PATTERNS OF PANCYTOPENIA PATIENTS IN A GENERAL MEDICAL WARD AND A PROPOSED DIAGNOSTIC APPROACH

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Background: There has been little systematic study on the clinical spectrum of pancytopenia. This study was done to describe the etiology, presentation and outcome of patients with pancytopenia presenting in a general medical ward. **Methods:** Hundred patients with pancytopenia were included in the study from October 2001 to October 2002. Patients on cancer chemotherapy were excluded. Blood counts, bone marrow examinations and trephine biopsies were performed according to standard methods. **Results:** In all cases, megaloblastic anemia constituted the largest group (n=39), and also seen in conjunction with hemolytic anemia and septicemia. Hypersplenism secondary to portal hypertension (cirrhosis) was the second most common diagnosis (n=19). Aplastic anemia, septicemia and myelodysplasia were other common causes. Two patients were the suspected cases of viral hemorrhagic fever. Thirteen (13%) patients expired. Absolute neutrophil count (ANC) less than 500 /µl was seen in 14 (14%) patients, among which 6 (15.3%) had megaloblastic anemia, 3 (37.5%) had aplastic anemia, and 2 (40%) had myelodysplasia. Eleven patients with platelet counts ≤ 10 x 10^9/L, 6 (54.5%) presented with bleeding; and 2 of these 8 had aplastic anemia and 1 patient with megaloblastic anemia. MCV values > 100fL and > 110fL were more frequent in patients with megaloblastic anemia with most prominent anisopoikilocytosis, microcytosis and fragmented RBCs. Macrocytosis was noted in 35 (89.7%) patients with megaloblastic anemia and 12 (63.1%) with hypersplenism, 4 (50%) with aplastic anemia. Hypersegmented neutrophils were noted in the blood films of 36 (92.3%) patients with megaloblastic anemia. **Conclusion:** Megaloblastic anemia, hypersplenism and aplastic anemia are the common causes of pancytopenia in our study.

Keywords: Pancytopenia, Megaloblastic Anemia, Hypersplenism, Aplastic Anemia

INTRODUCTION

Pancytopenia means a disorder in which all 3 blood elements (red blood cells, white blood cells and platelets) are decreased than normal.i[1] Although it is a common clinical problem with an extensive differential diagnosis, there is a relatively little discussion of this abnormality in major textbooks of internal medicine and hematology.ii[2],iii[3] Pancytopenia can be due to decrease in hemaopoietic cell production in the bone marrow e.g. by infections, toxins, malignant cell infiltration or suppression or can have normocellular or even hypercellular marrow, without any abnormal cells, e.g. ineffective hematopoiesis and dysplasia, maturation arrest of all cell lines and peripheral sequestration of blood cells.iv[4]

Few clear recommendations can be found as to the optimal investigative approach to pancytopenia. Some experts suggest that marrow examination is essential to the diagnosis, but it has not been established whether the procedure is necessary in all pancytopenic patients.[i,ii]

Common questions that a healthcare professional asks are 1) What are the most common causes of pancytopenia? and 2) What is the best diagnostic approach to the pancytopenic patient? In the present study, we have attempted to answer these questions by doing investigation of pancytopenic patients in a general medical ward. Our study was limited by its restriction to hospitalized patients. On the basis of our findings and available literature, we have formulated a diagnostic approach to the problem of pancytopenia.

MATERIAL AND METHODS

Pancytopenia was diagnosed in the presence of anemia (hematocrit value <0.35 in women, <0.40 in men), leucopenia (WBC ≤ 3.5 x 10^9/L) and thrombocytopenia (platelets < 150 x 10^9/L).

This study was carried in Medical Unit II of Holy Family Hospital, Rawalpindi from October 2001 to October 2002. All admitted patients with pancytopenia were studied and a total of 100 adult patients were selected for the study by non-probability convenient sampling. In all patients, a detailed relevant history including the treatment history, history of drug intake, radiation exposure, along with a physical examination of pallor, jaundice, hepatomegaly, splenomegaly and lymphadenopathy, was taken. Patients on cancer chemotherapy were excluded.

Blood counts obtained prior to transfusion were done on an automated blood analyser (Sysmex). In cases of very low counts, manual methods were used which included total leucocyte count, red cell and platelet count, using improved Neubauer chamber. Differential leucocyte count and red cell morphology was done manually by staining the blood smears by May-Granwald-Giemsa stains. Bone marrow aspiration and wherever required, a trephine biopsy were also performed. They were independently reviewed by one investigator without knowledge of the patient's clinical presentation. Anisocytosis and poikilocytosis were graded according to the degree of variation in size and shape.

Findings of aspiration and trephine biopsies were interpreted in the light of history, clinical examination and peripheral blood findings. Standard morphologic criteria were used in diagnosis (v[5],vi[6]). Bone marrow examination was done in 70 patients and 30 patients in whom bone marrow examination was not done were either very ill or were meeting other criteria of diagnosis or expired before the procedure.

Statistical methods include descriptive statistics (mean, median, SD). Cross tabulation was carried out to find out the correlation among different variables. Analysis was done on SPSS v10 for windows.

RESULTS

The age of the patients ranged from 12 to 82 years with a mean age of 36.7 years, in which 53% were males. The aetiological breakup of all patients is given in Table 1. Two patients were the suspected cases of viral hemorrhagic fever (VHF) among which 1 patient was diagnosed as having Cremean Congo hemorrhagic fever. Thirteen (13%) patients expired, among which 8 patients had septicemia and disseminated intravascular coagulation (DIC), 2 with VHF, 2 with disseminated malginancy and one with acute leukemia. Two patients had a drug history of interferon and ribavarin.

Clinical features of patients with pancytopenia are listed in Table 2. Patients with megaloblastic anemia had a mean age of 38.6 years and belong to almost all age groups. Similar ages (mean 35.6 years) are seen in Aplastic Anemia as well. Patients with hypersplenism had a slightly higher mean age of 41.37 years.

WBC counts did not vary between different diagnostic categories. However, absolute neutrophil count (ANC) less than 500 /µl was seen in 14 (14%) patients, among which 6 (15.3%) had megaloblastic anemia, 3 (37.5%) had aplastic anemia, 2 (40%) had myelodysplasia and 1 (50%) with leukemia. Platelet counts ≤ 10 x 10^9/L were noted in 37.5% (n=3) of patients with aplastic anemia verus 7.6% (n=3) of those with megaloblastic anemia. Of 11 patients with platelet counts ≤ 10 x 10^9/L, 6 (54.5%) presented with bleeding; and 2 of these 8 had aplastic anemia and 1 patient with megaloblastic anemia. Anemia was most marked in patients with aplastic anemia, acute leukemia and septicemia. (Figure 1). There was no marked variation seen in the ESR among various diseases.

The MCV was ≥ 100fL in 41 patients (41%). Highest MCV noted was 135fL seen in megaloblastic anemia. MCV values > 100fL and > 110fL were more frequent in patients with megaloblastic anemia than in those with aplastic anemia or hypersplenism (Figure 2). The MCV was < 100fL in 6 (15.3%) patients with megaloblastic anemia (Figure 2). The lowest MCV was 58fL seen in iron deficiency anemia.

Moderate to marked anisopoikilocytosis, microcytosis and fragmented RBCs were detected in all of the pancytopenic disorders, but were most prominent in megaloblastic anemia (data not shown). Macrocytosis was noted in 35 (89.7%) patients with megaloblastic anemia and 12 (63.1%) with hypersplenism, 4 (50%) with aplastic anemia and 4 (80%) with myelodysplasia. Microcytosis was seen in 3 (7.6%) patients with megaloblastic anemia, 7 (36.8%) with hypersplenism, 1 (12.5%) with aplastic anemia and 1 (20%) in myelodysplasia.

Hypersegmented neutrophils were noted in the blood films of 36 (92.3%) patients of 39 patients with megaloblastic anemia.

To calculate the sensitivity, specificity and predictive values of blood findings for megaloblastic anemia, data were examined for 100 pancytopenic patients whose diagnosis was established by marrow examination or response to cobalamin and folate therapy (Table 3). Neutrophil hypersegmentation had high specificity and predictive value for megaloblastic anemia. In contrast, MCV > 110fL was specific but not sensitive.

DISCUSSION

Pancytopenia is not an uncommon hematological problem encountered in our clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever and tendency to bleed. In all cases, megaloblastic anemia constituted the largest group, and also seen in conjunction with hemolytic anemia and septicemia. Hypersplenism secondary to portal hypertension (cirrhosis) was the second most common diagnosis. Aplastic anemia, septicemia and myelodysplasia were other common causes of pancytopenia (Table 1).

The approximately comparable series of pancytopenia is from Savage et al[ii], Iqbal et al[iv] and Qazi et alvii[7]. In all these studies, megaloblastic was found to be the largest cause of pancytopenia. In contrast to local studies, significant contributor of pancytopenia is HIV infections[ii], compared to only 1 patient in our study. Study done by Iqbal et al also included pediatric population and reported leishmaniasis in 4.8% of cases as compared to none seen in our study.[iv]

The major cause of megaloblastic anemia in our study is fever as 56.4% and chronic diarrhea (Table 2) as 38.5%. The percentage of chronic diarrhea in our study is not that common as in other studies.[iv,vii]

Table 1: Etiology of Pancytopenia

	Male	Female	Total
Megaloblastic Anemia			
16	11	27 (27%)	
with Hemolytic Anemia			
4	3	7 (7%)	
with Sepsis			
4	1	5 (5%)	
Total	*24*	*15*	*39 (39%)*
Hypersplenism			
With Cirrhosis			
6	6	12 (12%)	
With Chronic Malaria	1	2	3 (3%)
Undiagnosed	1	3	4 (4%)

Total	*8*	*11*	*19 (19%)*
Aplastic Anemia	6	2	8 (8%)
Myelodysplasia			
3	2	5 (5%)	
Septicemia and DIC			
3	2	5 (5%)	
Iron Deficiency Anemia with Leucopenia			
1	4	5 (5%)	
Connective Tissue Disease (SLE)			
-	3	3 (3%)	
Disseminated Tuberculosis			
1	2	3 (3%)	
AIDS and Septicemia			
-	1	1 (1%)	
Disseminated Malignancy			
2	-	2 (2%)	
Hypoplastic Marrow			
1	1	2 (2%)	
Viral Hemorrhagic Fever (CCHF)			
-	1	1 (1%)	
Acute Lymphocytic Leukemia			
1	-	1 (1%)	
Mixed Leukemia			
-	1	1 (1%)	
Undiagnosed			
3	2	5 (5%)	
Total			
53	**47**	**100**	

Table 2.: Clinical Features of Patients presenting with Pancytopenia (Percentages are calculated from totals of each disease)

Clinical Features	**Megaloblastic Anemia ***	**Hypersplenism**	**Aplastic Anemia**	**Others ‡**
Pallor	100%	100%	100%	100%
Fever	22 (56.4%)	11 (57.4%)	4 (50%)	22
Diarrhea	15 (38.5%)	1 (5.3%)	-	6
Anorexia	14 (35.9%)	1 (5.3%)	-	4
Jaundice	7 (17.9%)	7 (36.8%)	-	2
Lymphadenopathy	7 (17.9%)	-	1 (12.5%)	8
Bleeding †	12 (38.8%)	8 (42.1%)	4 (50%)	9
Splenomegaly	6 (15.4%)	19 (100%)	-	9
Hepatomegaly	7 (17.9%)	4 (21.1%)	-	13
Dyspnea	4 (10.3%)	1 (5.3%)	4 (50%)	5
Weight Loss	6 (15.4%)	1 (5.3%)	1 (12.5%)	6

* Other causes with secondary megaloblastic anemia also included

† Upper GI Bleeding, Epistaxsis, Petechie, Bleeding Gums are included

‡ Percentages not calculated because of different totals

Table 3: Sensitivity, Specificity and Predictive Values for various laboratory findings in Diagnosis of Megaloblastic Anemia in 100 pancytopenic patients *

Lab finding	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
MCV > 100 fL	82	91.8	86.4	88.8
MCV > 110 fL	51.2	100	100	76.2
Neutrophil Hypersegmentation	92.3	98.3	97.2	95.2

* Megaloblastic anemia excluded in 61 patients by marrow examination or response to therapy

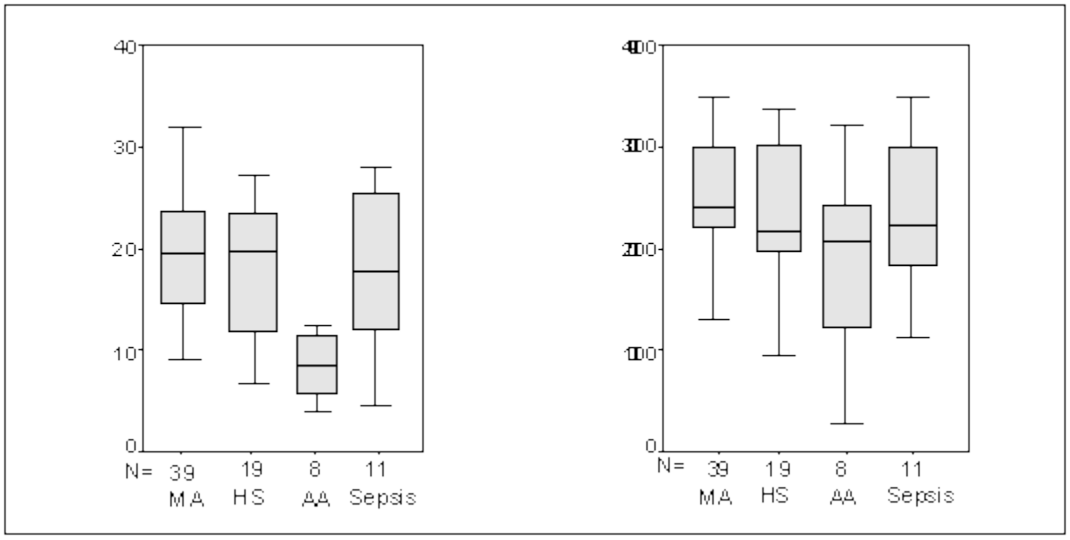

Figure 1: Box plots of Hematocrit and Total leucocyte counts

(MA = Megaloblastic Anemia, HS = Hypersplenism, AA = Aplastic Anemia)

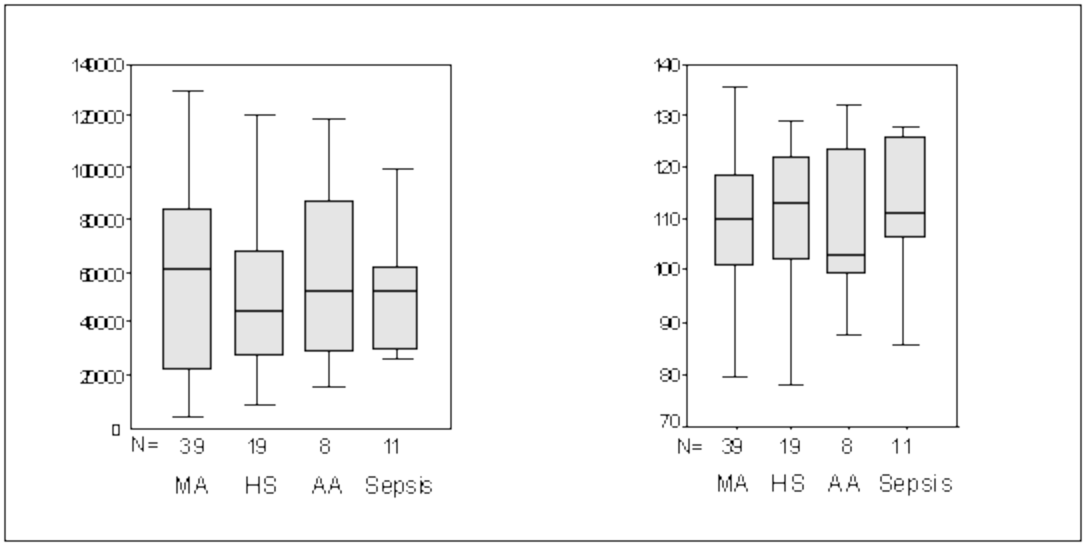

Figure 2. Box plots of Platelets and MCV

(MA = Megaloblastic Anemia, HS = Hypersplenism, AA = Aplastic Anemia)

Pallor is present in all cases. All the patients were empirically put on folate and cobalamin supplements with adequate clinical and therapeutic response along with improvement of hematological parameters. In the West, pancytopenia has become less common in patients with megaloblastic anemia[ii], as only 13.7% of cases reported in a study done in New York.viii[8]

An interesting finding in our study is the raised MCV above 100 fL in patients with megaloblastic anemia. Almost similar results were seen in studies done by Savage et al[ii], Iqbal et al[iv] and Qazi et al.[7] Thirty seven patients had raised MCV above 100 fL, and among them 32 (86.4%) were megaloblastic (Table 3). We can safely say that diagnosis of megaloblastic anemia should be considered on top when MCV is above 100 fL. In contrast of our finding, normal MCV vales have been reported previously in megaloblastic anemia [ii,viii] and ascribed to coexisting iron deficiency, chronic disease and hypersplenism. Hypersegmentation of neutrophils is found as diagnostic to megaloblastic anemia in our patients (Table 3). This demonstrates the value of peripheral blood film in the differential diagnosis of pancytopenia. Although morphologic abnormalities were almost invariable in patients with megaloblastic anemia, these changes were often minimal or absent in patients with aplastic anemia, leukemia and hypersplenism.

There is no significant variation seen in the age groups of various diseases. Megaloblastic anemia is present in all age groups, and similar is seen in aplastic anemia and hypersplenism. Two patients with viral hemorrhagic fever (one confirmed), were present in younger age groups. These patients developed DIC and pancytopenia, associated with septicemia. Both expired due to excessive bleeding. Other patients having septicemia had varied clinical presentations. We have seen that pancytopenia associated with septicemia has worst prognosis. These findings are comparable with other studies also.[iv,7]

Hypersplenism is another commonest cause of pancytopenia. In our study, hypersplenism (n=19) due to portal hypertension (n=12) and chronic malaria (n=3) constituted the major group, however some patients (4%)

remained undiagnosed. These patients were later on treated for tropical splenomegaly. Seventeen patients had positive anti-Hepatitis C virus (HCV) antibodies, among them 12 (70.5%) had cirrhosis. In remaining patients (29.5%), HCV as a cause of pancytopenia couldnot be ruled out. Suppression of bone marrow by hepatitis C virus could be a possibility. This has been well reported by Khokhar Nix[9] in his case reports, but we did not prove that.

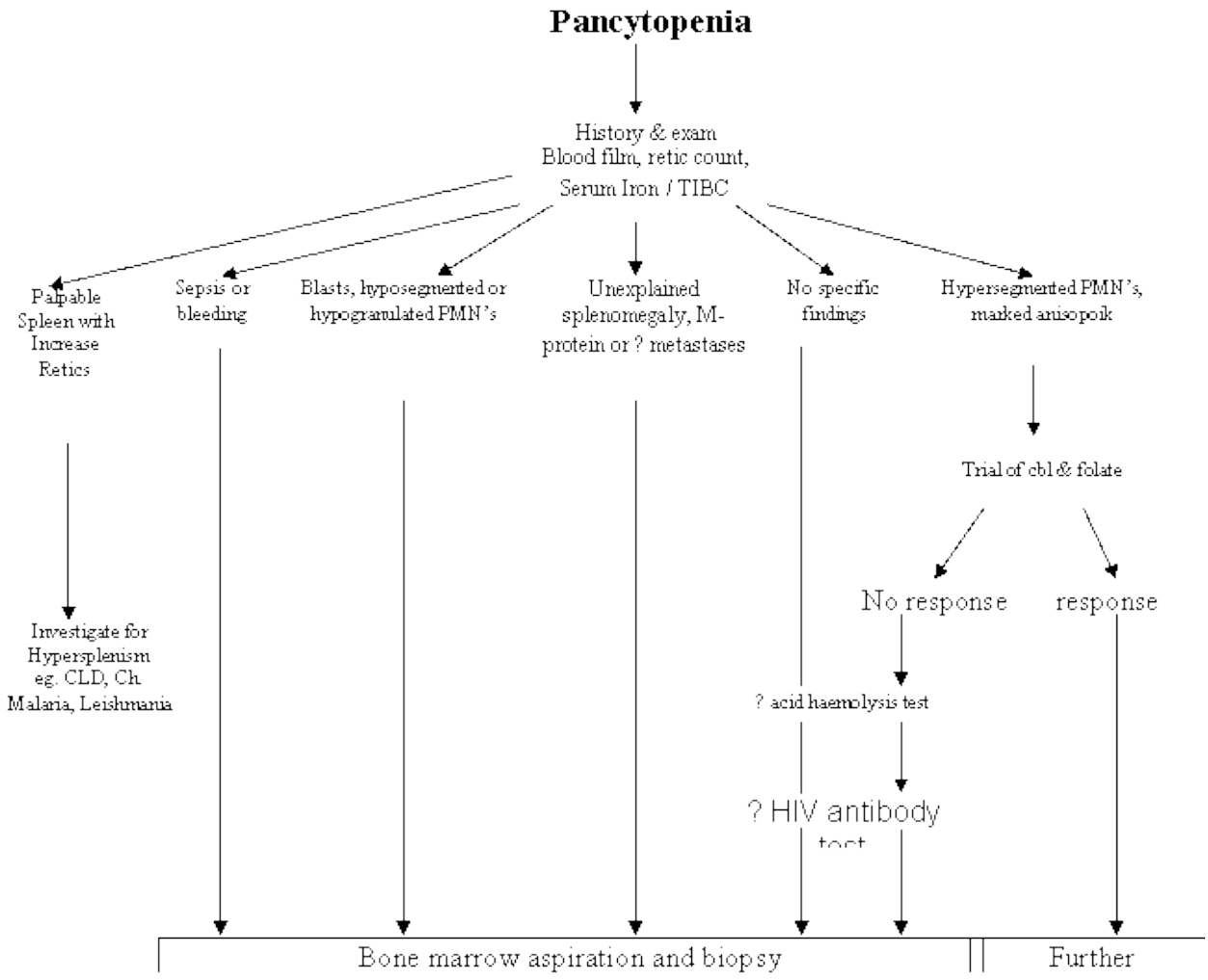

Figure 3: A diagnostic approach to the pancytopenic patient;

PMN = polymorphonuclear neutrophil, TIBC = Total iron binding Capacity,

Cbl = Cobalamin, HIV = human immunodeficiency virus, ansiopoik = anisopoikilocytosis

A DIAGNOSTIC APPROACH TO PANCYTOPENIA

Based on our findings and the prior literature [i-iii,v] we propose a diagnostic approach to pancytopenic patients in our setup (Figure 3). These guidelines can be useful for other centers as well. In all pancytopenic patients with neutrophil hypersegmentation or abnormalities of erythrocyte morphology, serum Cobalamin and folate measurements are indicated. Since these investigations are costly therefore, it is recommended that in all these patients, a trial of vitamin therapy should be given. A therapeutic response would include a rise in the granulocyte, platelet and reticulocyte count within first 1 to 2 weeks of treatment. Those patients with hypersegmented neutrophils, we suggest that bone marrow examination and biopsy is generally unnecessary, but can be performed later if there is no response to vitamin B_{12} and folate. Moreover, marrow examination is also not indicated in pancytopenia secondary to splenomegaly resulting from portal hypertension and with an unremarkable blood film.

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