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New Onset Pancytopenia in Adults: Clinico-etiological Profile at a Tertiary Care Hospital

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ABSTRACT

Objective: To evaluate and compare common disorders leading to new onset pancytopenia among both genders.
Methods: It was a cross-sectional study conducted at the Department of Pathology Watim Medical College and Watim General Hospital Rawat from November 2020 to November 2021. A total of 98 adult patients with persistent pancytopenia of one week were selected. Blood complete picture with peripheral smears along with bone marrow aspiration biopsy were done. Trephine needle biopsy and cytochemical staining were performed when required.
Results: There were 44 males and 54 female patients. Mean age was 43.49 ±19 years. Common presenting complaints were pallor (82.6%), weakness (63.2%), petechial hemorrhages (45.9%) and fever (23.5%). Mean hemoglobin value, white blood cell count and platelet count were 6.5± 1.65 g/dl, 3.20 ±1.43 x 10^9/L and 55.21 ±28.01 x 10^9/L respectively. Major causes were megaloblastic anemia with female predominance (p value: 0.003) in 43.8% patients, Aplastic anemia with male predominance (p value: 0.001) in 17.3%, portal hypertension induced splenomegaly in 13.2%, infectious diseases in 7%, leukemia in 5.1% and Myelodysplastic syndromes in 3.1%.
Conclusion: Megaloblastic anemia is the major cause of pancytopenia in female and aplastic anemia in male pancytopenic patients.
Keywords: Pancytopenia, Megaloblastic Anemia, Aplastic Anemia, Leukemia

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Introduction

Pancytopenia is a decrease in all three cell lines of blood including red blood cells, white blood cells and platelets. Patient can present with symptoms of anemia, leucopenia or thrombocytopenia and it may be found co-incidentally while carrying out investigations for any other disorder. It is not an ailment itself instead it is representation of some other ongoing illness. Pancytopenia is a common hematological phenomenon encountered in clinical practices and is a frequent reason for hematological consultations.[1]

Pancytopenia is caused either by decreased production of blood cells in the bone marrow or by increased destruction of blood cells in the circulation.[2] The primary causes behind pancytopenia are decrease in hematopoietic cell production, replacement of normal bone marrow cells by abnormal cells, suppression of marrow growth and differentiation, ineffective

hematopoiesis, defective cells production which are phagocytized in the circulation, antibody mediated sequestration and breaking up of cells, and destruction of cells in a hypertrophied reticuloendothelial system.[3]

Blood complete picture with peripheral smear followed by bone marrow examination along with trephine biopsy often helps to determine the underlying cause of pancytopenia. However, for extra medullary causes another set of investigations including liver function tests, malarial parasite antigen, renal function tests, viral profile and ultrasound abdomen are commonly required.[4,5] The causes of pancytopenia vary from region to region and among both genders. Very few studies are conducted till date in our region to study the pattern of etiological factors in pancytopenia. This study was conducted to evaluate and compare common disorders leading to new onset pancytopenia among both genders in twin cities. The results will be helpful in developing strategies to reduce the preventable common causes and early management of critical illnesses for the pancytopenic patients.

Methodology

This was a cross-sectional study conducted in Pathology Department of Watim Medical College and Watim General Hospital Rawat. The duration of study was from November 2020 to November 2021. Non probability convenient sampling was done. Adult patients of age 18 years and above were included in the study. The inclusion criteria for the study were persistent Pancytopenia on blood complete picture and peripheral blood film of more than one week and patients who gave consent for bone marrow aspiration biopsy. The exclusion criteria included patients with non-hematological malignancies, hemolytic anemias, bleeding disorders, renal failure, genetic marrow failures and pregnant females presenting with pancytopenia.

After approval from ethical review committee of Watim medical college, an informed written consent was taken from the patients after discussing the aim of the study including prospects to the patients. Demographic Data was collected which included name, age gender and ethnicity. Each individual was allotted a separate number. A detailed medical history was taken from the patient and a thorough physical examination was conducted. The blood sampling for the investigations was done which included complete blood count with peripheral film, erythrocyte sedimentation rate (ESR), malarial parasites (MP), liver function test, renal function tests and viral profile (HBsAg, Anti-HCV) along with ultrasound abdomen and PCR for Covid-19 in some suspected cases. Bone marrow aspiration biopsies were taken with Salah needles from posterior iliac crest using standard methods after applying aseptic measures and injecting local anesthesia. Bone marrow aspirate smears were prepared directly on the slides at the time of procedure and were air dried. Trephine biopsies were taken in cases when bone marrow aspirates could not be obtained. Touch imprints of trephine biopsy were made as an adjunct to biopsy which was preserved in 10% buffered neutral formalin. Sample for blood complete picture and peripheral smear was taken again at the time of bone marrow aspiration biopsy. Leishman stain was applied to stain all peripheral blood smears and aspirated bone marrow smears. Cytochemical stains like Periodic-Acid Schiff (PAS) and Myeloperoxidase (MPO) stains were also used when required.[4] Statistical analysis was done using SPSS version 22. Frequencies and percentages were calculated for categorical variables like age, gender and different causes of pancytopenia. Mean ±SEM were given for quantitative variables. Cross-tabs was used to calculate different causes of splenomegaly and to determine ratio among both genders. Chi-square was used for comparing causes of pancytopenia among genders.

Results

Total 98 out of 109 pancytopenic patients gave consent and underwent bone marrow aspiration biopsy. Out of these patients 44 were males and 54 were females. Most patients presented with complains of pallor (82.6%), weight loss and weakness (63.2%) and petechial hemorrhages on skin (45.9). Some patients also presented with symptoms of fever (23.5%) and dragging sensation in abdomen (11.2%). Mean age of the patients was 43.49 ±19.32 years. The hematological variables showed mean hemoglobin value of 6.5± 1.65 g/dl, white blood cell count 3.20 ±1.43 x 10^9/L and platelet count 55.21 ±28.01 x 10^9/L. Anisopoikilocytosis was seen in 88.8%, macrocytosis in 62.2% and microcytosis in 11.2% cases. The diagnosis in 78 patients was made on the basis of bone marrow aspiration biopsy. Cytochemistry in suspected cases of leukemias and myelodysplastic syndromes using myeloperoxidase, acid phosphatase and periodic acid-Schiff reactions were performed. Bone marrow trephine biopsy helped in finalizing the diagnosis in cases of aplastic anemia, multiple myeloma and hairy cell leukemia as mentioned in

Table *1*. Megaloblastic anemia due to folate (41.86%) and Vitamin B12 deficiency (58.14%) was found to be the major cause of pancytopenia (43.8%). There was significant female predominance among all the patients with *p*-value of 0.003. Aplastic anemia (17.3%) was the second major cause among the patients followed closely by splenomegaly due to portal hypertension (13.2%). However aplastic anemia was less prevalent among female group with a statistical significance of 0.001 as compared to portal hypertension induced splenomegaly. Leukemias were more prevalent in males however statistical significance was not remarkable. On the other hand, infectious diseases were seen more among female patients. Visceral leishmaniasis was found in three patients admitted with pyrexia of unknown origin. Two patients with typhoid fever had also developed pancytopenia. A case on bone marrow examination revealed ring forms of plasmodium falciparum. A patient of Covid-19 admitted in Covid unit was also diagnosed with pancytopenia. Splenomegaly without any other known etiological factor was seen in three patients. Hemophagocytosis with no known cause was seen in one patient while one patient had developed pancytopenia as a manifestation of systemic lupus erythematosus. Few rare cases which included Gaucher's disease, Paroxysmal nocturnal hemoglobinuria and Congenital dyserythropoietic anemia type 2 were also found. Remarkable statistical significance among both genders was not found in rest of the etiologies.

Table 1 Etiological comparison among both genders

Etiology	No of patients N (%)	Male: Female
Megaloblastic Anemia	43 (48.37%)	12:31
Aplastic Anemia	17 (17.34%)	14:3
Portal hypertension induced splenomegaly	13 (13.26%)	5:8
Leukemia Chronic Myeloid Leukemia- Chronic Lymphocytic Leukemia Hairy cell leukemia	5 (5.1%) 3 (3.06%) 1 (1.02%) 1 (1.02%)	4:1 2:1 1:0 1:0
Myelodysplastic Syndromes	3 (3.06%)	2:1
Multiple Myeloma	2 (2.04%)	2:0
Infectious Causes Leishmaniasis Typhoid Malaria Covid-19	7 (7.14%) 3 (3.06%) 2 (2.04%) 1 (1.02%) 1 (1.02%)	2:5 1:2 1:1 0:1 0:1
Hemophagocytosis	1 (1.02%)	0:1
Splenomegaly NOS	3 (3.06%)	1:2
Other causes Systemic Lupus Erythematosus Gaucher's disease	4 (4.08%) 1 (1.02%) 1 (1.02%)	2:2 0:1 0:1

Discussion

The spectrum of etiologies for Pancytopenia which is a trio of anemia, leucopenia and thrombocytopenia varies with age, gender and regions around the world. The range of disorders leading to pancytopenia begin with non-malignant causes like nutritional deficiencies, infectious diseases, systemic disorders to malignant causes including leukemias, lymphomas and hereditary bone marrow failure disorders.[5]

Patients with pancytopenia on blood complete picture are directed for bone marrow aspiration and trephine biopsy (in cases of dry tap) as it is a least hazardous procedure and can be carried out without hospital admission. It is one of the most useful and convenient procedure carried out for final diagnosis in these cases. Other biochemical and radiological investigations along with history and physical examination helped in reaching the final diagnosis of the above cases.[6]

Megaloblastic anemia resulting from nutritional deficiencies 0f folate and vitamin B12 was highly prevalent among our study group. Folate and vitamin B12 deficiencies are reported to be more than 23% and 14% respectively in South Asian population irrespective of socioeconomic status.[7] The dietary reasons for these deficiencies may include: prolonged cooking leading to destruction of more than 70% of folate and 40% of Vitamin B12 in diet, increasing trend of over-processed foods and strict vegan diets and declining rate of raw vegetables intake. Moreover, other causes include use of drugs like nitrous oxide, metformin and proton pump inhibitors causing decreased absorption of Vitamin B12 from intestines.[8] and deficiency of intrinsic factor and clinical interventions like gastric bypass surgeries which also result in Vitamin B12 deficiency. Studies conducted in South Asian women have shown very high prevalence of Vitamin B12 and folate deficiency in reproductive periods of life.[9] Our study revealed that highest percentage, 44% individual with pancytopenia had megaloblastic anemia with a significantly higher number of women affected with highest incidence rate was in the age group of 30 to 50 years. Similar studies conducted in different areas of Pakistan showed prevalence rate of 4l.7% in Karachi, 74.04% in Azad Jammu Kashmir and 28.7% in Peshawar.[4,10,11] Studies conducted in several areas of South Asia including India, Afghanistan and Bangladesh have shown high rates of megaloblastic anemia.[8,12] This is probably due to dietary habits and high rates of micronutrient deficiencies in these countries. Most studies conducted have not mentioned the ratio of genders affected by different etiologies of pancytopenia. Aplastic anemia was the other common cause (17.3%) followed by portal hypertension induced splenomegaly (15.3%). Aplastic anemia was found to be more prevalent among the male population, similar to studies conducted in other regions of the country and around the world. The reason behind this was higher exposure rate of males to industrial chemicals as well as pesticides and insecticides. Furthermore, in our study eight individuals with aplastic anemia gave history of using medicines advised by quacks in past six months. Researches conducted in Pakistan showed that prevalence of aplastic anemia was 19.4%, 18.26% and 15.2% in Karachi, Azad Jammu Kashmir and Peshawar respectively. A study conducted in Lahore showed highest prevalence of Aplastic anemia among pancytopenic patients due to excessive quackery practice in the region.[13] Hypersplenism was found in 16.7% individuals in a study conducted in Karachi. Similar results were shown regarding portal hypertension induced splenomegaly and aplastic anemia in analysis carried out in India and Bangladesh.[8,12] The rate of development of pancytopenia due to portal hypertension induced splenomegaly and aplastic anemia are markedly high in Asian population than rest of the world. [13] Infectious diseases are highly prevalent among Pakistani population and add to a

huge burden of disease. Death count of more than half results from infectious disorders like malaria, tuberculosis, typhoid fever and hepatitis in this region.[14,15] There are several risk factors supporting the spread of infectious diseases in Pakistan which include low socioeconomic status of a large group of population, lack of proper sanitization techniques, poor hygiene, outdoor sleeping habits, presence of cattle and domesticated animals, migration due to earthquake, floodings and from Afghanistan due to war in the region. In addition to this, deficiencies in healthcare system, laboratory services and unavailability of expert physicians escalate the development and spread of these communicable diseases.[16] In our study 07% individual suffered from infectious causes which included visceral leishmaniasis, malaria, typhoid fever and Covid-19 viral infection. A study conducted in Baluchistan region showed very high prevalence of infectious diseases (i.e., 26%) among the pancytopenic population including malaria, tuberculosis and hepatitis.[16] Another study conducted in Karachi showed that complicated malaria and typhoid fever resulted in development of pancytopenia among hospital admitted patients.[11] Leukemias (5.1% cases) and myelodysplastic syndromes (3.1%) which included chronic myeloid leukemia (3.1%), chronic lymphocytic leukemia (1%) and hairy cell leukemia (1%) were found predominantly in male patients. The studies conducted in Pakistan and India showed similar results[14] while those of industrialized and developed countries showed very high rates of leukemias in pancytopenic patients.[17,18] This high rate is suspected to be caused by more exposure to chemicals, ionizing radiations, increasing obesity and declining natural selection. Pancytopenia was found in a 34-years old female patient with systemic lupus erythematosus. Studies have shown that autoimmune disorders like SLE, rheumatoid arthritis, multiple sclerosis, grave's disease and Sjogren's syndrome can also result in pancytopenia.[19] It is yet to be worked upon that either it is the disease that is inducing cytopenias or the drugs used to treat these disorders that are instigating pancytopenia in these patients.[20]

Few rare disorders were also identified in this study including Paroxysmal nocturnal hemoglobinuria (PNH), Gaucher's disease and Congenital dyserythropoietic anemia type 2. PNH is an acquired hematopoietic stem cell disorder while rest of the two is autosomal recessive disorders.[21] These multiorgan disorders present with vague signs and symptoms like pallor, fatigue, bruising, hepatomegaly and splenomegaly.[22,23] Bone marrow aspiration biopsy helped in diagnosis of these cases however specialized tests like Acidified serum test (for PNH) and beta-glucosidase leukocyte enzyme assay (for Gaucher's disease) assisted in final diagnosis of these cases.

Conclusion

The data collected in this study suggested that the main causes behind pancytopenia in our population are predominantly nutritional deficiencies in females and aplastic anemia in males. It was followed by portal hypertension induced splenomegaly and infectious diseases. However, the significance of leukemias predominantly in the male individuals including myelodysplastic syndromes cannot be disregarded.

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