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Original Article

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Analysis of Various Etiologies of Pancytopenia in a Tertiary Care Center in Manipur–3 Years Experience

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ABSTRACT

Background: Pancytopenia refers to the reduction in all three cell lineages in peripheral blood, exemplified by anemia, leukopenia, and thrombocytopenia. The common causes of pancytopenia in India are megaloblastic anemia, aplastic anemia, acute leukemias, myelodysplastic syndromes (MDS), infections, hypersplenism, storage disorders, myelofibrosis, plasma cell dyscrasias, etc.

Methods: A combined retrospective study for 3 years from September 2019 to August 2022 was conducted on 50 patients who were newly presented with pancytopenia. Previously diagnosed and follow-up cases of aplastic anemia, acute leukemia, lymphoma, myeloproliferative or myelodysplastic neoplasm, plasma cell neoplasm, and patients receiving chemotherapy and/or radiotherapy for other neoplasms were excluded. All the records, including available clinical history, findings of peripheral blood film and bone marrow examination findings, were analyzed.

Results: There were 26(52%) males and 24(48%) females, with a male-to-female ratio of 1.1:1. Mean age at the time of presentation was 48 years in males and 44 years in females. The commonest cause of Pancytopenia was Nutritional anaemia (24%), followed by viral infections (16%) and other non-specific causes (16%).

Conclusion: The present study helped in identifying the various etiologies of pancytopenia, specifically in this region. Nutritional anaemia is defined as a co-occurrence of Iron deficiency anaemia and megaloblastic anaemia. Early diagnosis of pancytopenia by bone marrow examination helps in timely intervention, planning further investigations and providing treatment accordingly, as a significant number of pancytopenic patients are potentially curable.

Key-words: Anemia, Bone Marrow Examination, Leukopenia, Pancytopenia, Thrombocytopenia

INTRODUCTION

Pancytopenia is one of the most common indications for bone marrow examination and refers to tri-lineage depletion of the hematopoietic cells in peripheral blood, exemplified by anemia, leukopenia, and thrombocytopenia. Patients with pancytopenia commonly present with the symptoms of weakness, malaise, fever, petechial and purpuric rash.

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On examination, the common findings are pallor, lymphadenopathy, splenomegaly, bone tenderness, etc [1].

Various neoplastic as well as non-neoplastic etiologies of pancytopenia have been described. Although, cytotoxic therapies along with radiotherapeutic and chemotherapeutic myeloablation are common causes in patients receiving treatment for neoplastic diseases, various infections, ineffective marrow production, peripheral or autoimmune destruction of hematopoietic cells, congenital or acquired bone marrow failure syndromes and marrow space-occupying lesions, are seen in relatively different proportions across the globe [2].

Common causes of pancytopenia in India include megaloblastic anemia, aplastic anemia, acute leukemias,

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myelodysplastic syndromes (MDS), infections, hypersplenism, storage disorders, myelofibrosis, plasma cell dyscrasias, etc. Thorough clinical history, physical examination and baseline hematological investigations provide a systematic approach to planning further investigations and avoiding unnecessary tests [3].

It has been reported that early diagnosis and prompt specific treatment cure the majority of the cases. Early diagnosis also helps reduce the mortality and morbidity associated with pancytopenia in several untreatable cases by implementing supportive therapy [4].

Being a geographically smaller area with a low population, the available literature on studies done for pancytopenia is limited for Manipur. An older study done in the same region had identified hypoplastic anemia as the commonest cause of pancytopenia, followed by megaloblastic anemia and myelodysplastic anemia [5]. This study is an attempt to minimize the knowledge gap regarding the various etiologies and their frequencies of pancytopenia in this region.

MATERIALS AND METHODS

Place of the study- In this study, we conducted a retrospective prospective study in the Hematology section of the Pathology department, Regional Institute of Medical Sciences, Imphal, Manipur, India, for a period of 3 years from September 2019 to August 2022.

Inclusion criteria- Patients irrespective of age or gender who presented with pancytopenia, defined by anemia (hemoglobin concentration less than 10g/dl), leucopenia (total leucocyte count less than $4x10^9$/l) and thrombocytopenia (total platelet count less than $100x10^9$/l) were included.

Exclusion criteria- Previously diagnosed and follow-up cases of aplastic anemia, acute leukemia, lymphoma, myeloproliferative or myelodysplastic neoplasm, plasma cell neoplasm, patients receiving chemotherapy and/or radiotherapy for other neoplasms were excluded.

Methodology- After applying the inclusion and exclusion criteria, we analyzed the records and reviewed the slides of 50 patients. Available relevant clinical data were also collected. All prior bone marrow aspirations and biopsies were done for consenting individuals under strict aseptic conditions. Aspirations were done using 14G or 16G Salah's needles. Aspiration slides were stained using Leishman, Perl's and Myeloperoxidase (MPO) stains. Bone marrow biopsies were performed using 12G, 14G, 16G and 18G Jamshidi needles. Bone marrow biopsies were subjected to pre-processing decalcification for 5 hours using 5% Nitric acid, followed by routine processing for HPE. Biopsy sections were stained with H&E stain as well as Reticulin stain, wherever necessary. Simultaneous hemogram and peripheral blood smear examinations were performed. A hemogram was performed using Auto Hematology Analyzer BC-5150 by Mindray. Peripheral blood smears were stained with Leishman stain. Supravital staining for reticulocyte counts was done using the new methylene blue stain.

Statistical Analysis- All the results were analyzed using descriptive statistics in the form of graphs and tables.

Institutional ethical clearance- We acquired ethical approval from the Research Ethics Board (REB), RIMS, Imphal, bearing letter no. A/206/REB/Prop(Fp)238/166/22/2024 before the conduct of this retrospective study.

RESULTS

Out of the 50 cases, 26(52%) were males and 24(48%) were females with a male-to-female ratio of 1.1:1. The commonest age group in our study was 41 to 60 years (Fig. 1). Mean age at the time of presentation was 48 years in males and 44 years in females. The youngest patient was 4 years old and the oldest was 84 years of age. The most common indication for bone marrow examination was pancytopenia of unknown etiology, which comprised 26(40%) cases, followed by 8(16%) cases of pancytopenia with associated chronic liver disease. Pallor and weakness were the two most common complaints on clinical examination. The mean hemoglobin of all cases was 7.5g/dl, whereas the mean total leucocyte count was 2045.52/µl. The mean platelet count was 54,620/µl.

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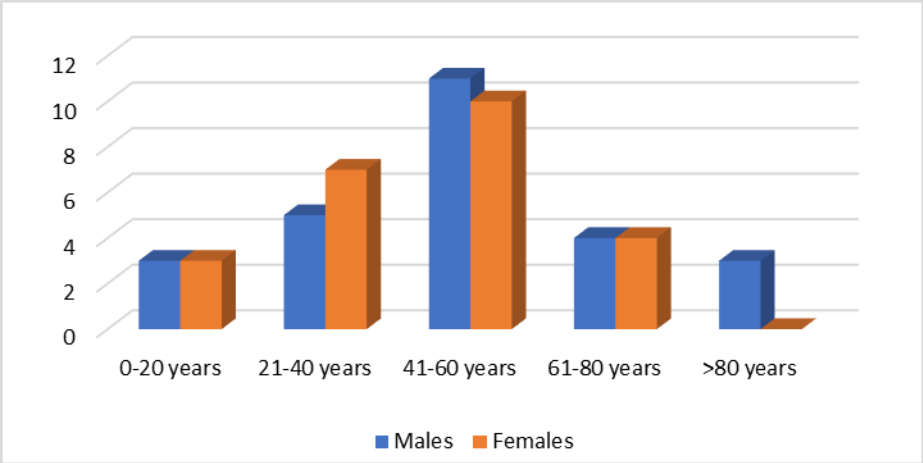

Fig. 1: Age group and gender-wise distribution of all cases of pancytopenia

The most common cause of Pancytopenia was Nutritional anaemia (24%) (Fig. 2), followed by viral infections (16%) and other non-specific causes (16%), as shown in Table 1. The viral causes included HIV, Hepatitis B and C infections. Four cases of acute leukaemia were diagnosed, which comprised two cases of Acute lymphoblastic leukaemia, one case of Acute myeloid leukaemia and one case of Acute Promyelocytic leukaemia. Hypoplastic leukaemia consisted of seven (14%) cases. There were four (8%) cases of megaloblastic anaemia (Fig. 3) and three (6%) cases of Iron deficiency anaemia (Fig. 4). Also, two (4%) cases of myelodysplastic syndromes were diagnosed. A 45-year-old male who presented with tiredness and limb tenderness was diagnosed with Multiple myeloma. An 83-year-old male who presented with lower back pain and bone tenderness was diagnosed with Mastocytosis.

Table 1: Distribution of all cases according to their diagnoses based on bone marrow aspiration

Causes	Age								Total
	<20 yrs		21 – 40 yrs		41 – 60 yrs		>60 yrs		
	M	F	M	F	M	F	M	F	
Reacting marrow (Non-specific)	0	1 (2%)	2(4%)	3(6%)	1(2%)	1(2%)	0	0	8(16%)
Viral infections (HIV, HCV, HBV)	0	0	2(4%)	2(4%)	3(6%)	1(2%)	0	0	8(16%)
Nutritional anaemia	0	0	0	0	4(8%)	4(8%)	3(6%)	1(2%)	12(24%)
Acute leukaemia	2(4%)	1(2%)	0	0	0	0	1(2%)	0	4(8%)
Hypoplastic anaemia	0	1(2%)	0	1(2%)	0	3	0	2(4%)	7(14%)
Iron deficiency anaemia	0	0	0	0	1(2%)	1(2%)	0	1(2%)	3(6%)
Myelodysplastic syndrome	0	0	1(2%)	0	0	0	1(2%)	0	2(4%)
Megaloblastic anaemia	1(2%)	0	1(2%)	1(2%)	1(2%)	0	0	0	4(8%)
Multiple myeloma	0	0	0	0	1(2%)	0	0	0	1(2%)
Mastocytosis	0	0	0	0	0	0	1(2%)	0	1(2%)

M- Males; F- Females

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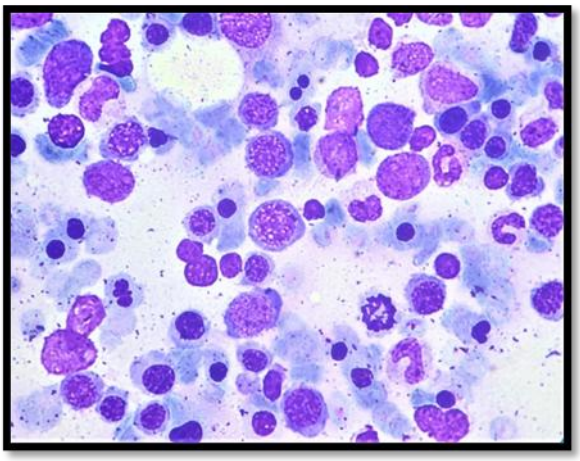

Fig. 2: Bone marrow aspirate showing Nutritional Anemia. Megaloblasts admixed with micronormoblasts (Oil immersion, Giemsa)

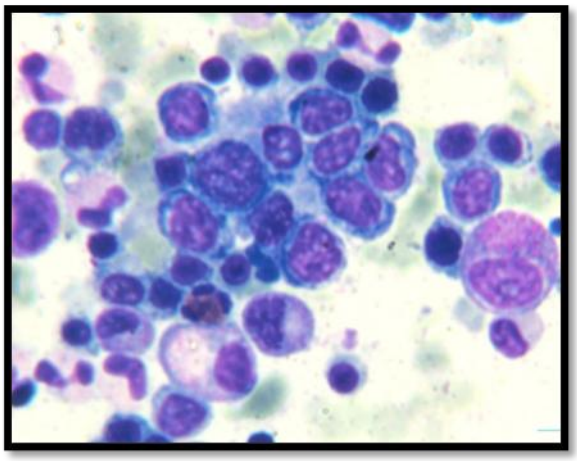

Fig. 3: Bone marrow aspirate of Megaloblastic anemia showing many megaloblasts (Oil immersion, Giemsa)

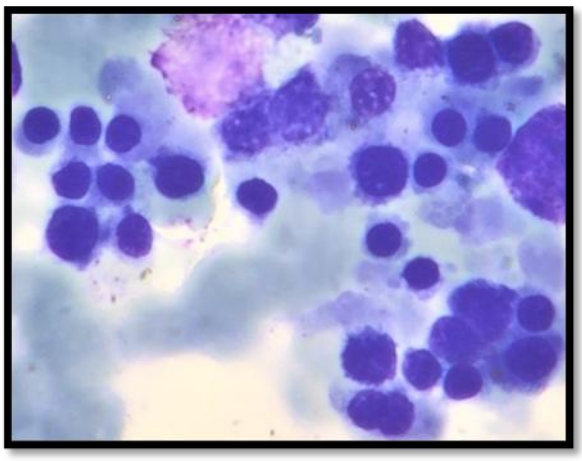

Fig. 4: Bone marrow aspirate showing Iron deficiency anemia (Oil immersion, Giemsa)

Concurrent bone marrow biopsy data were available in 25 cases. A positive histopathologic correlation was made in 20 (80%) cases compared to the bone marrow aspiration findings. In 5 (20%) cases, biopsy findings were negatively correlated. These included 3 cases diagnosed as reactive marrow and 2 cases diagnosed as hypoplastic marrow (Fig. 5) on bone marrow aspiration, as shown in Table 2.

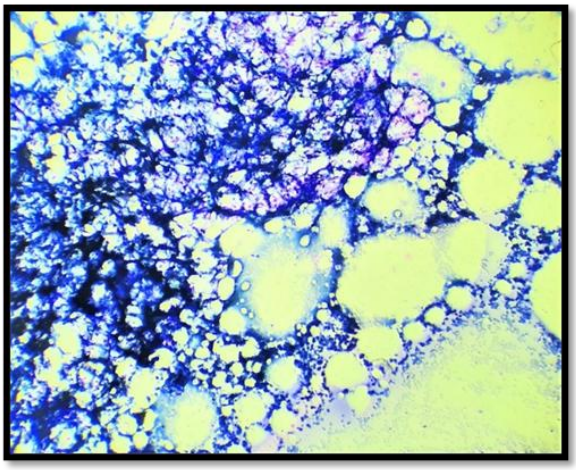

Fig. 5: Bone marrow aspirate showing Hypoplastic marrow (10X, Giemsa)

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Table 2: Comparison of discordant bone marrow aspiration compared to biopsy diagnosis

Age/Gender	Bone marrow aspiration diagnosis	Bone marrow biopsy diagnosis
70years/Female	Reacting marrow	Metastasis
56years/Male	Reacting marrow	Lymphoid aggregates
80years/Male	Reacting marrow	Myelofibrosis
60years/Female	Hypoplastic marrow	Necrosis
45years/Female	Hypoplastic marrow	Granulomatous lesion

DISCUSSION

The common presenting age group seen in our study was 41 to 60 years. Although variation in age ranges is evident, the mean age of patients in our study, which was 46 years, was found comparable with other studies. Also, a slight male predilection was synchronously seen, as shown in Table 3.

Table 3: Comparison of the present study findings with other studies

Study parameters	Gayathri *et al.* [6]	Sweta *et al.* [7]	Raina *et al.* [8]	Mangal *et al.* [9]	Patel *et al.* [10]	Present study
Region	Southern (Davangere, Karnataka)	Central (New Delhi)	Northern (Western Himalayas)	Eastern (West Bengal)	Western (Jodhpur, Rajasthan)	North Eastern (Imphal, Manipur)
Number of cases	104	100	69	91	546	50
Male: Female ratio	1.2:1	1.6:1	1:1.3	1.3:1	1.3:1	1.1:1
Most common age group	N/A	21 to 35 years	19 to 60 years	21 to 30 years	21 to 30 years	41 to 60 years
Mean age	41 years	42 years	39.06 years	N/A	40.3 years	46 years
Most common cause of pancytopenia	Megaloblastic anemia (74.04%)	Megaloblastic anemia (66%)	Megaloblastic anemia (36.2%)	Aplastic anemia (24.2%)	Acute leukemia (17.9%)	Nutritional anemia (24%)
Most common RBC morphology	Dimorphic (37.5%)	Macrocytic (49%)	N/A	Normocytic (67%)	Macrocytic (61%)	Normocytic (76%)
Most common marrow cellularity	Hypercellular	Hypercellular	Hypercellular	Hypercellular	Hypercellular	Hypercellular

The most frequent presenting symptom of pancytopenia was generalised weakness followed by fever and breathlessness, which was similarly observed in other studies [10-12]. However, fever was the most frequent presentation as observed by Vaidya *et al.* [13] and Khodke *et al.* [14]. Upon clinical examination, pallor was the most observed finding that synchronized with other studies [11,15]. The other clinical examination findings included splenomegaly, pedal edema, hepatomegaly, gum hypertrophy and bleeding, which were also reported in

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different studies [5,16]. Some investigators also reported a much higher incidence of hepatomegaly alone [11,14,17].

In a study done in 2008 in the same region, the commonest cause of pancytopenia was found to be hypoplastic marrow (22%), followed by megaloblastic anaemia (18%) and myelodysplastic syndrome (18%) [5]. However, there has been a drift in the etiology of pancytopenia in the region. Our new findings suggest that Nutritional anaemia is now the most common cause. It is defined as a co-occurrence of Iron deficiency anaemia and megaloblastic anaemia. However, in the published literature, many Indian authors have reported Megaloblastic anaemia as the commonest cause [6,7,8]. Others also reported Aplastic anaemia as the commonest etiology [9,18-20].

Common causes of Megaloblastic anaemia include: (a) vitamin B12 deficiency, often due to poor dietary intake, absorption issues (such as pernicious anemia), or certain medical conditions, (b) folate deficiency, which can occur due to inadequate dietary intake, increased demand (as seen in pregnancy), or malabsorption. Patients generally present with a wide array of symptoms, including fatigue, weakness, pallor/jaundice, dyspnea, dizziness, glossitis or neurological symptoms. Treatment is generally focused on addressing the underlying deficiency through dietary changes, oral supplements, or, in more severe cases, intramuscular vitamin B12 injections. If left untreated, a more serious sequelae of cardiovascular and neurological damage can manifest.

Iron deficiency anemia can be caused by: (a) inadequate dietary intake of iron, (b) increased iron requirements (infancy, childhood, pregnancy), (c) blood loss such as heavy menstruation, causes of gastrointestinal bleeding such as ulcers, polyps, or cancers, or physical and chemical injury. A positive association between iron deficiency anemia and vitamin B12 deficiency anemia has been recognized in the past [21]. It is of high clinical and laboratory practical importance to identify combined deficiency of iron and vitamin B12 as a vast majority are related to malabsorption syndromes, including pernicious anemia, *H. pylori* infection, celiac disease and gastric surgeries [22].

It has been illustrated that low vitamin B12 is not synonymous with vitamin B12 deficiency and megaloblastic anemia. Confirmation of an actual deficiency requires a serum vitamin B12 assay. Noteworthily, low vitamin B12 was also found with concurrent iron deficiency anemia among 18% of patients [23].

A definitive diagnosis of megaloblastic anemia requires a demonstration of megaloblasts on bone marrow examination; therefore, bone marrow aspiration in particular is the investigation of choice [24].

The incidence of hematological malignancies ranges between 1.61% - 14.5 % in different studies done in India [25,26]. The overall incidence of hematolymphoid malignancies in our study was 10%, which comprised Acute leukemias (8%) and Plasma cell neoplasm (2%). These findings were comparable with various other studies [16,27,28].

CONCLUSIONS

There are wide and varied causes of pancytopenia, which depend on different demographic variables, as evidenced by the differences in the findings of various studies. Detailed clinical examination and complete hematological evaluation are vital in ascertaining the underlying etiology of pancytopenia. The present study helped in identifying the various etiologies of pancytopenia specifically in Manipur. Early diagnosis of pancytopenia by bone marrow examination helps in timely intervention, planning further investigations and providing treatment accordingly, as a significant number of pancytopenia patients are potentially curable. Bone marrow aspiration smears are superior for morphological details, whereas biopsy is more reliable for assessing cellularity, interstitial fibrosis, granulomas and infiltration.

A planned and collaborative large-scale study in our region under the aegis of the state and central government, along with the implementation of similar programs for treatable causes of pancytopenia, such as the anemia eradication program, *'Anemia Mukt Bharat',* will give a boon to our society.

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CONTRIBUTION OF AUTHORS

Research concept- Dr Babina Sarangthem
Research design- Dr Babina Sarangthem
Supervision- Dr Babina Sorokhaibam
Materials- Dr Babina Sorokhaibam

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Data collection- Dr Mautoshi Debnath
Data analysis and interpretation- Dr Mautoshi Debnath
Literature search- Dr Yengkhom Daniel Singh
Writing article- Dr Yengkhom Daniel Singh
Critical review- Dr Babina Sarangthem
Article editing- Dr Yengkhom Daniel Singh
Final approval- Dr Babina Sorokhaibam

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