic sarcoma. Diagnosis was made only on biopsy. In one case of metastatic carcinoma, the marrow aspirate was cellular and particulate. In the other case, marrow aspirate was aparticulate but cellular. On aspiration, erythropoiesis was normoblastic in one case and dimorphic in the other case. On biopsy, erythropoiesis was normoblastic in one case. In other cases, erythropoiesis could not be commented on in biopsy as the tissue was inadequate.

VISCERAL LEISHMANIASIS AND REACTIVE HLH

There was a wide age range for visceral leishmaniasis (4-61 yrs). All patients of visceral leishmaniasis were males. 3 patients were in the 41-60-year-old age group. For reactive HLH, the age range was 19- 42 years, and 2(50%) cases were in the age group of 0- 20 years. All patients with reactive HLH were males.

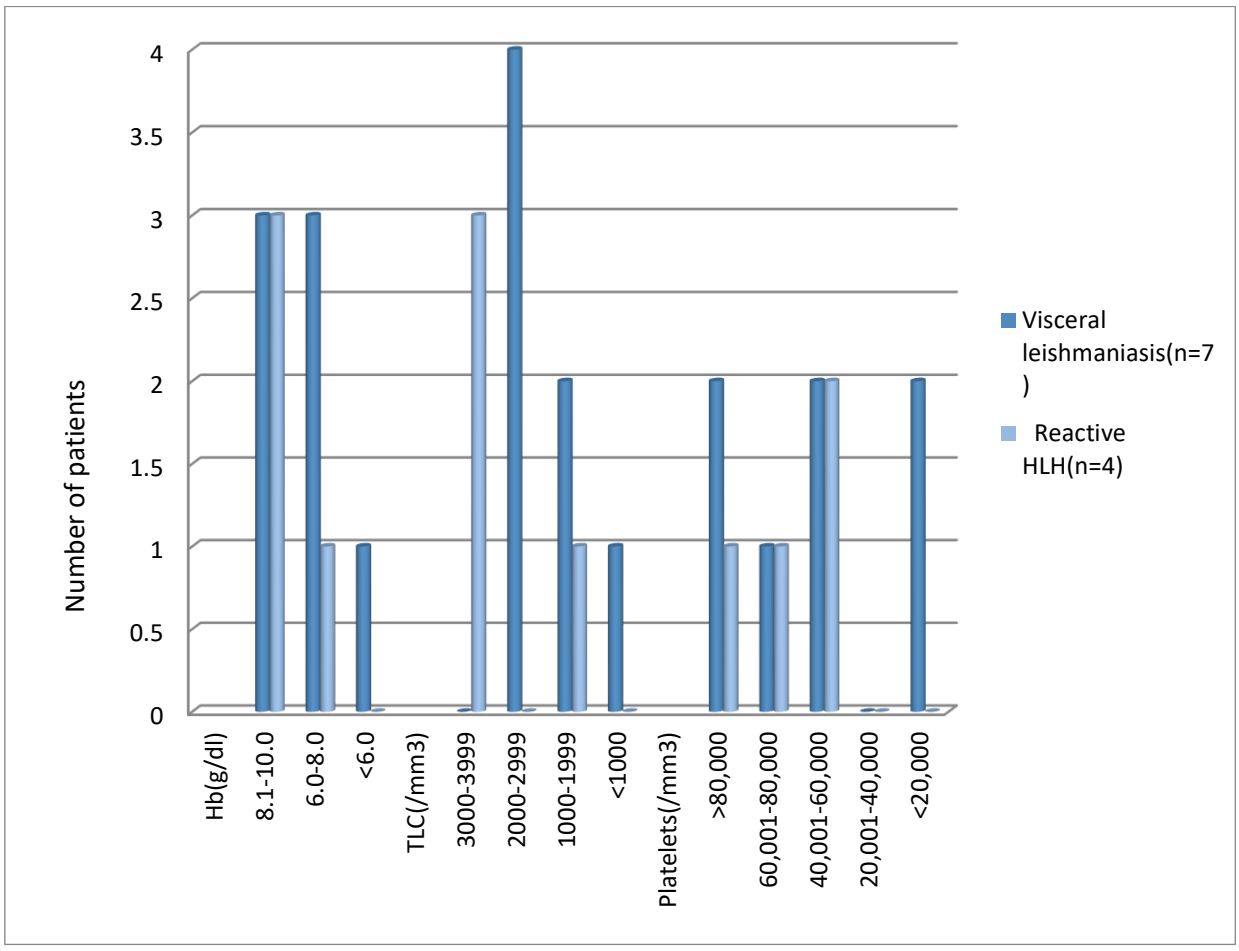

Figure 4 shows haematological findings in Visceral leishmaniasis and reactive HLH.

- Marrow was normocellular in 4/7 and 2/4 cases of visceral leishmaniasis and reactive HLH. Cellularity could not be assessed in 3/7(42.85%) of Visceral leishmaniasis cases because the procedure was not performed. In one case of reactive HLH, cellularity could not be assessed because the tissue was inadequate. Erythropoiesis was normoblastic in 4 cases of visceral leishmaniasis. Dimorphic erythropoiesis was seen in 3 cases of visceral leishmaniasis and reactive HLH. Megaloblastic erythropoiesis was seen in only one case of reactive HLH.

DISCUSSION

Pancytopenia is a common hematological problem encountered in our day-to-day clinical practice & should be suspected on clinical grounds when a patient presents with unexpected anemia, fever & bleeding tendencies.

This study was conducted at IGMC, Shimla, in the department of pathology from July 2015 to June 2016. 122 cases of pancytopenia were studied.

In the present study, the age range was ½- -82 years with a mean age of 45.6 years. In studies conducted by Lakhey et al, [1], Verma N et al,[8] and Graham S et al, [9,] age ranges were 5-82 yrs, 2-80 yrs, and 6-75 yrs, respectively, which were comparable to our study. In the present study, the M: F ratio was 1.97:1, with slight male predominance, and it shows concordance with other studies but discordance with Thakkar BB et al., [10], where the M: F ratio was 1.1:1

The most common presenting complaint was fever, present in 50% of patients, followed by easy fatigability in 43.4%. This correlates with other studies, except for the study by Khalisi et al[11.]., in which easy fatigability was the most common complaint, present in 67.6% of patients.

In the present study, Hb>6.0g/dl was present in 77.04% of patients, whereas in studies conducted by Basha M et al., [12] Hb>6g/dl was seen in only 16% of patients. Hemoglobin was >7.0g/dl and >5.0g/dl in 48% and 61.43% of patients,

respectively, in studies conducted by Metikurke SH et al. 13 and Aggarwal R et al.[14] In the present study, TLC was 3000-3999/mm^3 in 45.9% of patients. This was comparable with a study conducted by Santra G et al. 15, where TLC was 3001-3999/mm^3 in 40.6% of patients, whereas TLC in studies conducted by Aggarwal R et al. 14 and Basha M et al. 12 was 2500-3500/mm^3 and 3001-4000/mm^3 in 41.43% and 36% cases, respectively.

Platelet count >80,000/mm^3 was seen in 39.3% of cases in the present study, whereas platelet count>80,000/dl was seen in 28.57% and 18.0% of cases in studies conducted by Aggarwal R et al and Basha M et al, respectively. Platelet count was >50,000/mm^3 in a study by Santra G et al., observed in 60.36% of cases.

A dimorphic blood picture was the most common finding in the present study, occurring in 45.9% of patients, consistent with other studies except for Safei A et al. [16], where a normocytic normochromic picture was most common, observed in 48% of patients.

Hypercellular marrow was seen in 74% and 67% of patients in studies conducted by Basha et al and Safei A et al, respectively. At the same time, hypercellular marrow was seen in 45.1% of patients in the present study. Hypocellular marrow was observed in 14.75% of patients in the present study, comparable to 19% reported by Safei et al. In studies conducted by Aggarwal R et al. and Basha M et al., hypocellular marrow was seen in 44% and 6% of cases, respectively.

In the present study, megaloblastic anemia was the most common cause of pancytopenia, seen in 32.78% of cases. Frequency closely correlates with studies by Dahake17 and Vidya et al.,18 reported in 35% and 34.09% of patients, respectively. A higher frequency of megaloblastic anemia in the Indian subcontinent seems to reflect a higher incidence of nutritional deficiency.

Hematological malignancies were the second most common cause in our study, contributing 27.86% of cases, and frequency was comparable with studies conducted by Lakhey et al[1] and Shinwari N et al,[19] where frequency was 27.7 and 25% cases, respectively. Prevalence was quite high in a study conducted by Khalisi et al[11] in 56.2%. A lower prevalence was observed in a study by Basha M [21]et al., at 8.0% among patients. The differences in the frequency of hematological malignancies causing pancytopenia are attributable to variations in methodology, total number of patients, geographic area, period of observation, genetic differences, and exposure to cytotoxic drugs.

In our study, Acute leukemia was seen in 8.0% of cases, which comprised only AML. In other studies, acute leukemia included both AML and ALL cases. This could be because of the smaller number of pediatric patients in the present study.

Myelofibrosis was seen in 3.2% of cases of the present study, and the prevalence correlates with studies conducted by Dahake V et al[17] and Graham S et al,[17] seen in 3.1% and 3.3% cases, respectively. But frequency was lower in other studies conducted by Tilak V et al., [20] Khunger JM et al,[21] and Manzoor F et al,[22] ranging from 1.2-2.1%. This is probably because of the lower age range in these studies (2-8 to 70 years) compared with our study, where the age range was ½ to 82 years.

Hypercellularity of the bone marrow with abnormal cells confirmed the diagnosis of MDS. MDS is a disease characterized by ineffective hematopoiesis. It differs from AML by increased apoptosis in early and mature hematopoietic cells. MDS may thus be suspected in cases of pancytopenia, as also revealed in various studies. Prevalence of MDS was 0.8% in the present study, which was comparable to other studies by Jha et al, Premkumar M et al, and Sweta et al. In contrast, prevalence was higher in studies by Khodke K et al[23] and Manzoor F et al,[22] at 2% of patients each.

MM as a cause of pancytopenia accounted for 4.9% of cases in the present study and did not correlate with other studies, where prevalence ranged from 0.6-3.3%. Apart from hematological investigations, bone marrow examination, bone X-ray, serum electrophoresis, and urinary Bence Jones protein aided in the diagnosis.

The prevalence of NHL in the present study was 9.8%, lower than in other studies, which ranged from 2.4% to 3.3%, except in Khalisi et al.,[11] where it was 14.47%. As this study was conducted in Pakistan, the prevalence was likely higher due to geographic differences. Bone marrow examination was helpful in staging and the better management of NHL patients.

There was a single case of histiocytic sarcoma in the present study, and Kumar R et al[24] also reported 1/166 case of malignant histiocytosis.'

Metastatic deposits in the marrow were identified on aspiration in two cases. On further workup of the patients, one had primary small cell carcinoma of the lung, and the other was diagnosed as metastasis from poorly differentiated carcinoma of the stomach. Bone marrow examination helped determine the primary cause in these cases.

Metastasis was seen in 1.6% of patients in the present study, which correlates with a study by Dasgupta S et al.,[25] which reported 1.6%. Frequency was slightly lower in studies conducted by Jha et al.,[26] Shinwari N et al.,[19] and Vidya S et al.,[18] at 0.6%, 1%, and 1.2%, respectively.

Aplastic anemia was the third most common cause of pancytopenia, present in 9.8% of cases. A history of antibiotic and analgesic intake was present in 2 cases. In other studies, the number of patients with aplastic anemia was higher, ranging from 14% to 50%. Prevalence was higher in studies conducted by Devi PM et al[27] and Hayat S et al[28] because of a history of analgesic abuse and drug intake from quacks. Pathogenesis is not fully understood. However, two major etiologies have been invoked: an immunologically mediated suppression and an intrinsic abnormality of the stem cell.

Visceral leishmaniasis was seen in 5.7% cases in the present study, and it correlates with a study conducted by Premkumar M et al(5.7%), but does not correlate with studies conducted by Tilak V et,[20] Khodke K et al,[23] and Khunger JM et al,[21] where the frequency was lower, seen in 1.2%,2% and 2% cases, respectively. Frequency was higher in our study because this study was conducted in Himachal Pradesh, where there is a pocket of leishmaniasis, and the maximum number of patients were from that pocket. Santra G et al.[15] and Dasgupta et al.[25] reported higher frequencies of leishmaniasis at 9% and 13.6%, respectively.

Reactive HLH was seen in 3.2% of cases as a cause of pancytopenia in our study. Haemophagocytosis was secondary to Hepatitis E in one case and some other viral infections in other cases. It was also reported as a cause of pancytopenia in other studies conducted by Tilak V et al.[20], Santra G et al.[15] (due to enteric fever), and Nassem S et al.[29], with incidences of 1.2%, 1.8%, and 2.2% cases, respectively. Both bacterial and viral infections can cause hemophagocytic syndrome, which in turn can lead to pancytopenia. [30]

Another rare, interesting finding in this study was a single case of Pure red cell aplasia causing pancytopenia. It usually presents with anemia, but it can rarely present with pancytopenia. It was also reported as a cause of pancytopenia in studies conducted by Jha et al, [26] in 1/148 cases.

Normal marrow was seen in 18.9% of patients. Normal marrow was also obtained in studies conducted by Jha et al, [26](3.38%), and Pathak R et al, [22](5.8%). Pancytopenia in these patients can result from sequestration and/or destruction of cells by antibodies or from trapping of normal cells in a hypertrophied and overactive reticuloendothelial system.

In 11 cases of the present study, marrow findings were inconclusive; pancytopenia in these patients was probably due to hypersplenism, accounting for 9.0% of cases. Hypersplenism was seen in 11.4%,11%,8%, 6%, and 1.6% cases of studies conducted by Kumar R et al,[24] Shinwari N et al.[19], Manzoor F et al. [22], Basha M et al.[12], and Rehmani TH et al.[31], respectively.

The variation in the frequency of diagnostic entities causing pancytopenia has been attributed to differences in methodology, stringency of diagnostic criteria, geographic area, period of observation, and genetic factors.

Routine hematological parameters were non-specific and showed a significant overlap among the major causes of pancytopenia. However, the peripheral blood films were valuable in pointing towards the cause in patients with megaloblastic anemia and leukemia. Macro-ovalocytes and hypersegmented neutrophils were the main features in the majority of cases of megaloblastic anemia. The importance of bone marrow examination in pancytopenic patients has been well established in earlier studies by Bunch C. et al.[32], Imber M. et al.[33], and Keisu M. et al. 38. Bone marrow aspirate was sufficient for the diagnosis in most cases. However, biopsy was mandatory for the diagnosis of aplastic anemia, lymphoid malignancies, histiocytic sarcoma, and myelofibrosis.

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