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ORIGINAL ARTICLE

Bone marrow examination in Egyptian patients with bicytopenia/pancytopenia

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Abstract The incidences of diseases that cause peripheral blood (PB) cytopenias differ between countries according to the prevalent health problems. This study was carried out in order to identify bone marrow findings and underlying disorders in adult Egyptian patients with PB cytopenias (bicytopenia and pancytopenia). The study involved patients newly diagnosed as having PB cytopenias over a period of 1 year. Clinical and hematological parameters of patients were recorded. Bone marrow specimens were examined. Sixty-two pancytopenia and 50 bicytopenia patients were included in the study. The most common cause of pancytopenia was clonal hematopoietic disorders (34 %), hypersplenism (27 %), and aplastic anemia (21 %). The most common cause of bicytopenia was clonal hematopoietic disorders (34 %), ITP (24 %), and hypersplenism (18 %). Lymphoid neoplasms were the most common and account for 57 % of clonal pancytopenia patients and 65 % of clonal bicytopenia patients. Most hypersplenism patients (86 %) had history of hepatitis C viral infection. Our results show that, in Egypt, clonal hematopoietic disorders, hypersplenism due to chronic liver disease, ITP, and aplastic anemia are the common causes of PB cytopenias. In our setting, causes underlying bicytopenia are as important as those of pancytopenia.

Keywords Bone marrow examination · Pancytopenia · Bicytopenia · Hypersplenism · Aplastic anemia · HCV · Egypt

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Introduction

Peripheral blood (PB) cytopenias are a common hematological finding that is frequently encountered during everyday practice. It is defined as reduction in any of the three formed elements of blood (red blood cells, white blood cells, and platelets) below the normal reference range (Williams 1993). Bicytopenia is reduction in any two of the three cell lines, and pancytopenia is reduction in the three cell lines (Naseem et al. 2011). PB cytopenias occur because of a number of disease processes that affect the bone marrow. In addition, PB cytopenias may occur because of peripheral destruction of cells by immune process or sequestration in a hypertrophied reticuloendothelial system (hypersplenism). In these cases, PB cytopenias are associated with hypercellular bone marrow (Lu et al. 2013). Therefore, bone marrow examination is mandatory for evaluation and management of patients with PB cytopenias. The incidence of diseases that cause pancytopenia differs according to geographical distribution and genetic differences (International Agranulocytosis and Aplastic Anemia Study 1987). There are several published studies that explored bone marrow pictures in cases of pancytopenia (Gayathri and Rao 2011; Naseem et al. 2011; Doshi et al. 2012; Rangaswamy et al. 2012; Khan et al. 2013; Weinzierl and Arber 2013; Devitt et al. 2014); none of them is Egyptian. To the best of our knowledge, no study has analyzed adult bicytopenia patients. The aim of this work is to study bone marrow findings and underlying disorders in adult Egyptian patients with bicytopenia/pancytopenia.

Subjects and methods

The present study was conducted in the Hematology Unit, Clinical Pathology Department, Kasr Al-Ainy School of Medicine, Cairo University over a period of 1 year from

Table 1 Clinical and hematological parameters of patients with PB cytopenias, pancytopenia, and bicytopenia

Parameter	PB cytopenias n=112	Pancytopenia n=62	Bicytopenia n=50
Age (mean±SD years)	42.61±16.12	43.47±16.49	41.50±15.73
Males n (%)	47 (42)	27 (43.5)	20 (40)
Splenomegaly n (%)	68 (60.7)	40 (64.5)	28 (56)
Hepatomegaly n (%)	28 (25)	16 (25.8)	12 (24)
Lymphadenopathy n (%)	14 (12.5)	8 (13)	6 (12)
Hb% (mean±SD g/dL)	8.61±2.52	8.06±2.18	9.29±2.76
TLC (mean±SD $\times 10^3/\mu L$)	8.13±23.58	2.42±0.83	15.20±34.15
Platelets (mean±SD $\times 10^3/\mu L$)	61.27±58.22	53.54±40.61	70.86±73.86

PB peripheral blood, *Hb* hemoglobin, *TLC* total leukocyte count

September 2010 to August 2011. Inclusion criteria for analysis were hemoglobin (Hb) concentration less than 13 g/dL in males and 12 g/dL in females (McLean et al. 2009), total leukocyte count (TLC) less than $4\times10^3/\mu L$, and platelet count less than $150\times10^3/\mu L$ (Khan et al. 2013). Patients below the age of 18 years, under chemotherapy, recently received blood transfusion and follow-up cases were excluded from the study. Patients were subjected to history taking, clinical examination, complete blood count, peripheral blood smear examination, and reticulocyte count. Bone marrow aspiration (BMA) was done from the posterior iliac crest under local anesthesia with standard aseptic conditions. BMA smears were stained with Leishman stain for morphological examination and when required special stains such as myeloperoxidase stain was performed. Bone marrow biopsy (BMB) was performed in cases of dry tap, hypoplastic marrow, and for staging of lymphoma.

The patients' clinical and hematological parameters were recorded, and the data was tabulated. The data was expressed as mean ± standard deviation (SD) and percentages. One-way analysis of variance (ANOVA) test was used to compare means, and Fisher's exact test was used to compare percentages. A p value of <0.05 was considered statistically significant.

Results

During the study period, 175 adult patients were referred to the Hematology Unit, Clinical Pathology Department for bone marrow examination for various indications. Out of 175 patients, a total of 112 patients presented with PB cytopenias (62 pancytopenia patients and 50 bicytopenia patients).

Table 2 Diagnoses of pancytopenia and bicytopenia patients following bone marrow examination

Diagnosis	Pancytopenia n=62	Bicytopenia n=50
Clonal hematopoietic disorders	21 (34 %)	17 (34 %)
Acute myeloid leukemia	5 (8.1 %)	3 (6 %)
Acute lymphoblastic leukemia	2 (3.2 %)	2 (4 %)
Non-Hodgkin's lymphoma	4 (6.5 %)	5 (10 %)
Hodgkin's lymphoma	1 (1.5 %)	0 (0 %)
Hairy cell leukemia	3 (5 %)	0 (0 %)
Myelodysplastic syndrome	4 (6.5 %)	2 (4 %)
Multiple myeloma	1 (1.5 %)	2 (4 %)
Waldenstrom macroglobulinemia	1 (1.5 %)	2 (4 %)
Mast cell leukemia	0 (0 %)	1 (2 %)
Hypersplenism	17 (27.4 %)	9 (18 %)
Aplastic anemia	13 (20.9 %)	1 (2 %)
ITP	0 (0 %)	12 (24 %)
Normocellular bone marrow	5 (8.1 %)	7 (14 %)
Hypercellular reactive marrow	2 (3.2 %)	1 (2 %)
Immune peripheral destruction (SLE)	2 (3.2 %)	2 (4 %)
Megaloblastic anemia	2 (3.2 %)	1 (2 %)

ITP idiopathic thrombocytopenic purpura, *SLE* systemic lupus erythematosus

Table 3 Comparison of clinical and hematological parameters in the three common causes of pancytopenia

Parameter	Clonal disorders n=21	Hypersplenism n=17	Aplastic anemia n=13	p value
Age (mean±SD years)	44.33±17.64	47.47±14.81	35.23±19.46	0.15
Male n (%)	13 (62)	10 (59)	4 (31)	0.18
Splenomegaly n (%)	13 (62)	17 (100)	1 (8)	<0.001
Hepatomegaly n (%)	8 (38)	3 (18)	1 (8)	0.13
Lymphadenopathy n (%)	4 (19)	1 (6)	1 (8)	0.54
Hb% (mean±SD g/dL)	7.31±1.28	10.27±1.56	6.07±1.80	<0.001
TLC (mean±SD $\times 10^3/\mu L$)	2.23±0.80	2.76±0.70	2.09±0.91	0.05
Platelets (mean±SD $\times 10^3/\mu L$)	59.90±38.59	62.88±41.14	16.03±10.30	0.001

Hb hemoglobin, *TLC* total leukocyte count

Clinical and hematological parameters of patients with PB cytopenias, pancytopenia, and bicytopenia are shown in Table 1.

Thrombocytopenia and anemia were the most common form of bicytopenia seen in 35 cases (70 %), followed by thrombocytopenia and leukopenia in nine cases (18 %) and anemia and leukopenia in six cases (12 %).

Definitive diagnosis could be made based on clinical findings together with BMA/BMB interpretation in 55 (88.7 %) pancytopenia patients and 42 (84 %) bicytopenia patients. Nonspecific bone marrow findings were detected in seven (11.3 %) pancytopenia patients and eight (16 %) bicytopenia patients.

Clonal hematopoietic disorders were the commonest diagnosis among pancytopenia and bicytopenia patients. They were seen in about one third of patients. Lymphoid neoplasms were the most common and account for 57 % of clonal pancytopenia patients and 65 % of clonal bicytopenia patients. The second common cause of pancytopenia was hypersplenism followed by aplastic anemia. In bicytopenia patients, the second common cause was idiopathic thrombocytopenic purpura (ITP) followed by hypersplenism (Table 2). Most hypersplenism patients (86 %) had history of hepatitis C viral (HCV) infection.

Patients with the three common causes of pancytopenia/bicytopenia were compared regarding their clinical and hematological parameters (Tables 3 and 4).

Anemia was more severe among aplastic anemia patients and patients with clonal hematopoietic disorders than patients with hypersplenism (p<0.001).

Similarly, thrombocytopenia was more severe among aplastic anemia patients than patients with clonal hematopoietic disorders or hypersplenism (p=0.001).

The age, sex, and total leukocyte count (TLC) were comparable between the three groups of pancytopenia patients.

In contrast to pancytopenia patients, the age and sex of bicytopenia patients differ significantly according to the cause. The ITP patients were younger (p=0.03) and showed significant female predominance (p=0.003) when compared to patients with clonal hematopoietic disorders and hypersplenism.

There is a statistically significant different Hb levels among bicytopenia patients being lower among patients with clonal hematopoietic disorders and ITP than patients with hypersplenism (p <0.001). As expected, platelet count was significantly lower among ITP patients than patients with clonal hematopoietic disorders and hypersplenism (p=

Table 4 Comparison of clinical and hematological parameters in the three common causes of bicytopenia

Parameter	Clonal disorders n=17	ITP n=12	Hypersplenism n=9	p value
Age (mean±SD years)	46.94±15.67	31.91±14.32	41.78±8.58	0.03
Male n (%)	9 (53)	1 (8)	7 (78)	0.003
Splenomegaly n (%)	14 (82)	1 (8)	9 (100)	<0.001
Hepatomegaly n (%)	8 (47)	0 (0)	2 (22)	0.01
Lymphadenopathy n (%)	3 (18)	0 (0)	1 (11)	0.33
Hb% (mean±SD g/dL)	7.40±1.79	9.63±1.07	11.96±2.33	<0.001
TLC (mean±SD $\times 10^3/\mu L$)	30.23±55.85	12.59±8.28	4.28±1.97	0.22
Platelets (mean±SD $\times 10^3/\mu L$)	101.88±96.5	9.17±5.87	61.11±29.37	0.003

ITP idiopathic thrombocytopenic purpura, *Hb* hemoglobin, *TLC* total leukocyte count

0.003). TLC was comparable between the three groups of bicytopenia patients.

Discussion

A wide variety of disorders can cause pancytopenia; however, the frequency with which each condition is associated with pancytopenia differs according to geographical distribution and genetic differences (Devitt et al. 2014). In the present study, the most common cause of pancytopenia was found to be clonal hematopoietic disorders (34 %), followed by hypersplenism (27 %) and then aplastic anemia (21 %). Regarding bicytopenia patients, to our knowledge, this is the first report that evaluates bone marrow picture in adult patients with bicytopenia. The most common cause of bicytopenia was found to be clonal hematopoietic disorders (34 %), followed by ITP (24 %) and then hypersplenism (18 %). This means that bicytopenia is as important as pancytopenia being associated with clonal disorders (commonly, lymphoid neoplasms) in about one third of cases. In Western studies, nearly two thirds of adult cases with new onset pancytopenia had a clonal etiology; however, myeloid neoplasms were the most common (Imbert et al. 1989; Devitt et al. 2014). Hypersplenism was seen in 27 % of pancytopenia patients and 18 % of bicytopenia patients. In concordance with our study, hypersplenism was the second common cause of pancytopenia in Yemini patients (28 %) and was attributed to the increased prevalence of malaria, kala azar, and other infectious diseases in Yemen (Hamid and Safa 2008). In our group of patients, hypersplenism is attributed to HCV infection. Egypt has the highest prevalence of hepatitis C (Frank et al. 2000). HCV prevalence in Egypt is estimated to be 14.9 % in the year 2008 (El-Zanaty and Way 2009). Complications of chronic HCV infection occur because of progressive liver fibrosis, leading to cirrhosis. Cirrhotic patients develop portal hypertension that results in splenomegaly and subsequent cell sequestration (Weksler 2007). Hypersplenism consists essentially of thrombocytopenia and less frequently neutropenia and anemia (Tomikawa et al. 2002). Our hypersplenism cases showed less severe cytopenias, and the platelet count was the most affected. In a previous study on the prevalence of peripheral blood cytopenias in patients with hypersplenism due to chronic liver disease, thrombocytopenia was detected in 64 % of patients with a median platelet count of $114\times10^3/\mu L$ (Bashour et al. 2000).

ITP was detected in 24 % of bicytopenia patients. Although cases with ITP classically present with thrombocytopenia alone, our cases presented with bicytopenia in the form of anemia and thrombocytopenia. This could be explained by chronic bleeding or the presence of additional nutritional deficiency.

Aplastic anemia was the third common cause of pancytopenia (seen in 21 % of patients). In Asian countries, aplastic anemia was the commonest cause of pancytopenia that was detected in 29–79 % of cases (Jha et al. 2008; Biswajit et al. 2012; Kumar and Raghupathi 2012; Khan et al. 2013). In Western studies, the incidence of aplastic anemia among pancytopenia patients was found to be 5–10 % (Imbert et al. 1989; Devitt et al. 2014).

In the current study, 3 % of pancytopenia patients and 2 % of bicytopenia patients were diagnosed as megaloblastic anemia. Megaloblastic anemia was found to be the most common cause of pancytopenia among Indian patients and was detected in 44–74 % of cases (Tilak and Jain 1999; Khodke et al. 2001; Khunger et al. 2002; Gayathri and Rao 2011). This increased incidence of megaloblastic anemia correlates with the high prevalence of nutritional anemias in Indian patients (Gayathri and Rao 2011).

In conclusion, causes of peripheral blood cytopenias differ between countries according to the prevalent health problems like infection and nutritional deficiency. In Egypt, clonal hematopoietic disorders, hypersplenism due to chronic liver disease, ITP, and aplastic anemia are the common causes of PB cytopenias. Causes underlying bicytopenia are as important as those of pancytopenia, at least in our setting. Bone marrow examination is an important tool for investigation of cases with PB cytopenias.

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