Original Article

Clinico-hematological study of pancytopenia: A single-center experience from north Himalayan region of India

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Abstract

Background: Pancytopenia, an important hematological presentation is associated with different causes, which may vary in different regions. Uttarakhand, a north Himalayan state of India lacks studies of pancytopenia and the prevalent causes present in this region. Therefore, the present study was conducted to study the clinico-hematological profile of pancytopenia in a tertiary care center in the Uttarakhand, a north Himalayan state of India. It was also intended to study if these causes showed any variation from other studies done in different regions of India. **Materials and Methods:** The present observational study was conducted in a tertiary care institute situated in Uttarakhand state of India over a period of 1 year and 8 month from June 2017 to Feb 2019 including all the cases of pancytopenia. **Results:** The most common cause of pancytopenia was megaloblastic anemia (25%), followed by aleukemic leukemia and hypoplastic/aplastic anemia (19.1% each). Visceral leishmaniasis also constituted an important cause of pancytopenia in this study (11.7%). **Conclusion:** The study concludes that megaloblastic anemia and aleukemic leukemia are the most common cause of pancytopenia. Although leishmaniasis is considered to be non-endemic in this region, it constitutes an important cause of pancytopenia here. The clinicians, especially the physicians practicing the primary care and pathologists, should be aware of the different causes of pancytopenia present in this Himalayan region of India; therefore, delay in diagnosis can be prevented along with unnecessary investigations.

Keywords: Aleukemic leukemia, aplastic anemia, leishmaniasis, megaloblastic anemia, pancytopenia

Introduction

Knowledge of the common differential diagnoses of any clinical finding is helpful for the treating physician in its work-up. Pancytopenia is no exception, and awareness of common causes of pancytopenia helps the clinician in the requisition of relevant tests, which would avoid potentially uncomfortable and costly procedures. However, the causes of pancytopenia show a wide variation throughout the world, and there is a need for local knowledge of the causes of this condition.[1-10] The studies of pancytopenia from Uttarakhand, a north Himalayan state of India, are limited. In addition to clinical importance, the studies from this region may also vary from the rest of India due to geographical variation and, thus, may have epidemiological importance. It is also essential that physicians practicing primary care in this region should be aware of the common prevalent causes of pancytopenia and their necessary work-up.

Hence, the present study was conducted to study the clinico-hematological profile of pancytopenia in a tertiary care

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center in the Uttarakhand state of India. It was also intended to study if these causes showed any variation from other studies done in different regions of India.

Materials and Methods

The present observational study was conducted after institutional ethical approval in a tertiary care institute situated in Uttarakhand state of India. The study was conducted over a period of 1 year and 8 month from June 2017 to Feb 2019 including all the cases of pancytopenia diagnosed after detailed clinical history, hemogram, peripheral smear examination, bone marrow aspiration, trephine biopsy, flow cytometry, and relevant biochemical tests. Of these, the patients with the history of chemotherapy, radiotherapy, myelosuppressive drug, and incomplete clinical details were excluded from the study. Descriptive statistics were used and the proportions and percentages of each diagnosis were calculated along with the exact 95% confidence interval by the R statistical Environment, version 3.5.1 (Vienna, Austria).

All cases having hemoglobin (Hb) less than 10 gm/dl, total leukocyte count (TLC) less than 4000/mm^3, and platelet count less than 100,000/mm^3 were defined as pancytopenia. Blood counts were done by Beckman Coulter LH-750 or Sysmex XN-1000 automated counters. The low counts were cross-checked by peripheral blood smear examination. All peripheral smears were also examined for anisopoikilocytosis, hypochromasia, presence of atypical cell, and any parasites.

Bone marrow aspiration and trephine biopsy were performed after taking informed consent under local anesthesia from posterior superior iliac spine. Immunophenotyping of cases of leukemia was done on BD FACS Canto II flow cytometer. Immunohistochemistry was also done on trephine biopsy wherever required.

Results

A total of 541 bone marrow examinations were performed in the study period and out of which 131 cases had pancytopenia. Of these 131 cases, 63 cases were excluded as they had either history of taking myelosuppresive therapy, radiotherapy, or had incomplete clinical details which could not be recovered despite best efforts. The remaining 68 cases included in the study showed male-female ratio of 1.19:1 and median age of 35 years with the range of 2–75 years. Table 1 shows the clinical presentation of the cases of pancytopenia. It shows that hepato-splenomegaly was the most common presentation (52.9% of total cases). It was observed that median hemoglobin level was 7.2 gm/dl, TLC 2450/cumm, and platelet count 40,000/cumm. Table 2 shows the various causes of pancytopenia with distribution according to age and sex. It shows that megaloblastic anemia [Figure 1a] was the most common cause of pancytopenia followed by aleukemic leukemia and aplastic/hypoplastic anemia [Figure 1c]. In two cases, a diagnosis could not be made even after relevant investigations. A single case of plasma cell dyscrasia was also seen presenting as pancytopenia in the present study [Figure 2]. Of the total 13 diagnosed cases of aleukemic leukemia, 5 cases were acute myeloid leukemia, 1 case was acute promyelocytic leukemia, and 4 cases were acute lymphoblastic leukemia. Remaining 3 cases were reported as acute leukemia [Figure 1b]. In addition, a total 8 case of visceral leishmaniasis were also diagnosed on bone marrow, which were cause of pancytopenia in the study [Figure 1d]. Out of these, 5 cases were residents of Uttarakhand, whereas 3 were from adjoining plains. Table 3 shows the common causes of pancytopenia reported from various studies conducted across different regions of Indian along with their comparison with the present study.

Discussion

In India, studies on pancytopenia from north Himalayan region of India are lacking. This data, if available, would help clinicians in planning the diagnostic approach in patients with pancytopenia and will also help in starting early treatment. Keeping this in mind, the present study was conducted to know the causes of pancytopenia at a tertiary care center in Uttarakhand, North India. With the help of detailed clinical history, physical examination, and hematological investigations, pancytopenia can be diagnosed and the causes can be ascertained. In agreement with the majority of the published studies from India, the present study also observed that megaloblastic anemia

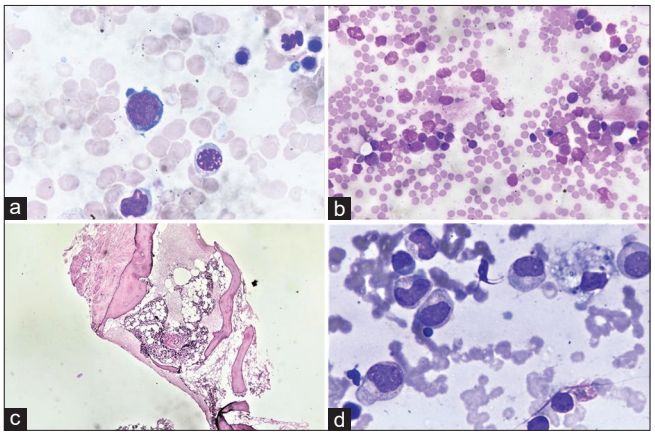

Figure 1: (a) Bone marrow aspirate showing megaloblastic maturation of erythroid precursors in megaloblastic anemia (Wright stain, ×1000). (b) Peripheral blood smear showing myeloblasts with fine cytoplasmic granules in acute myeloblastic leukemia (Wright stain, ×1000). (c) Bone marrow trephine biopsy showing markedly hypocellular marrow with most of marrow spaces replaced by fat in aplastic anemia (H and E, ×100). (d) Bone marrow aspirate showing intracellular and extracellular Leishmania donovani bodies (Wright stain, ×1000)

Table 1: Clinical presentation of cases with pancytopenia

Presentation	Number of cases (Percentage of total cases)
Weakness	32 (47%)
Splenomegaly	23 (33.8%)
Hepatomegaly	13 (19.1%)
Bleeding manifestations	3 (4.4%)
Abdominal pain	3 (4.4%)

Table 2: Various causes of pancytopenia with distribution according to age and sex

Age group (years)	<10		11-20		21-30		31-40		41-50		51-60		>60		Total	% (95% CI)
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F		
Megaloblastic anemia			3	2	2		2	1	1	1	1	3	1		17	25.0 (15.3-37.0)
Aleukemic Leukemia	3	2		1		4							2	1	13	19.1 (10.6-30.5)
Hypoplastic/Aplastic Marrow	1		2	2	1		1	1	1		1			3	13	19.1 (10.6-30.5)
Visceral leishmaniasis	1		1		2		2	1					1		8	11.8 (5.2-21.9)
Plasma cell dyscrasia											1		1	3	5	7.4 (2.4-16.3)
Splenomegaly						1		1						1	3	4.4 (0.9-12.4)
MDS										2					2	2.9 (0.4-10.2)
Myelofibrosis					1			1							2	2.9 (0.4-10.2)
Atypical lymphoid infiltrate											1		1		2	2.9 (0.4-10.2)
Undiagnosed							1				1				2	2.9 (0.4-10.2)
Hairy cell leukemia											1				1	1.5 (0.0-7.9)
Total	5	2	6	5	6	5	6	5	2	3	6	3	6	8	68	

Table 3: Comparison of common causes of pancytopenia in different studies from India

Study	Most common cause	Second most common cause	Third most common cause	Fourth most common cause
Kumar *et al.*[14]	Aplastic anemia (29.51%)	Megaloblastic anemia (22.28%)	Aleukemic leukemia (12.04%)	Hypersplenism (11.44%)
Gayathri *et al.*[12]	Megaloblastic anemia (74.04%)	Aplastic anemia (18.3%)	Sub leukemic leukemia (3.8%)	Malaria (2%)
Santra *et al.*[3]	AA (22.72%)	HS (15%)	Drug Induced (13%)	Kala-azar (9%)
Vandana *et al.*[4]	Megaloblastic Anemia (41.2%)	Dimorphic Anemia (8.7%)	Hypoplastic Anemia/Aplastic Anemia (8.7%)	Acute Leukemia (7.5%)
Jain *et al.*[13]	Hypersplenism (29.2%)	Infections (25.6%)	Myelosuppressants (16.8%)	Megaloblastic Anemia (13.2%)
Khunger *et al.*[9]	Megaloblastic anemia (72%)	Aplastic anemia (14%)		
Present study	Megaloblastic anemia (25%)	Aleukemic leukemia (19.11%) and Hypoplastic Anemia/Aplastic Anemia (19.11%)	Leishmaniasis (11.76%)	Plasma cell dyscrasia (7.4%)

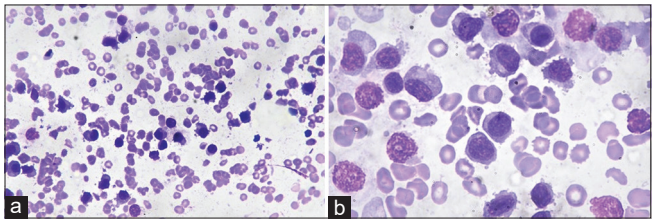

Figure 2: (a) Bone marrow aspirate showing plasma cells with eccentrically placed nucleus (Wright stain, ×100) and (b) plasma cells showing perinuclear hoff (Wright stain, ×1000) in multiple myeloma

was the commonest cause of pancytopenia. This is in contrast to the Western world, where leukemia is the leading cause of pancytopenia.[8,10] Hence, megaloblastic anemia should always be kept as first differential diagnosis while evaluating a case of pancytopenia in Indian settings. Thus, the data so observed in the present study would also be of immense help to physicians practicing primary care as they would be aware that megaloblastic anemia is the most common cause of pancytopenia in this region. This would be useful in avoiding irrelevant diagnostic work-ups and unnecessary financial burden on the patients. In addition, the primary care physicians, who are the first contact with the general population, may also be helpful in avoiding further complications of pancytopenia by simply preventing Vitamin B12 and folic acid deficiency. This knowledge would also help in preventing the misdiagnosis in the cases of pancytopenia due to megaloblastic anemia. Chen *et al.* concluded that cytopenia due to megaloblastic anemia must not be confused with myelodysplastic syndrome or erythroleukemia.[11]

Aleukemic leukemia, hypoplastic/aplastic anemia, and visceral leishmaniasis are the other important causes of pancytopenia in the present study. Although hypoplastic/aplastic anemia has been reported as an important cause of pancytopenia in other studies from Indian subcontinent, aleukemic leukemia and visceral leishmaniasis have been rarely reported as an important cause [Table 3] Incidence of aleukemic leukemia is 19.11% in our study, which is higher than most of the study from India, and underlines the need for urgent epidemiological surveillance and public health control of this disease.[12-15] Kumar *et al.* also reported aleukemic leukemia as third most common cause of pancytopenia with overall percentage of 12.04%, which is slightly lower than our study.[14]

Pancytopenia associated with leishmaniasis may be commonly observed in endemic regions.[16,17] However, the relatively high share of pancytopenia cases due to leishmaniasis is more remarkable because Uttarakhand region is a non-endemic region for this parasitic infection.[18-20] Recent previous reports have suggested that there is a focus of leishmaniasis at high altitude in Garhwal region of Uttarakhand[21,22] and the present findings support this contention. This may be associated with the migration of population, deforestation, or change in environmental factors.

Recent reports have observed certain rare causes of pancytopenia that include breast carcinoma, myxedema coma, or Stevens-Johnson syndrome.[23-25] Although no such cause was reported in the present study, it is necessary that clinicians and the pathologists should be aware of such rare causes of pancytopenia. Similar to our study, Le Clef *et al.* meticulously combined bone marrow biopsy histopathological features and blood count to achieve precise diagnosis of cytopenia.[26] The knowledge of this approach may be helpful in avoiding diagnostic pitfalls in pancytopenia, especially by the physicians practicing primary health care.

However, an important limitation of the present study is that it is a cross-sectional observational study, done in a referral tertiary care center; therefore, the possibility of selection bias may be present and exact causes of pancytopenia prevalent in the region may not have been predicted in the study. Thus, the authors suggest that further larger studies may be done to ascertain the prevalent cause of pancytopenia in this region.

Conclusion

The study concludes that megaloblastic anemia and aleukemic leukemia are the most common causes of pancytopenia. Although leishmaniasis is considered to be non-endemic in this region, it constitutes an important cause of pancytopenia here. The clinicians, especially the physicians practicing the primary care along with the pathologists, should be aware of the different causes and morphological features of pancytopenia present in this Himalayan region of India. This knowledge will not only prevent delay in diagnosis but also unnecessary laboratory investigations which may harm both the health and pocket of the patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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