Pancytopenia in adult Iraqi patients in Medical City of Baghdad (A prospective and retrospective study)

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Abstract

Background: Pancytopenia is a term used to describe the simultaneous presence of anemia, leucopenia and thrombocytopenia. Different hematological and non hematological disorders may present with pancytopenia e.g. aplastic anemia, acute leukemia, megaloblastic anemia, etc...
Aim of the study: The aim of this study is to identify the causes and presenting symptoms of pancytopenia in Iraqi patients.
Patients and Methods: This study evaluated 173 patients admitted to Baghdad Teaching Hospital between January 2004 and August 2006. Criteria for inclusion were; anemia (PCV < 0.30 L/L), plus leucopenia (WBC count < 4 × 10^9 /L) and thrombocytopenia (platelet count < 100 × 10 9/L). Cases of pancytopenia induced by chemotherapy or radiotherapy were excluded. The adult patients were randomly selected regarding age and sex. This study included 94 male and 79 female patients, with age range from 15 to 79 years. Peripheral blood examination and bone marrow aspiration were done in all patients, while bone marrow biopsy done in 98 patients.
Results: The major causes were acute leukemia in 66 (38.2 %) patients, aplastic anemia in 31 (17.9 %) patients, megaloblastic anemia in 29 (16.8 %) patients and myelodysplastic syndrome, non-Hodgkin lymphoma , systemic lupus erythematosus, hypersplenism, hairy cell leukemia, kala-azar, paroxysmal nocturnal haemoglobinuria and multiple myeloma constituted the remainder causes. The maximum age group of patients presented with pancytopenia ranging in 21-30 years with male to female ratio 1.2:1. The major presenting symptoms were bleeding tendency found in 69 (39.9 %) patients followed by easy fatigability found in 56 (32.4 %) patients and fever in 48 (27.7 %) patients , while common presenting signs were pallor, petechiae, splenomegaly, hepatomegaly and lymphadenopathy. The most common peripheral blood findings were anisopokoilocytosis, circulated immature cells and blasts cells.
Conclusions: Acute leukemia, aplastic anemia and megaloblastic anemia are the major causes of pancytopenia, however, uncommon and rare causes like myelodysplastic syndrome, non-Hodgkin lymphoma, systemic lupus erythematosus, hypersplenism, hairy cell leukemia, kala-azar, paroxysmal nocturnal haemoglobinuria and multiple myeloma could be presented with pancytopenia. Major presenting symptoms were bleeding tendency, easy fatigability and fever, while common presenting signs were pallor, petechiae, splenomegaly, hepatomegaly and lymphadenopathy. Careful physical examination and peripheral blood smear examination play an important role in planning investigations of pancytopenia.

الخلاصة

موطئة : نقص خلايا الدم الشامل هو مصطلح يستعمل لوصف تزامن وجود فقر الدم ، نقص خلايا الدم البيضاء و نقص الصفائح الدموية. مختلف الأمراض الدموية وغير الدموية من الممكن أن تظهر على شكل نقص خلايا الدم الشامل ، مثال ذلك فقر الدم اللاتكوني ، ابيضاض الدم الحاد ، فقر الدم للكرية الحمراء الجذعية الضخمة، وغيرها .

الغرض من الدراسة هو لتحديد أسباب و أعراض الظهور لنقص خلايا الدم الشامل للمرضى البالغين في العراق.

الطرائق والمواد : هذه الدراسة أجريت لتقيم 173 مريض لنقص خلايا الدم الشامل أدخل إلى مستشفى بغداد التعليمي بين شهري كانون الأول 2004 وشهر أب 2006.

معايير الشمول لهذه الدراسة كانت فقر الدم (حجم الكريات المرصوصة أقل من 0.30) ، نقص خلايا الدم البيضاء (عدد خلايا الدم البيضاء أقل من4 $\times 10^9$) و نقص الصفائح الدموية (عدد الصفائح الدموية أقل من 100 $\times 10^9$). حالات نقص خلايا الدم الشامل الناتج من العلاج الكيميائي أو العلاج الإشعاعي قد استثنيت من الدراسة .

فحص الدم المحيطي و سحب نخاع العظم قد أجري لجميع المرضى ، بينما خزعة نخاع العظم أجريت ل(98) مريض.

النتائج: الأسباب الرئيسية لنقص خلايا الدم الشامل كانت ابيضاض الدم الحاد وجد في 66(38.1%) مريض ، فقر الدم اللاتكوني في 31(17.9%) مريض ، فقر الدم للكريه الحمراء الجذعية الضخمة في 29(16.7%) مريض بالإضافة إلى سرطان الغدد الليمفاوية اللاهوجكنية ، متلازمة اعتلال النمو النخاع ، داء الذئب الاحمراري ، ابيضاض الدم شعري الخلايا ، طحل ، الكلازار ، البيلة اليحمورية الاشتدادية الليلية و ورم نخاع العظم المتعدد تمثل الأسباب المتبقية.

اكثر المرضى الذين يعانون من نقص خلايا الدم الشامل كانت اعمارهم بين 21-30 سنة مع نسبة الذكور الى الاناث (1.2 : 1) والتي كانت مطابقة مع الدراسات الاخرى.

أعراض الظهور الرئيسية كانت الميول النزيفية وجدت في 69(39.8%) مريض ثم سهولة التعب في 56 (23.2%) مريض والحمى في 48 (27.7%) مريض ، بينما العلامات الظاهرة الشائعة كانت الشحوب ، البثور الجلدية ، تضخم الطحال ، تضخم الكبد و تضخم الغدد الليمفاوية. نتائج الدم المحيطي الأكثر شيوعا كانت اختلاف في حجم وشكل كريات الدم الحمراء ، الخلايا الغير ناضجة الدائرة في الدم والخلايا الجذعية .

الاستنتاج : ابيضاض الدم الحاد ، فقر الدم اللاتكوني ، فقر الدم للكريه الحمراء الجذعية الضخمة ، هي الأسباب الرئيسية لنقص خلايا الدم الشامل بينما الاسباب الغير شائعة والنادرة من الممكن أن تظهر على شكل نقص خلايا الدم الشامل مثال ذلك سرطان الغدد الليمفاوية اللاهوجكنية ، متلازمة اعتلال النمو النخاعي ، داء الذئب الاحمراري ، ابيضاض الدم شعري الخلايا ، طحل ، الكلازار ، البيلة اليحمورية الاشتدادية الليلية و ورم نخاع العظم المتعدد.أعراض الظهور الرئيسية كانت الميول النزيفية ، سهولة التعب ، والحمى بينما العلامات الظاهرة الشائعة كانت الشحوب ، البثور الجلدية ، تضخم الطحال ، تضخم الكبد و تضخم الغدد الليمفاوية. الفحص البدني الدقيق وفحص الدم المحيطي يلعبا دورا مهما في التخطيط لفحوصات نقص خلايا الدم الشامل .

Introduction

Pancytopenia is not a disease entity but a triad of finding or a term used to describe the simultaneous presence of anemia, leucopenia and thrombocytopenia that may result from a number of processes; these disorders may affect bone marrow either primarily or secondarily, resulting in manifestation of pancytopenia [(1)]. Pancytopenia can be due to decrease in hemopoietic 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 [(9)]. The presenting symptoms are usually attributable to anemia or thrombocytopenia. Leucopenia is an uncommon cause of initial presentation but can become the most serious threat of life during the course of the disorder [(2, 3, 4)]. The anemia presents with pallor, weakness, easy fatigability, lassitude

and dysponea on exertation. Neutropenia results in infection causing sore throat, ulceration of the mouth, and pharynx, fever with chills and sweating, chronic skin infection, recurrent chest infection and pneumonia. Thrombocytopenia presents with bleeding manifestation and results in haemorrhages into the skin either echymosis or petechia. Epistaxis, bleeding for gums and GIT [10].

Common questions that a healthcare professional asks are (1) what are the most common causes of pancytopenia ? and (2) what is the best dagnostic approach to the patients ? [9]. The incidence of various disorders causing pancytopenia widely varies due to geographical distribution, environmental factors and genetic disturbances. The management and prognosis of pancytopenia depends on the underlying pathology [1]. Although pancytopenia 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 [9].

Material & methods

This study was carried out in Hematological Unit of Baghdad Teaching Hospital and Teaching Laboratories of Medical City from January 2006 to August 2006, including 55 prospective and 118 retrospective studies of patients presented with pancytopenia. A total of 173 adult patients were selected for this study who attended the center from January 2004 to August 2006.

The adult patients were randomly selected regarding age and sex. This study included 94 male and 79 female patients, with age range from 15 to 79 years.

The criteria for inclusion in this study were: anemia (PCV < 0.30 L/L), leucopenia (WBC count < 4 $\times 10^9$ /L) and thrombocytopenia (platelet count < 100 $\times$ 10^9 /L) [2,4,9]. In this study we exclude the cases of pancytopenia which were induced by cytotoxic drugs or radiotherapy.

A detailed history and clinical examination were carried out on 55 patients prospectively and the relevant information was noted including clinical history which includes (treatment history, history of drug intake and radiation exposure), along with a physical examination include (pallor, mucocutanous bleeding, hepatomegaly, splenomegaly and lymphadenopathy). Another 118 retrospective cases were collected from a previously diagnosed patients with pancytopenia , 66 cases their clinical notes, reports and slides were available , while 52 cases only their reports were depended .

The investigations which were done for those prospectively studied patients include;

1. Full blood count (carried out prior to transfusion for all patients) that include measurement of PCV, total WBC count and platelet count.
2. Blood film was done for all cases of pancytopenia**.**
3. Reticulocyte count was done in 112 required cases**.**
4. Bone marrow aspiration was done for all patients of pancytopenia.
5. Special stains were done for indicated cases including: Iron stain was done for (45) cases, Sudan black B stain was done for (40) cases and Peroidic acid-schiff stain was done for (34) cases.
6. Bone marrow trephine biopsy was done in 98 cases.

Results

This study was conducted on 173 cases of pancytopenia, the youngest patient was 15 years old while oldest patient was 79 years old, the mean age is 38 years and the maximum age group of patients presented with pancytopenia was ranging from 21-30 years. Male constitute (54.3 %) of patients and female were (45.7 %). Male to female ratio is about 1.2: 1.

The various causes of pancytopenia found in this study are listed in table 1. Acute leukemia represented 38.2 % of all cases of pancytopenia (66/173), [63.6 % (42/66) of which was acute myeloblastic leukemia and 10.7% (13/66) was acute lymphoblastic leukemia, while acute undifferentiated leukemia represented 16.7 % (11/66) of acute leukemia]. Acute promyelocytic leukemia represents 42.8 % (18/42) of all AML, as shown in table 2.

The second common cause of pancytopenia was aplastic anemia 17.9 % (31/173) , while the 3rd common cause was megaloblastic anemia which represent 16.8 % (29/173), other causes were Non-Hodgkin lymphoma 6.4 % (12/173) , myelodysplastic syndrome 5.8 (10/173) , undiagnosed cases 4.6 % (8/173) , SLE 3.5 % (6/173) , hairy cell leukemia 2.3 % (4/173), hypersplenism 1.7 % (3/173) , PNH and kala-azar each of them represent 1.1 % (2/173) and multiple myeloma 0.6 % (1/173), as shown in table 1.

The distribution of presenting symptoms including bleeding tendency (mucocutanous bleeding) was found in 39.9 % (69/173), easy fatigue was found in 32.4 % (56/173), while fever was found in 27.7 % (48/173). The commonest sign was pallor found in 69.9 % (121/173) of patients followed by feature of bleeding tendency represented by petechiae and echymosis which were found in 45.7 % of patients. Other clinical signs found in this study were splenomegaly 27.2 %, hepatomegaly in 17.3 % and lymphadenopathy in 13.3 % of patients.

Peripheral blood findings are shown in table 3, in which the anisopoikilocytosis were found in 84.9 %, circulated immature cells (exclude blasts) in 32.3 %, circulated blasts in 31.7 %, NRBC in 30.6 %, macrocytosis in 23.6 %, hypersegmented neutrophils in 11.5 %, and relative lymphocytosis in 4.0 %.

Table 1. Causes of pancytopenia in 173 randomly cases study

Disorder	No. of cases	Percentage
Acute leukemia	66	38.2 %
Aplastic anemia	31	17.9 %
Megaloblastic anemia	29	16.8 %
Non-Hodgkin lymphoma	11	6.4 %
Myelodysplastic syndrome	10	5.8 %
Undiagnosed cases	8	4.6 %
SLE	6	3.5 %
Hairy cell leukemia	4	2.3 %
Hypersplenism	3	1.7 %
PNH	2	1.1 %
Kala-azar	2	1.1 %
Multiple myeloma	1	0.6 %
Total	173	100 %

Table 2. Various types of acute leukemia presented with pancytopenia in 173 randomly cases study

Types	% from AL	No.	Subtypes	No.	Percentage
AML	63.6	42	AML-M1	11	26.2 %
			AML-M2	8	19.0 %
			AML-M3	18	42.9 %
			AML-M4	1	2.4 %
			AML-M5	4	9.5 %
			AML-M6	0	0 %
			AML-M7	0	0 %
ALL	19.7	13	ALL-L1	4	30.8 %
			ALL-L2	9	69.2 %
			ALL-L3	0	0 %
AUL	16.7	11	--	--	--
Total	100	66	--	--	100 %

Table 3. Distribution of peripheral blood finding

Diagnosis	Total No	Aniso-cytosis	Immatue cells (exclude blast)	blasts	NRBC	Macro-cytosis	HSN
Acute leukemia	66	51	29	52	23	-	-
Aplastic anemia	31	29	2	-	3	9	-
Megaloblastic anemia	29	25	5	-	11	27	24
NHL	11	10	6	-	5	-	-
MDS	10	9	5	3	3	4	-
Undiagnosis	8	6	2	-	1	1	-
SLE	6	6	2	-	1	1	-
Hairy cell leukemia	4	3	-	-	-	-	-
Hypersplenism	3	3	1	-	1	-	-
PNH	2	2	1	-	1	-	-
Kala-azar	2	2	2	-	1	-	-
Multiple myeloma	1	1	1	-	-	-	-
Total No.	173	147	56	55	53	41	20
Percentage	100	84.9 %	32.3 %	31.7 %	30.6 %	23.6 %	11.5 %

Discussion

Pancytopenia means a disorder in which three blood elements (RBC, WBC and Platelets) are decreased below the normal range. Till date there is limited number of studies on the frequency of various causes of pancytopenia. Most of these studies found that aplastic anemia [1,14,5,11,15] or megaloblastic anemia [4,9,6,12,13] were the commonest causes of pancytopenia, unlike this study where the most common cause was acute leukemia which represent 38.2 % of all pancytopenic patient.The second and third common causes were aplastic anemia (17.9 %) and megaloblastic anemia (16.8 %) respectively.

The differences between our study and above studies may be attributed to the following explanations:

1. Differences in environmental, social and genetic factors between our society and other societies where these studies done, although most of reports are from south Asia, only one from Europe and one from Zimbabwe which may not reflect the real causes of allover the world. The exposure to radiation of

depleted uranium used in war was being a factor.

2. The high prevalence of acute leukemia in our study may be attributed to the high referral rate of acute leukemia to the Hematological department in Baghdad teaching hospital where most of our cases were collected and this may not reflect the actual prevalence in the general population in our country.

3. The high prevalence of AML in our study may be attributed to that all our patients were adults in which AML accounts for about 90 % of acute leukemia in adults [2,3,16].

4. The high prevalence of acute leukemia in contrast to the nutritional deficiency as a cause of pancytopenia may be attributed to the fact that most patients with these deficiencies may be treated in out patient clinic.

5. The high prevalence of aplastic anemia in the East than in the West (e.g. in India, Japan and Far East) in which the incidence of aplastic anemia is at least three time higher than in USA and Europe, where the environmental factors and perverse use of Insecticide have been implicated as a cause of this disease [1,4,15].

6. The high prevalence of megaloblastic anemia in Indian subcontinent which was the commonest cause in some studies and 2nd cause in others, may be attributed to the high prevalence of nutritional anemia in that part of the word . Among nutritional anemia, vitamin B-12 deficiency is more prevalent than folate deficiency [1,4,9,11].

Other causes of pancytopenia as NHL represent 6.4 % of cases, while in study of Kumar R, et al 2001 [13] found that the acute leukemia and lymphoma both represent 3rd common cause of pancytopenia . SLE represents 3.5 % of cases which contrast with the study of Ishtiaq O, et al 2004 [9] where found it represents 3% of cases. Other rare causes of pancytopenia come in variable prevalence in contrast to other studies due to unavailable data.

In this study some cases were undiagnosed (4.6 %) due to loss of patients or incomplete follow up.

The maximum age group of patients presented with pancytopenia ranging in 21-30 years which contrast to other studies as in studies of Mussarrat Niazi et al 2004 [1] and study of Kishor K, et al 2001 [4], where the maximum age group was ranging in 21-30 years.

This study showed the higher incidence of pancytopenia in male (54.3 %) than female (45.7%) which is contrast to other studies as in study of Kishor K, et al 2001 [4] and Ishtiaq O, et al 2004 [9], where they show male: female ratio of about 1.3:1 .

The initial manifestations of pancytopenia varies widely and depend on the severity of pancytopenia and can be manifested by symptoms of anemia, neutropenia and thrombocytopenia , which occur either singly or in combination depending on degree of reduction [2,7,8]. In this study the most common presenting symptoms are; bleeding tendency 39.8 %, easy fatigability 32.3 % and fever 27.7 %, while in the study of Mussarrat Niazzi and Fazl-i-Raziq 2004 [1]; the most common presenting symptoms are easy fatigability, fever and bleeding. This difference may be attributed to the high prevalence of acute leukemia as a common cause of pancytopenia in this study, in which the majority of cases were AML particularly FAB AML-M3. Its known that up to 90 % of patients with FAB AML-M3 present with bleeding tendency and up to half of patients with acute leukemia present with bleeding manifestations , and this may be due to thrombocytopenia or DIC, while fever present in 15-20 % of patients which may result from

infections secondary to neutropenia or from leukemia itself [3] .

The most common presenting sings in this study were pallor 69.9 %, petechiae 45.7 % , splenomegaly 27.2 %, hepatomegaly 17.3 % and lymphadenopathy 13.3 %; while Kishor K , et al 2001 [4], found that the common presenting signs are pallor, splenomegaly, hepatomegaly, petechiae and lymphadenopathy ,also in study of Mussarrat Niazi, Fazl-i-Raziq 2001 [1] was found that the commonest signs are pallor and hepatomegaly. This difference between studies may be attributed to the difference in the most common causes of pancytopenia.

The most common peripheral blood findings in our study was different degree of anisopoikilocytosis that found in 84.9 %, circulated immature cells in 32.3 %, and circulated blasts cells in 31.7 %; while in study of Kishor K, et al 2001 [4], was found that common peripheral blood findings are anisopoikilocytosis , hypersegmented neutrophils and dimorphic pictures. This difference between these findings may also attribute to the difference in the most common causes of pancytopenia in both studies.

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