Original article

A Clinical-Hematological Study of Pancytopenia Patients Attending Nanakaly Hospital in Erbil City

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Abstract

Background: Pancytopenia is a triad of low hemoglobin, white blood cells and platelets. 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.

Objectives: This study aimed to determines the etiology and clinical profile of pancytopenic patients attending Nanakaly hospital.

Materials and Methods: During a period of 6 months, 60 pancytopenic patients attended Nanakaly hospital, their ages ranged between one-81years. A control group of 50 age-matched apparently healthy person were tested for complete blood picture and reticulocyte count. History, physical examination and hematological parameters at presentation were recorded. Hematological profile included hemoglobin, total and differential leukocyte count, platelet count, reticulocyte count, peripheral blood and marrow smears together with marrow biopsy were assessed. Pancytopenic cancer patients on chemotherapy were excluded. Pancytopenia was defined as hemoglobin less than 10g/dl, WBC less than 4 $x10^9$/L and platelet count less than 150 x 10^9/L.

Results: The mean Hb concentration, WBC count and platelet count in studied group were significantly lower than in control group. Hematological malignancies were the commonest cause of pancytopenia and accounted for (51.7%), they included: Acute leukemia (35%), myelodysplastic syndrome (11.7%), hairy cell leukemia (3.3%) and myelofibrosis (1.7%).

Aplastic and megaloblastic anemia each of them accounted for (16.7%), hypersplenism was responsible for (10%). Other less common causes included enteric fever, kalaazar and secondary metastasis each of them accounted for (1.7%). Pallor was present in every case. Fever was present in (63.3%) and (25%) had bleeding manifestations at the time of presentation

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Conclusions: The most common causes of pancytopenia were acute Leukemia, aplastic anemia and Megaloblastic anaemia, but rare causes like myelofibrosis, enteric fever, kala azar and secondary metastasis should also be kept in mind.

Keywords: Pancytopenia, Bone marrow, malignant hematology.

Introduction

The term pancytopenia denotes simultaneous reduction in all the formed elements of the blood *i.e,* erythrocytes, leukocytes and platelets. Pancytopenia is not a disease entity but a triad of findings that may arise from a number of disease processes [(1)]. It is, therefore exists when hemoglobin level is below 10 g/dl, leukocyte count below 4 x 10^9 /l and platelet count below 150 x 10^9/l Hence, a patient of pancytopenia may have symptoms due to anaemia, weakness and dyspnoea on exertion; bleeding manifestation, like skin and mucosal bleeding, due to thrombocytopenia; and fever, ulceration of mouth and recurrent chest infections due to neutropenia.[(2)]

Bone marrow aspirate/biopsy examination which is routinely performed to every pancytopenic patient is of high diagnostic value [(3)]. The center of hematological diseases in Erbil, Nanakaly Hospital, receives many patients whose complete blood count show pancytopenic parameters. However, no statistical figures are available here regarding number of cases as well as their underlying causes. Therefore, we deemed necessary to do our work on this group of patients to determine these figures and to compare them with results of studies done in the other parts of Iraq and nearby countries.

The aims of this study were to determine the spectrum of pancytopenia with it is frequency, common clinical presentation and etiology on the basis of

full clinical and laboratory examination specially bone marrow examination in our locality.

Materials and methods

This prospective study was conducted during the period extending from 13th Dec.2008 to 15th July 2009, at Nanakaly Hospital for Blood Diseases. A total of 60 patients with pancytopenia were included in this study. All patients presenting with pancytopenia during the study period were included. For purposes of this work, pancytopenia was defined as a hemoglobin less than 10g/dl, WBC less than 4 $x10^9$/L and platelet count less than 150 x 10^9/L. Patients who were already diagnosed cases of pancytopenia due to different causes and those receiving chemotherapy or therapeutic radiation, were excluded from this study.

Diagnostic work up of cases included three basic investigations i.e. a complete blood count, analysis of stained blood, marrow aspirate smears and bone marrow trephine biopsy. Laboratory tests were performed at the Nanakaly Hospital's laboratory. Two ml venous blood were collected into an EDTA anticoagulated tube; a full blood count, was done for every patient using automated blood counter (Beckman Coulter® model A^{c}T diff 2), Reticulocyte preparations and Leishman's stained peripheral blood were prepared freshly and examined for each patient. Bone marrow aspiration and biopsy were performed at Nanakaly hospital for all the patients. Marrow aspirate smears were prepared, stained with Leishman's stain and examined. Marrow trephine biopsy specimens were fixed in Bown's solution and were sent to Rizgary Teaching Hospital for processing and interpretation.

Data were tabulated and statistically analyzed using statistical package for social sciences (SPSS version 15). Chi square and tests of association were used whenever applicable, analysis of variance (ANOVA) was used to compare between means of 3 groups or more of patient. A p-value of equal or less than 0.05 was considered as statistically significant.

Results

During the period of this study, 60 patients attending Nanakaly hospital fulfilled the criteria of pancytopenia according to the study protocol. There

were 31 males and 29 females patients. Their ages ranged between one and 81 years with a mean age of (33.3 years). The commonest presenting features, in order of frequency were: Pallor (100% of cases), fever in (63.3%), bleeding in (25%) and infections in (8.3%) of cases.

Organomegaly was noted in (33.4%) of cases. These cases included (16.7%) with splenomegaly, (11.6%) had hepatosplenomegaly, (3.3%) had hepatomegaly alone and one case had lymphadenopathy. Table (1) represents a statistical summary of the routine hematological parameters of studied patients.

Majority of patients showed normal red cell morphology (68.3%), macrocytosis was reported in (26.7%) of cases and hypochromia was found in (5%) of cases. All patients had marrow aspirate and trephine biopsy examinations and according to marrow findings the causes of pancytopenia were determined, the frequency of various causes of pancytopenia in this series is shown in table (2). Types of malignant blood diseases are illustrated in table 3.

Leukemic patients included 12 males and 9 females, their mean age was 18 years, and there were 12 cases of acute lymphoblastic leukaemia and 9 cases of acute myeloblastic leukemia.

Comparing the various parameters among the three leading causes of pancytopenia (malignant blood diseases, aplastic anemia and megaloblastic anemia) there were significant differences regarding the WBC count, where patients with aplastic anaemia had the lowest figures ($p < 0.04$), the platelets, too, were significantly lower in aplastic anaemia than the other two conditions ($p< 0.001$).There were no significant differences among the three groups regarding the Hb and reticulocyte counts ($p = 0.11$ and $p = 0.97$) respectively. Other hematological parameters showed in table 4.

Discussion

Pancytopenia is commonly encountered in hematological practice, it usually indicates a serious condition and it necessitates prompt action. The pattern of diseases leading to pancytopenia may vary in different population groups depending on racial factors, nutritional status and prevalence of infection [(4)]; the frequency of various causes varies among different age groups too.

In this study we had 60 cases of pancytopenia. The mean age of studied patients was 33.3 years which is very close to that reported from other developing countries [1, 5, 6, 7, 8]. The clinical presentation of our patients was classical and the relative frequencies of various presenting features were comparable to the finding of other workers [1, 3, 6, 7, 8, 9, 10]. Organomegaly was reported in 33.4% of studied patients, of these 16.7% had splenomegaly, 11.6% had hepatosplenomegaly and only 3.3% had hepatomegaly alone. The frequency of splenomegaly in this study was similar to that reported by Ishtiaq *et al* from Pakistan [7]. Abdul Hamid reported a frequency of 48% in a series of pancytopenic patients in Yemen, he attributed this relatively high frequency to the high prevalence of malaria, kalaazar and other infectious diseases [8].

Among studied patients presentation varied according to the underlying condition, thus bleeding occurred most frequently among aplastic anemia patients (60%), while none of megaloblastic anemia patients had bleeding. Fever occurred most frequently among acute leukaemia patients (71.4%) and only in (40%) of aplastic anemia patients, accordingly fever with organomegaly at presentation favors the diagnosis of acute leukemia, while bleeding unassociated with organomegaly is likely to be due to aplastic anemia. In this work the mean Hb concentration was 8.14 g/dl, this figure is higher than that reported by [8, 10] this discrepancy is due to the lower frequency of aplastic anemia, in which anaemia is more severe, in this series compared to their studies. The mean W.B.C and platelet counts (2.19 and 55.35 X 10^9/L respectively) were similar to results observed by other workers [8, 10]. Pancytopenia has multiple causes and the prognosis is dependent on the cause. The frequency of these causes has been reported in a limited number of studies [8, 9].In the present study hematological malignancies as a cause of pancytopenia was accounted for (51.7%) of cases. Acute leukemia was the most common cause of pancytopenia; it was responsible for 35% of cases. Acute lymphoblastic type constituted 20% of pancytopenic cases, while acute myelogenous leukemia formed 15% of cases. In a study done by Jalaee and Keihani in Tehran, acute leukemia was

the commonest cause of pancytopenia [11], similar results were reported from Sweden too, where neoplastic diseases and radiation related marrow damage accounted for 32 % of cases while aplastic anemia accounted for 19% of cases [12]. In studies from India [4, 13] acute leukemia was the second most common cause of pancytopenia, In many Asian countries acute leukemia ranked the 3rd or even the 4th cause of pancytopenia, being next to megaloblastic, Aplastic anemia or malaria [1, 2, 3, 5, 6, 8, 10, 14, 15].

The relatively high frequency of acute leukaemia as a cause of pancytopenia in this study may be due to the fact that our locality has been the battle field for a series of wars since the 1960s and various weapons, including chemicals with potential leukaemogenic effects have been used, another reason may be the blooming economy of Kurdistan over the last decade may have reduced the relative frequency of nutritional anemias.

The frequency of other blood malignancies included were as follow; myelodysplastic syndrome (11.7%), hairy cell leukemia (3.3%) and myelofibrosis (1.7%). Devi *et al* reported a frequency of (18%) of myelodysplastic syndrome [1], Iqbal *et al* reported an incidence of (2.4%) in the same series reported a similar frequency for myelofibrosis [16].

The second major causes of pancytopenia in this study were a plastic anemia and megaloblastic anemia, each of them accounted for 16.7% of cases. A detailed history and thorough clinical examination did not help in establishing the cause of marrow hypoplasia, one of aplastic patients was diagnosed as Fanconi anemia after chromosomal study. The relative frequency of aplastic anaemia in this study is in agreement with findings of many other workers [9, 10, 12, 17], however in many other studies aplastic anaemia was the commonest cause of pancytopenia [1, 3, 15, 17, 18].

Epidemiologically, aplastic anemia has a pattern of geographic variation opposite to that of leukemia, with higher frequency in the developing world than in the industrialized West [19]. Large prospective studies indicate an annual incidence of two new cases per million populations in Europe and Israel [20]. Its exact incidence in Kurdistan is not known due to lack of population – based studies. Studies from Thai land [21] and

China [22] showed the incidence to be about three folds that in the west. Its exact etiology still not known but an autoimmune mechanism has been inferred from positive responses to non-transplant therapies and laboratory data [3]. Megaloblastic anemia in this series was as common as Aplastic anaemia, it accounted for (16.7%) of cases. Similar results were reported from Pakistan by Naeem *et al* and Memon *et al* [3, 15]. In Yemen Abdul Hamid and Shukry showed that megaloblastic anemia is the third commonest cause of pancytopenia and accounted for (14.7%) of cases [8]. Studies from India, had shown megaloblastic anemia to be the first most common cause of pancytopenia and accounted for 44% to 72% [9, 17]. Increased incidence of megaloblastic anemia in those studies perhaps correlates with the high prevalence of nutritional anemia due to religious and socio-economical reasons. In Europe in a study on 213 cases of pancytopenia, carried out by Imbert *et al*, (7.5%) of cases were due to megaloblastic anemia [23]. Mosso *et al*, showed the incidence of megaloblastic anemia to be (7.41%) [24].

Megaloblastic anemia due to vitamin B12 or folic acid deficiency is now a well –recognized and established cause of pancytopenia [25]. It can either present as bicytopenia or pancytopenia, or rarely with thrombocytopenia only [26]. The frequency of pancytopenia among patients with megaloblastic anaemia has range of 11% to 47% [6] in almost all these studies, pancytopenia was the main presentation and so was the case in this study**.**

Conclusion

We concluded that physical examination and peripheral blood picture play an important role in planning investigations in pancytopenic patients. The most common causes of pancytopenia were acute Leukemia, aplastic anemia and Megaloblastic anaemia, but rare causes like myelofibrosis, enteric fever, kala azar and secondary metastasis should also be kept in mind.

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دراسة الخصائص السريرية والدموية من قلة كريات الدم الشاملة للمرضى الذين يراجعون مستشفى نانه كه لي في مدينة أربيل

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الملخص:

الخلفية: قلة الكريات الشاملة هو ثالوث الهيموغلوبين المنخفض، وقلة خلايا الدم البيضاء والصفائح الدموية. على الرغم من أنها مشكلة سريرية شائعة مع وجود التشخيص التفريقي الواسع، هناك مناقشة قليلة نسبيا لهذه الحالات في الكتب الرئيسية للطب الباطني وأمراض الدم.

الأهداف: تهدف هذه الدراسة إلى تحديد المسببات والتعريف السريري للمرضى الذين يعانون من قلة الكريات الشاملة الذين حضروا لمستشفى نانه كه لي.
المواد والطرق: خلال فترة 6 أشهر، حضر 60 مريضا يعانون من قلة الكريات الشاملة الى مستشفى نانه كه لي ، تراوحت أعمارهم بين 1-81 سنة. تم اختيار مجموعة السيطرة من 50 شخصا من الاصحاء المتطابقين بالعمرو تم اخذ صورة الدم الكاملة وتعداد الشبكيات. وقد تم تسجيل تاريخ المرض، والفحص السريري ومعلومات فحص الدم . وتضمن الملف الدموي الهيموغلوبين، وعدد وتفاصيل الكريات البيض، عدد الصفائح الدموية، عد الخلايا الشبكية، الدم المحيطي ومسحات نخاع جنبا إلى جنب مع خزعة نخاع. تم استبعاد مرضى السرطان على العلاج الكيميائي مع قلة الكريات الشاملة. وقد عرفت قلة الكريات الشاملة كالاتي : الهيموجلوبين أقل من 10 غم/د ل، كرات الدم البيضاء أقل من 4 * 10^9/لتر وعدد الصفيحات أقل من 150 *10^9 / لتروكانت متوسط تركيز الهيموغلوبين ، وعدد كرات الدم البيضاء والصفائح الدموية في المجموعة المدروسة أقل بكثير مما كانت عليه في المجموعة الضابطة.

النتائج. : كانت الأورام الخبيثة الدموية السبب الأكثر شيوعا لقلة الكريات الشاملة وتمثل (51.7٪)، وشملت: سرطان الدم الحاد (35٪)، ومتلازمة اعتلال نخاع العظم (11.7٪)، سرطان الدم الشعيري (3.3٪) وتليف نخاع العظم (1.7٪). فقر الدم اللاتنسجي وفقر الدم الوبيل كل منها تمثل (16.7٪)، وفرط نشاط الطحال مسؤولة عن (10٪). وتضمنت أسباب أخرى أقل شيوعا مثل حمى المعوية، والحمى السوداء والانتشار الثانوي للسرطان كل منها تمثل (1.7٪). كان الشحوب موجود في كل حالة. كانت الحمى موجودة في (63.3٪) و مظاهر النزيف في (25٪) وقت المراجعة.
الاستنتاجات: كانت الأسباب الأكثر شيوعا لقلة الكريات الشاملة هي سرطان الدم الحاد وفقر الدم اللاتنسجي وفقر الدم الوبيل، ولكن الأسباب النادرة مثل تليف نخاع العظم ، حمى المعوية، الحمى السوداء والانتشار الثانوي للسرطان ينبغي أيضا أن يوضع في الاعتبار.
كلمات البحث: قلة الكريات الشاملة، نخاع العظام، أمراض الدم الخبيثة.

Table 1: Statistical summary of the routine haematological parameters of studied patients:

Haematological parameters	**Mean ± SD** **Patients (n = 60)**
Hb (g/dl)	8.14 ±1.78
WBC×10^9/L	2.19 ± 0.91
Platelets×10^9/L	55.35 ± 39.82
Reticulocyte count (%)	0.82 ±0.87
MCV (fl)	90.12 ± 12.5
MCH(pg)	31.1 ±4.98
MCHC(g/dl)	34.7 ± 2.51

Table 2: Causes of pancytopenia

Causes of pancytopenia	Frequency	Percent
Malignant blood diseases	31	51.7
Aplastic anaemia	10	16.7
Megaloblastic anaemia	10	16.7
Hypersplenism	6	10
Enteric fever	1	1.7
Kalazar	1	1.7
Secondary metastasis	1	1.7
Total	60	100

Table 3: Malignant blood diseases causing pancytopenia:

Malignant blood diseases	Frequency	Percent from(60) studied patients
Acute leukaemia	21 (67.7%)	35
Myelodysplastic syndrome	7 (22.6%)	11.7
Hairy cell leukaemia	2 (6.5%)	3.3
Myelofibrosis	1 (3.22%)	1.7
Total	31(100%)	51.7

Table 4: comparison of hematological parameters between the three major causes of pancytopenia:

	Diagnosis	No	Mean ±SD	P-value	Significance
Age	A. Acute leukemia	21	18.14±17.4	< 0.001	A X C B X C
	B. Aplastic anemia	10	26±21.20		
	C. Megaloblastic anemia	10	55.8±14.85		
HB (g/dl)	A. Acute leukemia	21	8.21±1.67	0.11	
	B. Aplastic anemia	10	6.85±1.57		
	C. Megaloblastic anemia	10	8.15± 1.92		
WBC×10^9/L	A. Acute leukemia	21	2.1 ± 0.9	0.04	A X C
	B. Aplastic anemia	10	2 ± 0.89		
	C. Megaloblastic anemia	10	2.89 ± 0.54		
Platelets×10^9/L	A. Acute leukemia	21	50 ± 34.3	< 0.001	A X C
	B. Aplastic anemia	10	22.1± 17.6		
	C. Megaloblastic anemia	10	92.1±41.32		
Reticulocyte Count (%)	A. Acute leukemia	21	0.74± 0.62	0.97	
	B. Aplastic anemia	10	0.71± 0.28		
	C. Megaloblastic anemia	10	0.71±0.30		
Bone marrow cellularity	A. Acute leukaemia	21	78.18±8.73	< 0.001	A X B A X C B X C
	B. Aplastic anemia	10	29.5 ± 6.4		
	C. Megaloblastic anemia	10	90±4.08		
Bone marrow Blast cell (%)	A. Acute leukaemia	21	62.42±23.8	< 0.001	A X B A X C
	B. Aplastic anemia	10	2.7±0.94		
	C. Megaloblastic anemia	10	2.5±0.97		