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Clinicohematological profile of patients with peripheral blood cytopenias in clinical practice

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Abstract:

BACKGROUND: In clinical practice, the cytopenias may result from relatively benign causes such as viral infections and Vitamin B12/folic acid deficiency to more sinister causes such as bone marrow failure. In this study, we looked into the clinicohematological profile and etiological factors of bicytopenia and pancytopenia.

OBJECTIVES: To study the etiology and clinicohematological profile in patients of peripheral blood cytopenias.

MATERIALS AND METHODS: This was a cross-sectional study conducted at a tertiary care hospital over a period of 1 year. Cytopenias were defined as pancytopenia when there was simultaneous presence of hemoglobin <10 g/dL, total leukocyte count <4000/dL, and platelets < 100000/dL or as bicytopenia when two of the three blood cell lines were depressed. All patients who presented with pancytopenia and bicytopenia were included, and their clinicohematological profile was recorded.

RESULTS: A total of 204 patients (103 males and 101 females) were diagnosed to have cytopenias. Pancytopenia was observed in 69/204 and bicytopenia was seen in 135/204 cases. The various causes of cytopenias included infections (n = 126 [61.76%]), megaloblastic anemia (MA) (n = 48 [23.52%]), drugs (n = 12 [5.8%]), hypersplenism (n = 8 [3.9%]), bone marrow failure syndromes such as aplastic anemia and myelodysplastic syndrome (n = 7 [3.4%]) and leukemias (n = 3 [1.4%]). We found a significant association between MA and pancytopenia (odds ratio [OR] = 2.47, P < 0.05) and also between infections and bicytopenia (OR = 5.8, P < 0.05).

CONCLUSION: The present study concluded that infections and MA are the most common cause of bicytopenia and pancytopenia, respectively. The more serious disorders affecting the bone marrow constitute only <5% of all cases of cytopenias.

Keywords:

Bicytopenia, bone marrow failure syndromes, cytopenias, infections, megaloblastic anemia, pancytopenia

Introduction

Cytopenias are relatively common hematological picture encountered in daily clinical practice. The causes can be many ranging from viral fevers, megaloblastic anemia (MA), autoimmune disorders, congenital and acquired bone marrow failure syndromes and hematological malignancies.[1,2] The clinical pattern and the outcome depend on the etiology.[3,4] Bicytopenia is defined as a condition in which two out of three cell lines (red blood cells [RBCs], white blood cells, and platelets) are depressed, and in pancytopenia, all three formed elements of blood are decreased in number.[3,5] Bicytopenia may represent a separate entity or it could be the initial manifestation of development of pancytopenia.[2,5] Most of the studies on cytopenias have been done in western population or in children. The

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clinicohematological profile and etiology of cytopenias, especially bicytopenia are not well defined in adult Indian population.[5,6] Hence, the present study was undertaken to study the profile of adult patients presenting with bicytopenia and pancytopenia.

Materials and Methods

It was a cross-sectional study conducted over a period of 1 year, from June 2014 to June 2015, at a tertiary care hospital of Maharashtra. All patients with cytopenias (bicytopenia or pancytopenia) were included. Cytopenia was defined as pancytopenia when there was simultaneous presence of Hb <10 g/dL, total leukocyte count (TLC) <4000/dL, and platelets platelets < 100000/dL or as bicytopenia when two of the three blood cell lines were depressed.[4-6] The patients <12 years of age, pregnant and lactating women, and the patients who are already diagnosed to have aplastic anemia, myelodysplastic syndrome (MDS), hematological malignancy, or those on myelotoxic therapy for malignancies were excluded. Written informed consent was taken from all individuals, and the institutional ethical committee clearance was obtained.

A detailed clinical history and examination was done for all the individuals. Two milliliters of ethylenediamine tetraacetic acid anticoagulated blood was subjected to automated Beckman Coulter 500 FC series analyzer. Complete hemogram including Hb, RBC count, total leukocyte count (TLC), differential leukocyte count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), packed cell volume, and peripheral blood smear (PBS) examination was recorded. Bone marrow aspiration and biopsy was done in all patients of bone marrow failure, leukemia, and most of the patients of MA; after obtaining written consent. Additional tests to find the etiology such as dengue, human immunodeficiency virus (HIV), other viral infections, and malaria were done as indicated. Serum B12 and folate levels were done when the PBS was suggestive of MA. In case the results of diagnostic tests for specific etiology were negative and the patient had a clinical profile of viral illness with activated lymphocytes on PBS, he/she was labeled to have presumed viral infection. Bleeding manifestations and transfusion requirements if any were recorded in various etiologies.

IBM SPSS Statistic version 20.0 (Chicago, IL) was used for statistical analysis. $P \leq 0.05$ was considered as statistically significant.

Results

A total of 204 patients (103 females and 101 males) were diagnosed to have bicytopenia (n = 135 [66.17%]) and pancytopenia (n = 69 [33.83%]). The mean age of the patients was 38.8 years (range: 18–87 years). Pancytopenia was observed in 69/204 (33.83%) and bicytopenia was seen in 135/204 (66.17%) patients. Various causes of cytopenias were infections (n = 126 [61.76%]), MA (n = 48 [23.52%]), drugs (n = 12 [5.88%]), hypersplenism (n = 8 [3.92%]),

Table 1: Etiology of cytopenias

Etiology	Pancytopenia *n* (%)	Bicytopenia *n* (%)	Total *n* (%)	*P*
Infections	21 (10.2%)	105 (51.47%)	126 (61.76)	0.0006
Dengue infection (94)				
Presumed Viral Infections (25)				
Malaria (5)				
HIV (1)				
HLH (1)				
Megaloblastic Anaemia	26 (12.7%)	22 (1.07%)	48(23.52)	0.02
Only B12 deficiency (19)				
Only folic acid deficiency (10)				
Combined B12 & Folic acid deficiency (14)				
B12 & Folic acid Not tested (05)				
Drugs	8 (3.92%)	4 (1.96%)	12 (5.88)	0.15
Zidovudine (3)				
Methotrexate (3)				
Cotrimoxazole (2)				
Sulfasalazine (2)				
Ganciclovir (1)				
Azathioprine (1)				
Hypersplenism	7 (3.43%)	1 (0.49%)	8 (3.92)	0.35
Bone Marrow failure	6 (2.94%)	1 (14.29%)	7 (3.43)	-
Leukemia	1 (0.49%)	2 (0.98%)	3 (1.47)	-
Total	69 (33.83%)	135 (66.17%)	204 (100)	<0.001

HIV, Human Immunodeficiency Virus; HLH, Hemophagocytic Lymphohistiocytosis

Table 2: Hematological Profile of Patients with Cytopenias

	Infections (*n*=126)	Megaloblastic Anemia (*n*=48)	Drugs (*n*=12)	Hypersplenism (*n*=8)	Bone marrow failure (*n*=7)	Leukemia (*n*=3)	*F* statistics	*P*
Hb (mean gm% ±SD)	12.27±2.47	6.32±1.78	8.14±0.80	8.05±0.77	5.63±2.21	7±1.14	63.34	<0.05
TLC (mean/uL±SD)	3008.65±576.21	3353.33±1846.36	2895±597.82	3840±3816.24	2828.57±647.34	21200±24190.70	26.13	<0.05
Platelet count (mean/uL±SD)	58834.52±33224.65	99125±73021.60	114833.33±82332.84	79375±20444.612	66142.86±51187.33	44000±40583.24	6.70	<0.05
MCV (mean fl±SD)	80.05±8.47	113.20±12.35	80.54±10.31	73.11±6.08	84.5±11.04	83.07±5.48	27.53	<0.05
MCH (mean pg/cell±SD)	29.88±4.03	33.88±3.19	27.92±2.94	27.6±2.35	28.14±5.43	27±2.64	11.45	<0.05
MCHC (mean g/dl±SD)	30.48±2.59	30.6±1.23	29.42±3.70	30.25±3.11	30.43±2.44	30.67±1.16	0.488	0.785
PBS	Normocytic (120) Macrocytic (6)	Macrocytic (40) Dimorphic (8)	Normocytic (8) Macrocytic (4)	Normocytic (8) Dimorphic (1)	Normocytic (3) Dimorphic (3) Macrocytic (1)	Normocytic with blasts (3)		

Hb, Hemoglobin; TLC, Total leucocyte count; MCV, Mean cell volume; MCH; Mean cell haemoglobin; MCHC, Mean cell haemoglobin concentration; PBS, Peripheral blood smear

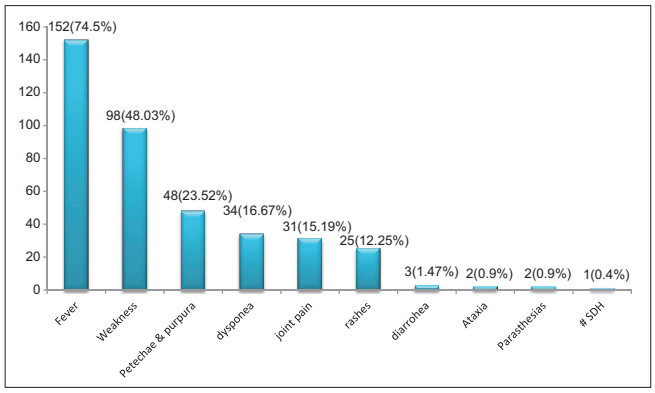

Figure 1: Clinical Presentation of study subjects. #SDH – Subdural Hemorrhage

bone marrow failure syndromes – aplastic anemia and MDS ($n = 7$ [3.43%]) and leukemia ($n = 3$ [1.47%]). Table 1 depicts the various etiologies of cytopenias in our study.

Infections were the most common cause of peripheral blood cytopenias (126/204 [61.76%]). In the subgroup of bicytopenias, infections were the most common etiology (105/135 [77.77%]) whereas they were the second most common cause of pancytopenia (21/69 [30.43%]). A significant association was found between bicytopenia and infections (odds ratio [OR] = 5.8 [3.08–10.90], $P < 0.05$). Among the infections, dengue fever was the most common (94/126 cases) followed by presumed viral infections (25/126).

MA accounted for 48/204 (23.52%) cases of cytopenias. MA was found to be the most common cause of pancytopenia (26/69 [37.68%]) and the second most common cause of bicytopenia (22/135 [16.29%]). A significant association was observed between pancytopenia and MA (OR = 2.47 [1.27–4.79], $P < 0.05$). Vitamin B12 deficiency (B12 levels <211 ng/dL) was found in 33/48 (68.75%) patients of MA whereas folic acid deficiency (serum folate level <5.38 ug/dL) was noted in 24/48 (50%) patients. Bone marrow studies were done in 44/48 patients which showed megaloblastoid changes. All 48 patients were treated with B12 and/or folic acid, and there was correction of cytopenias in all these patients after replacement therapy.

Drugs accounted for 12/204 (5.88%) cases of cytopenias. The cause-effect relationship was established in these cases as the cytopenias in all these patients improved after stopping the offending drug. There were five patients of HIV, two of them were on cotrimoxazole prophylaxis and remaining were on zidovudine-based regimen. The other drugs implicated were methotrexate (in 3 patients of rheumatoid arthritis), sulfasalazine (in 2 patients of ankylosing spondylitis), ganciclovir (in a postrenal transplant recipient), and azathioprine (in 1 patient of ulcerative colitis). Bone marrow aspiration and biopsy was done in 4/12 patients (all HIV-positive

patients), which was normocellular in three patients and hypocellular in one patient.

Hypersplenism was noted in 8/204 cases. Four patients had underlying noncirrhotic portal fibrosis and two patients had postmalarial splenomegaly. Pancytopenia was observed in 7/8 patients with splenomegaly. Seven patients (7/204) were diagnosed to have bone marrow failure (aplastic anemia: 4 and MDS: 3). All patients of aplastic anemia and 2/3 patients of MDS had pancytopenia. We encountered three (3/204) patients of acute myeloid leukemia (AML).

The common presentation included fever (152/204 [74.50%]), generalized weakness (98/204 [48.03%]), petechiae and purpura (43/204 [21.07%]), dyspnea on exertion [34/204 (16.66)], arthalgia (31/204 [15.19%]), and skin rashes (25/204 [12.25%]). Petechiae and purpura were noted in 43 patients with infections and 5 patients with aplastic anemia and MDS. One patient of aplastic anemia had serious bleeding manifestation in the form of subdural hemorrhage. Hepatomegaly was noticed in 27/69 and 20/135 patients of pancytopenia and bicytopenia (z-score: 3.90, $P = 0.0001$), splenomegaly in 22/69 and 13/135 patients of pancytopenia and bicytopenia (z-score: 3.98, $P < 0.05$), and lymphadenopathy was found in 17/65 and 12/135 patients of pancytopenia and bicytopenia (z-score: 3.05, $P = 0.0023$). Figure 1 illustrates the presenting complaints in our patients of cytopenias.

The hematological profile highlighted that the mean Hb was lowest in MA (6.322 gm% ± 1.78 gm%), mean TLC was lowest in bone marrow failure group (2828.57/μL ± 647.34), and mean platelets were lowest in leukemia group (44000/μL ± 40583.24). Mean MCV in MA (113.20fL ± 12.34) was significantly higher than MCV of other etiologies causing cytopenias (80.07 ± 8.64, $P < 0.05$). Severe anemia (Hb <8 g/dL) was noted in 59 patients (28.92%) and MA was the most common cause of severe anemia (37/59; 62.71%). The mean MCV, MCH, and MCHC were 90.94 ± 18.93 fL, 30.08 ± 4.48 pg/cell, and 30.58 ± 2.62 g/dL in pancytopenia and were 86.30 ± 15.86 fL, 30.75 ± 4.13 pg/cell, and 30.48 ± 2.54 g/dL in bicytopenia. The difference was not statistically significant in the parameters between pancytopenias and bicytopenias. The hematological profile of the patients with cytopenias is depicted in Table 2.

Table 3: Blood Transfusion requirements in study subjects

Etiology	Number of patients requiring transfusion *n* (%)	Total	*P*
MA	26 (54.2)	48	0.358
Bone marrow failure syndromes and leukemia	7 (70)	10	

MA, Megaloblastic anaemia

Blood transfusion was required in all three patients of leukemia, 4/7 (57.14%) patients of bone marrow failure, 26/48 (54.2%) patients of MA, and 3/135 (2.22%) patients of infections. There was no statistical difference between the proportion of MA patients and proportion of patients with bone marrow failure and leukemias requiring blood transfusion (54.16% vs. 70%; $P = 0.358$; Table 3). However, there was a significant difference in number of units transfused per patient in MA versus more sinister causes such as aplastic anemia/MDS and leukemias (2 vs. 8.57, $P < 0.05$). Platelet transfusion was required in three patients of aplastic anemia, two patients of MDS, and one patient of leukemia.

Discussion

We studied a total of 204 cases of cytopenias (bicytopenias and pancytopenias). While studies are available on clinicohematological profile of pancytopenia, the data on patients presenting with bicytopenia are scarce.[3,4,6,7] Bicytopenia was observed in 135/204 (66.17%) cases and pancytopenia in 48/204 (33.83%) cases. A study done in pediatric age group in Pakistan by Sharif *et al*.[8] had shown that bicytopenia and pancytopenia constitute 62.9% and 37.1% of total cases of peripheral blood cytopenias. The age of our patients ranged from 18 to 87 years, with a mean age of 38.8 years. Cytopenias common in 3rd and 4th decade have been observed in other studies also.[6,7,9] While few studies have reported a higher male preponderance,[4,6,7] we found no gender predilection.

Various causes of peripheral blood cytopenias as compared to other studies are shown in Table 4.

Table 4: Comparison of causes of cytopenia in various studies

Series	Commonest cause	2nd common cause	3rd Common cause
Kumar R *et al*.[6]	Aplastic anemia (29.5%)	Megaloblastic anemia (22.3%)	Subleukemic leukemia (12%)
Khunger *et al*.[17]	Megaloblastic anemia (72%)	Aplastic anemia (28%)	Subleukemic leukemia (5%)
Gayethri *et al*.[7]	Megaloblastic anemia (74.04%)	Apastic anemia (18.3%)	Subleukemic leukemia (3.8%)
Jain *et al*.[9]	Hypersplenism (29.2%)	Infections (25.6%)	Myelosuppressants (16.8%)
Tilak V *et al*.[5]	Megaloblastic anemia (68%)	Aplastic anemia (7.7%)	Malaria (4.2%)
Hamid *et al*	Hypersplenism (45.3%)	Megaloblastic anemia (14.7%)	Aplastic anemia (13.3%)
Present study	Infections (61.76%)	Megaloblastic anemia (23.52%)	Drugs (5.83%)

The most common cause of peripheral cytopenias in our study was infections (61.7%); majority of these patients (105/135 [83.33%]) had bicytopenia. However, most of other studies had shown MA to be the most common cause.[5-7] The reason for this difference is that all other studies have studied only pancytopenia and have not taken patients with bicytopenia into consideration whereas in this study, we included both bicytopenia and pancytopenia. Dengue fever was the most common infection encountered. No serious bleed was noted in this group of patients, and none of them required platelet transfusion. We had only one case of HIV who presented with pancytopenia due to HIV per se; the cytopenias in rest of HIV cases were due to drugs such as zidovudine and cotrimoxazole. This was in contrast to the other studies where HIV was documented to be the most common infectious cause of pancytopenia.[9-12] These results could have been because of the geographical location of the center and its catchment area where there are frequent outbreaks of arboviral infection. Furthermore, with better medical care for HIV patients, cytopenias are more likely to be due to drugs rather than uncontrolled HIV infection. We had five cases of malaria presenting with cytopenias (2 as pancytopenia and 3 as bicytopenia). Hamid and Shukry[13] also found malaria to be a common cause of pancytopenia. We had 25 cases of presumed viral infections which were self-limiting and we did not do extensive diagnostic evaluation. The viral infections, other than dengue, which could cause peripheral cytopenias are parvovirus B19, cytomegalovirus, herpes simplex virus, and Epstein–Barr virus.[14-16]

The most common cause of pancytopenia in the current study was MA (37.68%). MA has been documented as the most common cause of pancytopenia in previous studies also.[3,4,6-8,17] The second most common cause of pancytopenia was infections (21/69 [30.43%]) similar to the study by Jain and Naniwadekar.[9] Out of 48 patients of MA, Vitamin B12 deficiency was documented in 68.75% cases of MA. Early Indian series in 1960s documented folate deficiency to be more common cause of MA.[18,19] Subsequent studies done in 1980s and 1990s highlighted that B12 deficiency is far more common than folate deficiency.[20-24] Increased prevalence of B12 deficiency as compared to folic acid deficiency has been reported from countries outside India also.[25-28]

In our study, we had only 10/204 (4.9%) cases of bone marrow failure syndromes and AML (aplastic anemia-4, MDS-3, AML-3) which is lower than that observed in other studies.[6,7,17,29,30] This is because we had picked up the cases of cytopenias from general medicine out-patients department (OPD) and general medicine wards and had consciously excluded the already diagnosed cases of bone marrow failure, hematological malignancies, and those on myelosuppressive drugs. This has been done to evaluate the causes of cytopenias in general clinical practice.

Conclusion

The etiology of cytopenias can be diverse; with reversible and benign causes being the most common. In our study, the most common cause of cytopenias was infections and the counts recovered in most cases on recovery from the disease. MA remains the most common cause of pancytopenia with Vitamin B 12 deficiency being more common than folic acid deficiency. More serious etiologies such as aplastic anemia, MDS, and leukemia form only a small fraction of all causes of cytopenias in general practice even in a tertiary care center. The requirement of multiple transfusions points toward a more serious etiology like bone marrow failure syndromes and leukemia. Drugs should always be considered a potential cause of cytopenias even in the presence of autoimmune diseases and HIV.

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Conflicts of interest

There are no conflicts of interest.

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