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Etiological Profile of Pancytopenia in a Tertiary Care Hospital of Kashmir Valley

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Abstract: ***Background: Pancytopenia is a haematological entity characterized by anaemia, leucopenia and thrombocytopenia simultaneously. The causes of pancytopenia are diverse. The spectrum of different etiologies leading to pancytopenia vary globally, as well as within different geographical regions of the same country like India. Aims and objectives: To evaluate various causes of pancytopenia in patients admitted to a tertiary care hospital of Kashmir valley. Material and Methods: A total of 132 patients of pancytopenia over a period of 18 months were enrolled. Clinical history, relevant physical examination and primary haematological investigations followed by bone marrow aspiration and trephine biopsy was done in all patients. Results: Seventy four were males with fifty eight females in 132 studied patients. Male to female ratio was 1.3:1, with a mean age of 43.81 years. Commonest cause of pancytopenia was megaloblastic anaemia found in 96 patients (72.73%), followed by acute leukaemia in 9 patients (6.81%), multiple myeloma in 7 patients (5.3%), lymphoma in 5 patients (3.79%), aplastic anaemia in 4 patients (3.03%), myelodysplastic syndrome in 4 patients (3.03%), and tuberculosis in 4 patients (3.03%). There were 3 patients (2.27%) of pancytopenia due to drugs. Conclusion: Megaloblastic anaemia is commonest cause of pancytopenia, followed by acute leukaemia and multiple myeloma.***

Keywords: Pancytopenia, megaloblastic anemia, leukemia, multiple myeloma, aplastic anemia.

1. Introduction

Peripheral pancytopenia is presence of anemia, leucopenia and thrombocytopenia simultaneously. Pancytopenia is not a disease per se, but a triad of findings because of decrease in levels of formed elements of blood (erythrocytes, leucocytes and thrombocytes) below a certain normal level.[1] By definition hemoglobin less than 13.5g/dl in males or 11.5gm/dl in females, the leucocyte count less than $4x10^9$/L and platelet count less than $150x10^9$/L constitute pancytopenia.[2] Both hematopoietic and non-hematopoietic disorders can present as pancytopenia. The etiologies of pancytopenia range from simple drug induced bone marrow failure to fatal leukemias. Different mechanisms lead to development of pancytopenia like diminished production as in aplastic anemia, ineffective hematopoiesis in megaloblastic anemia, sequestration by overactive reticuloendothelial system as in hypersplenism, and bone marrow infiltration by cancer or abnormal cells as in glycogen storage diseases.[3]

Since underlying pathology and severity of pancytopenia define the management and prognosis of the patients,[4] and so it is imperative to find underlying cause of pancytopenia. Studies in this regard have shown variation as regarding spectrum of etiologies from different regions of India.[5,6,7,8] Similar studies from this region are lacking, so the present study was undertaken to evaluate various causes of pancytopenia, their distribution and various clinical features among study subjects.

2. Materials and Methods

This was a prospective study carried out over a period of eighteen months in the Department of Medicine, Govt. Medical College Srinagar. Patients admitted to department during this period and fulfilling the criteria of pancytopenia were included in the study. Inclusion criteria were simultaneous presence of blood haemoglobin level <13.5 g/dl in males, or 11.5 g/dl in females, leukocyte count <4 × 10^9/L, and the platelet count <150 × 10^9/L.[1] Written consent was taken from all. Patients with diagnosed malignancy or on treatment of malignancy, radiation exposure in past were excluded.

In each individual patient detailed medical history including age, sex, smoking, alcohol intake, history of drug intake, toxic chemical or radiation exposure was asked. Particular attention was given to presence of easy fatigability, fever, bone pains, weight loss, anorexia, recurrent infections, easy bruising. A detailed physical examination was contemplated in every patient for pallor, jaundice, hepatosplenomegaly, lymphadenopathy, sternal tenderness and gum hypertrophy. In all patients complete blood counts and peripheral smear, liver function tests, kidney function tests, ultrasonography, X-ray chest were done. Additional investigations were done, if found necessary dictated by the patients clinical scenario which included erythrocyte sedimentation rate (ESR), urine and stool examination, liver serological investigations for enteric fever, malaria, blood culture, ELISA for HIV, hepatitis B and C viruses, coagulogram, skull and lumbar radiographs, urinary and serum electrophoresis. Vitamin B12 and folic acid levels were not done. Blood count samples were collected in ethylene diamine tetra acetic acid (EDTA) vials and reported by semiautomatic cell counter (Sysmex KX-21). Peripheral blood smears were stained by Leishman's stain and counts cross checked manually.

Bone marrow aspiration and trephine biopsy was done in posterior iliac spine in all patients after taking aseptic precautions and adequate anaesthesia using Salah and Jamshidi needles, respectively. All the patients in the study were investigated in a systematic manner, cause of pancytopenia was ascertained and the required data analysis done.

3. Results

A total of 132 pancytopenia patients were studied. Males outnumbered females, with 74 males (56.06%) and 58 females (43.93%). Male to female ratio in the study was 1.3: 1. Many cases were within the age group of 31 – 40 years, comprising a total of 30 patients (22.72%).The age of the patients ranged from 16 – 90 years with a mean age of 43.81 years.

The commonest presenting complaint was easy fatigability (90%), dyspnea (62%), followed by fever (46%). Pallor (100%), splenomegaly (31%) and hepatomegaly (24.32%) were the common physical examination findings.

The commonest etiologies of pancytopenia in the studied patients were megaloblastic anemia (72.72%) followed by acute leukemia (6.81%), multiple myeloma (5.30%), lymphomas (3.78%), aplastic anemia (3.03%), myelodysplastic syndrome (3.03%), tuberculosis (3.03%) and drug induced (2.27%). The results are shown in Table 1.

Megaloblastic anemia accounted for 96 cases whose age ranged from 16 – 80 years (mean age of 41.26 years). Males comprised 52 cases (54.17%) while 44 (45.83%) were females. Out of total 96 cases in megaloblastic group, on bone marrow examination 59 cases (61.46%) were of megaloblastic anemia and 37 cases (38.54%) were of dimorphic anemia i.e.; a combination of iron deficiency and megaloblastic anemia with iron deficiency masking megaloblastic picture. Gender wise distribution of various etiologies of pancytopenia is shown in Table 3.

Of the total 132 cases of pancytopenia, 9 were acute leukemia, with a mean age of 46.11 years, with 6 patients of acute lymphoblastic leukemia (ALL) and 3 of acute myeloid leukemia (AML). In the AML group, 2 patients had AML-M_3 and 1 had AML-M_2.

We encountered 7 cases of multiple myeloma in the studied patients with a mean age of 64.71 years, with presenting complaint of fever in four patients and renal failure, bone pains and pathological fracture in rest of patients.

There were 5 cases of lymphomas, 3 non – Hodgkin's and 2 Hodgkin's with a mean age of 62.82 years. Four patients each of aplastic anemia and tuberculosis leading to pancytopenia were seen in this study. Lastly, three cases of drug induced pancytopenia were observed in the study, all the three patients were on antiepileptic drugs, two on phenytoin and one on carbamazepine.

Table 1: Distribution of various etiologies of Pancytopenia

Etiology	*No. of cases (%age)*
Megaloblastic Anemia	96 (72.72)
Acute Leukemia	09 (6.81)
Multiple Myeloma	07 (5.30)
Lymphomas	05 (3.78)
Aplastic Anemia	04 (3.03)
Mylodysplastic Syndrome	04 (3.03)
Tuberculosis	04 (3.03)
Drug induced	03 (2.27)

Table 2: Age and gender wise distribution of cases

Age group (yrs)	*Males*	*Females*	*No. of cases (%age of total cases)*
10 – 20	07	08	15 (11.36)
21 – 30	12	06	18 (13.64)
31 – 40	14	16	30 (22.73)
41 – 50	12	12	24 (18.18)
51 – 60	12	08	20 (15.15)
61 – 70	10	06	16 (12.12)
71 – 80	06	02	08 (6.06)
Above 80	01	--	01 (0.76)
Total	74	58	132 (100)

Table 3: Gender wise distribution of etiologies of Pancytopenia

Etiology	*Males (%age)*	*Females (%age)*	*Total No. of cases*
Megaloblastic Anemia	52 (54.17)	44 (55.83)	96
Acute Leukemia	05 (55.56)	04 (44.44)	09
Multiple Myeloma	04 (57.14)	03 (42.86)	07
Lymphomas	04 (80.00)	01 (20.00)	05
Aplastic Anemia	02 (50.00)	02 (50.00)	04
Myelodysplastic Syndrome	03 (75.00)	01 (25.00)	04
Tuberculosis	03 (75.00)	01 (25.00)	04
Drug induced	01 (33.33)	02 (66.67)	03
Total	74	58	132

4. Discussion

Pancytopenia is not a disease itself, but many serious and life threatening conditions can manifest with pancytopenia. It has different etiologies, with a variation in frequency of different diseases leading to pancytopenia in different population groups. Differences in methods, strict diagnostic criteria, period of observation, age groups under study and exposure to chemicals and myelosuppressive drugs are the reasons ascribed for this variation.[9]

In the present study of 132 patients, definite male predominance was observed with a male to female (M:F) ratio of 1.3:1 and a mean age of 43.81 years. In a similar study of 104 patients by Gayathri et al., the male to female ratio was 1.2:1 and mean age was 41 years.[5]

Most common age group of presentation was 4th decade of life in our study, as shown in Table 2 .Other studies have reported 3rd and 4th decade as commonest age groups of presentation [7,10,11,12]

Megaloblastic anemia was commonest cause of pancytopenia in the present study, accounting for 96 patients (72.72% of total patients). Khunger JM et al., found megaloblastic anemia in 72% of cases.[2] Similar results were found in studies by Tilak V et al., and Gayathri BN et al., were megaloblastic anemia incidence was 68% and 74.04% respectively.[4,6].

The incidence of acute leukemia varies between 1.61% - 14.5 % in different Indian studies.[8,13] Acute leukemia being the second commonest etiology in the present study, was present in 9 patients(6.78% of total patients). The results

were comparable with Khunger JM et al., who found an incidence of 5% of acute leukemia in the studied patients.[2]

We had seven cases (5.30% of total patients) of multiple myeloma. The study by Khodke K et al., reported an incidence of 4%. The results were still comparable.[14] There were 5 cases (3.78% of total patients) of lymphomas, mostly non-Hodgkin's lymphoma with incidence varying between 0.9% to 10% in different studies.[7]

Dasgupta et al., reported an incidence of 2.42% of myelodyspastic syndrome, while our study had 3.03% incidence of myelodysplatic syndrome. We had only four patients (3.03% of total patients) of aplastic anemia, which has been reported as commonest etiology of pancytopenia in different studies.[11,12,15,16] Reasons for low incidence of aplastic anemia could be selected admission, as our hospital does not admit pediatric patients which could have missed some patients of aplastic anemia especially with hereditary causes. Secondarily, incidence of aplastic anemia as etiology of pancytopenia varies between 7.7-52.7% and our findings were still comparable.[7]

In our study we encountered four patients (3.03% of total cases) of tuberculosis, all of them presented with unexplained fever and weight loss. In developing countries like India, tuberculosis is a common disease. Pancytopenia is seen mostly with disseminated (miliary) tuberculosis, with degree of pancytopenia determined more by duration of tuberculosis than by its severity.[17] Despite advances in treatment of tuberculosis, mortality remains high if tuberculosis occurs with pancytopenia.[18]
We had three patients (2.27% of total cases) were drugs resulted in pancytopenia. All three cases were caused by antiepiletic drugs treatment, two patients were on phenytoin and one was on carbamazepine. All patients were taking treatment for epilepsy. Etiological comparison of various studies on pancytopenia done in India is shown in Table 4.

Table 4: Etiological comparison of various studies in India

	Year	*No. of patients*	*Commonest Etiology*	*2nd commonest Etiology*
Tilak and Jain [4]	1999	77	Megaloblastic Anaemia (68%)	Aplastic Anaemia (7.8%)
Khodake et al.[14]	2000	50	Megaloblastic Anaemia (44%)	Aplastic Anaemia (14%)
Kumar et al.[5]	2001	166	Aplastic Anaemia (29%)	Megaloblastic Anaemia (22%)
Khungar et al.[2]	2002	100	Megaloblastic Anaemia (72%)	Aplastic Anaemia (14%)
Gayathri and Rao [6]	2011	104	Megaloblastic Anaemia (74%)	Aplastic Anaemia (18%)
Manzoor et al.[19]	2012	50	Megaloblastic Anaemia (56%)	Aplastic Anaemia14%)
Dahake et al.[20]	2014	94	Megaloblastic Anaemia (34%)	Aplastic Anaemia (23%)
Dasgupta et al.[7]	2015	248	Aplastic Anaemia (33.5%)	Megaloblastic Anaemia (20.9%)
Present study	2015	132	Megaloblastic Anaemia (72.7%)	Acute leukaemia (6.8%)

5. Conclusion

In the present study, the commonest etiology of pancytopenia was megaloblastic anemia followed by acute leukemia and multiple myeloma. In Indian scenario while evaluating etiology of pancytopenia, megaloblastic anemia should always be kept in mind and responds well to treatment. Thus, present study concludes that with detailed clinical history, physical examination and necessary hematological investigations including bone marrow in pancytopenia patients, helps in understanding disease process, to diagnose or to rule out the various etiologies and further laboratory testing and necessary treatment of these patients.

6. Authors' Statement

The authors have no conflicts of interest to disclose.

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