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Original Article

Spectrum of Pancytopenia in Local Population

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ABSTRACT

Objective: To determine the frequency of pancytopenia aetiologies in local population.
Study Design: Cross sectional study
Place and Duration of Study: Haematology Department, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Jun 2020 to Jul 2021.
Methodology: A total of 263 patients having pancytopenia were inducted in study from 30 June 2020 to 1 July 2021. All patients having pancytopenia were included in the study and all patients receiving chemotherapy/cytotoxic drug therapy were excluded. Blood complete picture (Blood CP), reticulocyte count, peripheral blood smear, bone marrow aspirate smear and trephine biopsies were done according to standard protocols.
Results: Out of 263 patients diagnosed with pancytopenia, megaloblastic anemia was commonest and present in 25.85% (68 cases) followed by leukemia in 25.09% (66 cases), aplastic anaemia in 14.44% (38 cases), mixed deficiency anaemia 9.50% (25 cases), non-haemopoietic infiltrate/metastasis 7.60% (20 cases), infectious/inflammatory/sepsis 4.56% (12 cases), myelodysplastic syndrome 3.42% (9 cases), lymphoma 3.04% (8 cases), hypersplenism 1.90% (5 cases), granulomatous inflammation 1.52% (4 cases), visceral leishmaniasis 1.14% (3 cases), storage disorders 1.14% (3 cases), histiocytic lymphohistiocytosis 0.80% (2 cases) respectively.
Conclusion: Megaloblastic anaemia is the commonest pancytopenia cause followed by leukemias, aplastic anaemia, mixed deficiency anaemia, non-haemopoietic infiltrate (metastasis), infections/inflammations/septicaemias, lymphomas, visceral leishmaniasis, myelodysplastic syndrome, hypersplenism, granulomatous inflammation, storage disorders and histiocytic lymphohistiocytosis.

Keywords: Bone marrow aspiration, leukemia, megaloblastic anaemia, pancytopenia.

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INTRODUCTION

Decrease in all three main blood parameters below normal limits and coexistence of anaemia, leucopenia and thrombocytopenia is known as pancytopenia. Thus it is a 'triad' of findings and not a disease by itself. The pathophysiology of pancytopenia is variable and may include ineffective haematopoiesis or pathological changes in the marrow, decreased haematopoiesis as in aplastic anemia, peripheral destruction of cellular elements either due to infection or immune-mediated damage and entrapment of normal cells in reticuloendothelial system as in hypersplenism.[1]

The common clinical manifestations of pancytopenia are usually pallor (100%), fever (86.7%), fatigue (76%), dizziness (64%), splenomegaly (48%), weight loss (45.3%), bleeding (38.7%), anorexia (37.3%), night sweats (28%), hepatomegaly (21.3%) and lymphadenopathy (14.7%).[2] Bone marrow biopsy is a vital tool in pancytopenia management; allowing comprehensive marrow architecture evaluation, abnormal infiltrate distribution pattern and focal bone marrow lesions detection. Benign conditions such as infection and nutritional anaemia are equally important in addition to malignant causes as in bone marrow failure syndromes and malignancies.[3]

The rationale of this study was to determine the frequency of pancytopenia aetiologies in local population.

METHODOLOGY

This study was conducted at Haematology Department, Armed Forces Institute of Pathology, Rawalpindi, from Jun 2020 to Jul 2021. Permission from Institutional Ethical Review Board of AFIP was sought prior to commencement of project (certificate number 378). Since this was a cross sectional study with non-probability consecutive sampling technique, total of 263 consecutive patients were included within the time period mentioned above.

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Inclusion Criteria: All patients of either gender having pancytopenia with age ranging from 2 - 80 years were included in the study. Pancytopenia was defined as Haemoglobin (Hb) level <13.5 g/L for males and <11.5 g/L for females, Total Leucocyte Count (TLC) <4 × 109/L and Platelet (Plt) count <150 × 109/L (4).

Exclusion Criteria: All patients receiving chemotherapy/cytotoxic drug therapy were excluded.

All patients underwent meticulous history taking; age, history of previous treatment, exposure to chemical agents, drugs or radiation exposure were noted. Fever, night sweats, malaise, weight loss, bone pains etc were inquired in systemic history. Physical examination of all patient was done for pallor, jaundice, gum hypertrophy, hepatomegaly, splenomegaly and lymphadenopathy, carried out prior to bone marrow aspiration. Preliminary baseline haematological investigations like blood complete picture (Blood CP), reticulocyte count, and peripheral smear examination were done in each patient before performing bone marrow aspiration. Semi-automated cell counter (Sysmex) was used for blood counts estimation and again cross-checked manually during peripheral smear examination. Bone marrow aspiration and trephine biopsy were done with standard technique from posterior iliac crest with local anaesthesia under aseptic conditions. After procedure, the bone marrow aspirate smears were prepared directly on glass slides immediately after aspiration and air dried. Trephine biopsy touch imprints were prepared as adjunct to biopsy, preserved in Zenker's solution and dispatched for processing & examination. Peripheral and bone marrow smears were stained with Leishman stain whereas cresyl blue was used for reticulocyte count and haematoxylin & eosin (H&E) stain for trephine biopsy. Cytochemical stains such as Myeloperoxidase and Periodic-acid Schiff, were used as and when required.

Data analysis was done using SPSS version 23. Age range, gender distribution and frequencies of causes pancytopenia and clinical findings in pancytopenia were calculated, respectively.

RESULTS

Amongst 263 patients having pancytopenia, minimum age was 2 years and maximum age was 80 years, with a mean of 34.2 years + 16.3. Most commonly involved age range was 41-50 years with n = 63(23.9%) followed by 21-30 years with n = 58(22.0%) cases (Table-I). In terms of gender distribution; female patients were n = 97 cases (36.9%) and males were n = 166 cases (63.1%).

Megaloblastic anemia was the commonest aetiology of pancytopenia and present in 25.85% (68 cases) followed by leukemia in 25.09% (66 cases), aplastic anaemia in 14.44% (38 cases), mixed deficiency anaemia 9.50% (25 cases), non-haemopoietic infiltrate/metastasis 7.60% (20 cases), infectious/inflammatory/sepsis 4.56% (12 cases), myelodysplastic syndrome 3.42% (9 cases), lymphoma 3.04% (8 cases), hypersplenism 1.90% (5 cases), granulomatous inflammation 1.52% (4 cases), visceral leishmaniasis 1.14% (3 cases), storage disorders 1.14% (3 cases), histiocytic lymphohistiocytosis 0.80% (2 cases), respectively.

Clinical findings of patients with pancytopenia were; anemia, pallor and malaise in 223(85%) cases followed by splenomegaly in 92(35%) cases, hepatomegaly in 73(28%) cases, bleeding in 63(24%) cases, respectively.

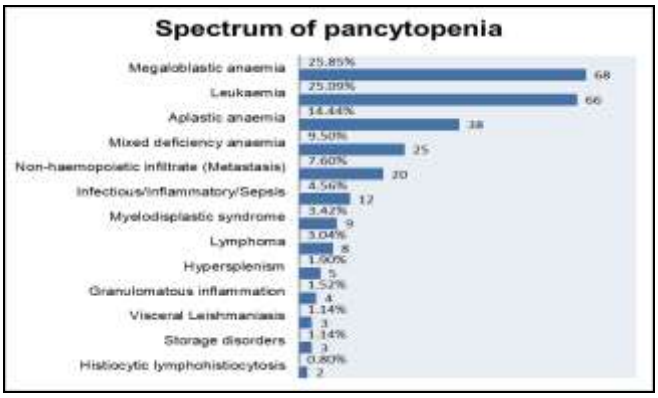

Figure-1: Spectrum of pancytopenia with frequencies (n=263)

DISCUSSION

Pancytopenia remains a perplexing and common haematological disorder. It is not a disease by itself but rather a triad of findings occurring as a response to a number of pathological processes affecting bone marrow either directly or indirectly leading to pancytopenia.[5] Pancytopenia management includes detailed history taking, thorough physical examination, laboratory investigations (haematological, chemical and histopathological) alongwith aid from relevant imaging modalities.[3]

Megaloblastic anaemia accounted for 68 patients (25.85%) having pancytopenia in this study. Megaloblastic anaemia (vitamin B12 or folic acid deficiency) is an established cause of cytopenias, presenting either as bicytopenia or pancytopenia and

rarely thrombocytopenia only. Commonest presenting

habits/food standards and self abstinence of essential

Table-I: Number of cases according to age groups in aetiological spectrum of pancytopenia (n=263)

Aetiology	n(%)	Age (years)							
		1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Megaloblastic anaemia	68(25.85 %)	0	8	9	10	25	5	7	4
Acute leukemia	66(25.09%)	3	10	18	17	15	1	2	-
Aplastic anaemia	38(14.44%)	2	15	17	-	4	-	-	-
Mixed deficiency anaemia	25(9.50 %)	-	9	8	7	1	-	-	-
Non-haemopoietic infiltrate (Metastasis)	20(7.60 %)	-	-	-	-	9	5	6	-
Infectious/Inflammatory/Sepsis	12(4.56 %)	-	5	4	3	-	-	-	-
Myelodysplastic syndrome	9(3.42 %)	-	-	-	-	5	-	4	-
Lymphoma	8(3.04 %)	-	-	2	5	1	-	-	-
Hypersplenism	5(1.90 %)	-	-	-	4	1	-	-	-
Granulomatous inflammation	4(1.52 %)	-	-	-	2	2	-	-	-
Visceral Leishmaniasis	3(1.14 %)	1	2	-	-	-	-	-	-
Storage disorders	3(1.14 %)	3	-	-	-	-	-	-	-
Histiocytic lymphohistiocytosis	2(0.80 %)	2	-	-	-	-	-	-	-
Grand Total	263(100.00%)	11	49	58	48	63	11	19	4

Table-II: Comparison with previously published studies

Study	Country	Year	Cases	Commonest cause	2nd common cause
Niazi M et al (9)	Pakistan	2004	89	Aplastic anaemia (38.3%)	Megaloblastic anaemia (24.7%)
Osama I et al (14)	Pakistan	2004	100	Megaloblastic anaemia (39%)	Hypersplenism (19%)
Hamid GA et al (15)	Yemen	2008	75	Hypersplenism (45.3%)	Megaloblastic anaemia (14.7%)
Devi PM et al (16)	India	2008	50	Hypoplastic anaemia (22%)	Megaloblastic anaemia (18%)
Memon S et al (10)	Pakistan	2008	250	Aplastic anemia (23.9%)	Megaloblastic anemia (13.04%)
Tariq M et al (17)	Pakistan	2010	50	Aplastic Anaemia (36%)	Megaloblastic anaemia (16%)
Aziz T et al (6)	Pakistan	2010	88	Megaloblastic anemia (40.9%)	Aplastic Anaemia (31.9%)
Gayathri BN et al (5)	India	2011	104	Megaloblastic anemia (74.04%)	Aplastic Anaemia (18.3%)
Raphael V et al (12)	India	2012	80	Megaloblastic anemia (41.2%)	Dimorphic anaemia (8.7%)
Jain A et al (1)	India	2013	250	Hypersplenism (29.2%)	Infectious (25.6%)
Jan AZ et al (11)	Pakistan	2013	205	Aplastic anemia (28.3%)	Leukemias (23.9%)
Yokuş O (13)	Turkey	2016	137	Megaloblastic anemia (24.1%)	Chronic liver disease (21.1%)
Hossain et al (18)	Bangladesh	2017	36	Aplastic anemia (27.7%)	Megaloblastic anemia (16.6%)
Present study	Pakistan	2021	263	Megaloblastic anemia (25.85%)	Leukemias (25.09%)

feature of megaloblastic anaemia was pallor (anemia). Vitamin B12 deficiency is more common in adults whereas folate deficiency is commoner in children. Higher number of megaloblastic anaemia in our study depicts a higher prevalence of nutritional deficiency in local population. Moreover chronically ill patients have been reported with folic acid deficiency subsequent to which megaloblastic changes occur in marrow and ultimately leading to pancytopenia. Similar findings have been also published in local studies as megaloblastic anaemia being the commonest aetiology of pancytopenias by Aziz T, Iqbal W and Qazi RA *et al*.[6] Megaloblastic anemia coming out as the most frequent cause may be due to underprivileged socioeconomic status, poor eating food nutrients.

An important finding of this study was that acute leukemias were the second most common pancytopenia aetiology with 25.09%, where as in majority of previously published studies either megaloblastic or aplastic anaemia were among the top two causes. Since leaukemias are generally on the rise and the previous published data is quite old, this needs to be further established by prospective, larger sample size and multidepartmental/institutional studies. As per Hao T et al, compared to all cancers, leukemia cases have been increasing much faster ie from 28700 cases in 1998 to 60300 in 2018, up 110% in the USA.[7] Here in Pakistan leukemias are showing a rising trend as well, according to Globocan 2020

leukemia has risen to 5th most common malignancy gradually.[8]

Third most frequent cause of pancytopenia in this study was aplastic anaemia contributing 14.4%, corresponding well with the previously published data by Niazi M *et al.*,[9] who documented aplastic anaemia as 38.2%, followed by megaloblastic anaemia, 22%. Another study done by Memon S *et al.*,[10] in paediatric patients also showed aplastic anaemia as the most common aetiology, 23.9% followed by megaloblastic anaemia, 13.04% and study conducted by Jan AZ *et al.*,[11] showed aplastic anemia 28.3%, haematological malignancies 23.9% and megaloblastic anemia 19.5% as the commonest causes of pancytopenia.

Mixed deficiency anaemia (microcytic and macrocytic) was the fourth common cause and accounted for 9.50% of pancytopenia, corresponding well with the published data by Memon S et al of 8.6%.[10] and by Raphael V et al as 8.7%.[12] Although iron deficiency anemia is quite prevalent in our local population and the most common preventable nutritional deficiency. The lower percentage in our and previous studies could be attributed to iron deficiency/mixed anaemias usually present as anemia rather than pancytopenia and diagnosed on smear examination with subsequent treatment.[10]

Metastasis as aetiology of pancytopenia was at fifth place with 7.60% of the cases whereas in a study published by Yokuş O *et al.*,[13] metastasis was present at third place with 19.1%. Infectious/Inflammatory/Sepsis causes of pancytopenia were present in 4.56% cases corresponding well with majority of the previously published data. However, one study by Jain A *et al.*,[1] showed infections as second most common cause of pancytopenia with 25.6% cases which is markedly different from rest of the published data as evident from Table-II.

Rest of the pancytopenia aetiological spectrum comprised of myelodysplastic syndrome in 3.42% (9 cases), lymphoma 3.04% (8 cases), hypersplenism 1.90% (5 cases), granulomatous inflammation 1.52% (4 cases), visceral leishmaniasis 1.14% (3 cases), storage disorders 1.14% (3 cases) and histiocytic lymphohistiocytosis in 0.80% (2 cases), respectively.

It is further reiterated our study shows that leukemias are on the rising trend, as already explained above and patients with pancytopenia should be meticulously screened.

A detailed comparison with previously published studies is tabulated in Table-II.

LIMITATIONS OF STUDY

This is a retrospective study, further prospective studies with larger sample size, may be conducted.

CONCLUSION

Megaloblastic anaemia is the most common cause of pancytopenia which is due to underprivileged socioeconomic status, poor eating habits/food standard and self abstinence of essential food nutrients. An important finding of this study is leukemias being the second most common cause. Bone marrow aspiration/examination remains a vital tool in diagnosing etiology of pancytopenia which directs the management plan.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SSS & AM: Data acquisition, data analysis, critical review, approval of the final version to be published.

HUD & AJ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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