ORIGINAL ARTICLE

Varying drifts in the etiopathologies of pancytopenia our acquaintance

AMIR NAZIR[1], NAZIA NAZIR[2], KHALID MAHMOOD[3], ASIFAALIA[4], AHMAD HASSAN KHAN[5], ALLAH NAWAZ[6]
[1]Associate Professor of Medicine Sargodha Medical College, Sargodha
[2]Consultant Psychiatrist. Govt. General Hospital G.M Abad Faisalabad
[3]Assistant Professor Surgery Sargodha Medical College (UOS)/DHQ Hospital Sargodha
[4]Associate professor, Gynae obs, Rai Medical college Sargodha
[5]Associate Professor Surgery, Sargodha Medical College
[6]Assistant Professor surgery Sargodha Medical College
Correspondence to: Dr Amir Nazir, Email: amirnazir234@yahoo.com, Cell No: +923236084511

ABSTRACT

Study objectives: Are to conclude pancytopenia causes, disease severity and presenting symptoms of this illness.

Methodology: Mainlycross sectional (descriptive), multicenter and heterogeneous study of seventy patients and on the basis of complete blood count (CBC), patients were admitted with signs symptoms of anemia and pancytopenia in DHQ and Niazi teaching hospitals Sargodha from 01-01-2020 to 30-06-20 (6 months) and were evaluated for the underlying reason.

Results: After CBC, peripheral blood film, serum B12, folate, ferritin, iron levels, bone marrow trephine biopsy and examination (where indicated) we foundout of total 70 patients megaloblastic anemia was most prevalent in46 patients,8patients had dimorphic blood picture showing mixed iron and B12 deficiency, hypersplenism in 5 cases, blast cells (leukemias) in 4 patient, 4 patients got aplastic anemia, myelodysplastic syndrome in1 case, multiple myeloma in 1 old aged patient and 1 case of hodgkins lymphoma was also noted.

Conclusion: Megaloblastic anemia (B12 and folate deficiencies) are the rapidly correctable causes of pancytopenia in our study followed by mixed deficiency anemia and aplastic anemia.

Key words: Pancytopenia, Megaloblastic Anemia, Mixed deficiency anemia

INTRODUCTION

Till 1920 pancytopenia was not considered as distinct hematological issue and aplastic anemia was the name given to pancytopenia by hematologists and concerned physicians[1]. On the other hand in our daily clinical practice pancytopenia is commonly experienced clinicopathological issue and pancytopenia is defined as hemoglobin < 12 g/dl(female) or13.5 g/dl (males),platelet count < 150×10^9/L (thrombocytopenia) and WBCs (total white cell count)< 4.0 x 10^9/L (leucopenia), revealed by doing a differential count (decrease in all types of white blood cells)[2]. Usually bone marrow biopsy may not be required to distinguish the underlying causes of pancytopenia as it is not always aplastic anemia, leukemia ormyelodysplastic syndrome and megaloblastic anemia, mixed deficiency anemia and hypersplenism can also be the etiologies needing no bone marrow biopsy[3]. Instantaneous treatment and early recognition of the underlying cause is of extreme significance because most of the times cause is reversible and manageable except myelodysplastic syndrome, acute myeloid leukemia, aplastic anemia and malignancies causing difficult treatment issues with poor outcomes as well[4].Bone marrow infiltrations, reduced blood cells production, inadequate hematopoeisis and bone marrow aplasia's are some other serious etiologies of pancytopenia other than B12 and mixed deficiency[5].Also in hypersplenism antibody mediated cell devastation by defective hematopoesis causes confiscation of cellsin reticuloendothelial system (spleen) [6,7].CBC with peripheral blood films, Serum B12, folic acid, iron, ferritin, bone marrow aspirations and trephine biopsies (when needed) are the clinico hematological frame works for detecting underlying causes of pancytopenia is the main intend of this study.

METHODOLOGY

70 patients (41 females and 29 males) were admitted with signs and symptoms of anemia and pancytopenia on the basis of complete blood examination (CBC) in this observational prospective study and were evaluated for the underlying reason from 01-01-2020 to 30-06-20 (6 months) in DHQ and Niazi Teaching Hospitals Sargodha. All patients were incorporated in this study after a written consent and a foreordainedperforma was used as well. Pancytopenia was defined as10gm/dl of hemoglobin levels, platelets < 150,000/cumm and WBC's count of less than 4000/cumm and severe pancytopenia as bone marrow cellularity less than 20%, neutrophils count less than 500/ul, platelets< 20000/ul and reticulocytes less than 1%.Relevant history of pancytopenia was ascertained as occupational history, history of radiation exposure, drug overuse, fever (viral infections), bleeding tendencies, weight loss, nutritional deficiency of eggs, milk, meat in diet, altered bowel habits, abdominal pain and previous history of blood transfusions. On examination icterus, pallor, pedal edema, hepatosplenomegaly, mouth ulcers, sternal tenderness, gum hypertrophy, lymphadenopathy were the main concerns. Patients were also evaluated for underlying malignancy and evidence of hypersplenism. Withmechanized blood analyzer CBC (complete blood count) was done with all hematological profilesthat is hemoglobin value (Hb), total and differential leukocyte count (TLC and DLC), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC),

reticulocyte count and packed cell volume (PCV) were observed and scrutinized.Peripheral blood film for nucleated RBC's, inclusions, micro, macro, anisocytosis were done in all patients.Platelets and neutrophils were requested to be studied for morphology, hypersegmentation and flawed maturation respectively. Under aspetic measures bone marrow aspiration and trephine biopsies (if required) from back of hip bone or posterior iliac crest were performed after patients or custodians consent.Serum B12, folic acid, iron and ferritin were done in all patients. Liver and renal function tests, erythrocyte sedimentation rate, enteric fever investigations, HIV test, blood culture sensitivity, serum protein electrophoresis and hepatitis B, C screening were done where indicated. Urine examination, abdomen pelvic ultrasound and bone radiography were also done in all patients.

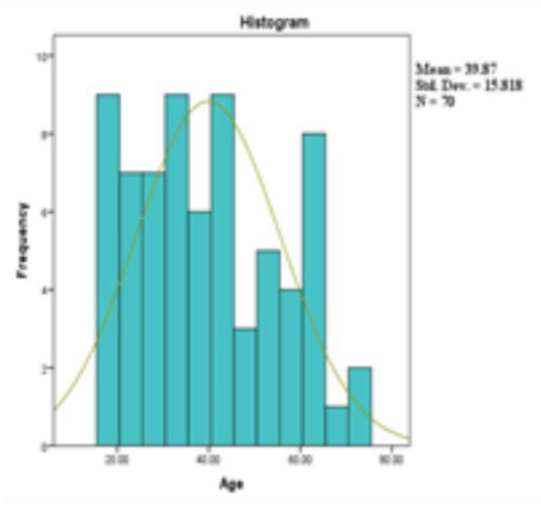
Definitive diagnosis was reached after tabulating, recording and analyzing hematological findings, patient's history and examination.

RESULTS

Out of total 70 patients 41 were females and 29 were males with median presenting age of 40 years. In our series of cases females had more pancytopenia as compare to malesand most of the patients were under 50 years of age.

Gender distribution (Total 70 pts.)		
Males	29	41%
Females	41	59%

In our study generalized tiredness, exhaustion and weakness were the commonest symptoms in 90% cases, mild to moderate shortness of breath in 59% cases, intermittent low grade fever in 33% cases, 9% had bleeding tendencies as purpura, ecchymosis, epistaxis and gum bleeding.



Hemoglobin varied from 2- 9.5gm/dl in our study. 19 patients out of 70 had hemoglobin levels less than 4 gram per/dl showing severe kind of anemia on admission, 4- 6 gm/dl hemoglobin was present in 29cases and 22 cases had above six hemoglobin. MCV (mean corpuscular volume) was also high (mean116 fL)in all patients of pancytopenia due to megaloblastic anemia (B12 and folate deficiency) and was normal in other pancytopenia causes,serum iron levels werelow (mean 47mcg/dl) in mixed deficiency anemia,absolute platelet count assorted between 2000- 105,000 (mean 52,100), less than 4000/cu mm was the total leukocyte count (TLC mean-2500/cu mm).

After hematological, biochemical and analytic strung upwe found that most patients of pancytopenia had no underlying malignant disorders. Megaloblastic anemia was the commonest reason of pancytopenia in46patients.Erythroid megaloblastic hyperplasia,in granulocyte series eminentband forms and giant metamyelocytes, blue cytoplasmic blebs,allochronicnuclear maturation and colandernuclear chromatinwere observed on bone marrow aspiration. Severe anemia was treated with blood transfusions, folic acid (oral) and iv mecobalamin and 8had dimorphic blood picture showing dietary dearth with mixed iron and B12 deficiency.5 cases had hypersplenism (normocellular bone marrow),4 patients had blast cells (leukemias), bone marrow aspiration in aplastic anemia(4 cases)revealed focal hematopoeticactivity, fat spaces predominance, reduced erythropoiesis,megakaryopoeisis,myelopoeisiswith hypocellular bone marrow,1case had myelodysplastic syndrome with hypercellularity and trilineage dysplastic changesand1old aged person had multiple myeloma with marrow picture of 45% plasma cells with abnormal escalation.1case of hodgkin's lymphoma was also noted.

Signs and symptoms of patients presenting with pancytopenia

Symptoms	Number of patients	Percentage
Fatigue and asthenia	63	90%
Shortness of breath	41	59%
Fever	23	33%
Bleeding tendencies	6	9%
Signs		
Generalized pallor	68	97%
Splenomegaly	17	24%
Hepatomegaly	10	14%
Lymphadenopathy	9	13%
Jaundice	5	7%

Pancytopenia major etiologies with features of 70 patients

	Megaloblstic anemia	Mixed iron +B12 deficiency anemia	Hyperspleenism	Leukemias	Aplastic anemia
ımber of patients	46	8	5	4	4
ɛdian age (40yrs)					
larged spleen	30	4	6	3	0
morrhage	3	0	1	3	2
moglobin	3.8-9.5 gm%	3-9gm%	3.7- 8.9	2.5-8.7	2-7
mphadenopathy	1	0	1	3	0
3C counts (/cc)	1800- 3700	2000-3600	1800-3900	1200-4000	1100-3400
itelets count ousand/cc)	30- 105	25-90	30-90	4-80	2-55
ripheral blood smear	Macrocytic smear with polymorphs hypertsegmentation	dimorphic blood picture	Normochromic and normocytic smear, some micro/ macro	Blast cells normochromic and normocyticc smear,	Normochromic normocytic picture, with lymphocytosis (correlative)
ne marrow (where eded)	Erythroid megaloblastic hyperplasia and giant metamyelocytes	Erythroid hyperplasia, many intermediate/ late	M: E ratio reversal with hypercellularit	More than 20% blasts with	Hypocellularity with predominant plasma cells and

DISCUSSION

In our routine daily clinical practice we came across many cases of pancytopenia and this condition createschallenges to both hematologists and treating physicians.There are many causes of pancytopeniabut prevalence of these causes differ according to age, gender and country[8,9]. Patients with this condition usually presents with signs symptoms of infection, anemia and bleeding tendencies and there are tiresome list of pancytopenias requiring detailed appraisal for proper management[10].These causes may not be fatal as transitory pancytopenia by flu viruses and B12 deficiency but can be calamitous as aplastic anemia and myelodysplastic syndromes. Malignant etiologies are more common in developed countries while in developing countries nutritional deficiencies (B12 and folic acid) and bone marrow aplasiaare more prevalent causes of pancytopnia. Chronic and malignant causes are more common in old age as well[11,12]. Hypercellular bone marrow is the feature of myelodysplastic syndrome(MDS), hypersplenism, megaloblastic anemia, leishmaniasis and malaria while hypocellular bone marrow is more commonly observed in hypoplastic myelodysplastic syndrome (MDS), aplastic anemias and Paroxysmal nocturnal hemoglobinuria (PNH)[13].

In our series of cases females had more prevalent pancytopenia as compare to males.Clinical features in our study are comparable with one study conducted at Berlin (Germany)which suggests that symptomsof anemia andleucopeniaare more common as compare to thrombocytopenwhich may be a life threatening condition as described by de- Gruchy[14].

Out of 70 patients 19 patients had hemoglobin levels less than 4 gram per/dl showing severe kind of anemia on admission. Patients from18-45years of age were suffering more from this illness showing pancytopenia is more in young adults especially in females ascompare to males. Results of our study are comparable with two studies one conducted in India and one in Karachi Pakistan[15 16]. Our results differ from another study regarding gender prevalence which was conducted at Larkana showing pancytopenia in females 27% and males 73%. This variation may be due to increased exposure of males to radiations, industrial toxins, pestisides or insectisides[17].

B12 deficiency (B12 < 200pg/ml, folate levels <2ng/ml) are most prevalent causes of pancytopenia in our study causing 66%of pancytopenia cases and also most of them had decreased serum heptoglobin levels, raised indirect bilirubins (hemolysis) increased LDH levels andthese results are comparable with two studies one by Gayathri and other by Satya Narayan Rao[18].Avoidance of animal products (vegetarians), poor nutrition and malabsorption are the usual reasons of megaloblastic anemias[19]. Mixed iron plus B12 and folate deficiency are the second most common cause of pancytopenia in our study in 11% of cases. Liver cirrhosis with hypersplenism in 7% case is third most common cause of pancytopenia in our study. Then are the leukemias and aplastic anemia in 6% each.

CONCLUSION

A rapidly correctivenon hematologicaldisorder that is megaloblastic anemia and mixed deficiency anemia were the commonest underlying disorder of pancytopenia in our study. Study reveals that nutritional deficiency plays an important role as underlying pancytopenia causes and early diagnosis and prompt treatments are of utmost importance in managing pancytopenic patients. A proper history, examination, laboratory tests and radiological findings can escape the need of bone marrow examination for determining the underlying pancytopenia cause.

Study limitations:

1. The conclusion of pancytopenia etiology may be limited in our study as a prospective study with large specimen size,5-10 years of follow up assessmentespecially in economically incapacitated countries is required to determine underlying pancytopenia causes.
2. This study was established in hospital with limitedamount of patients and short duration.

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