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Hyperleucocytosis in acute and chronic leukaemias (Myeloid & lymphoid Types)

Background: Leukemia is a clonal and uncontrolled proliferation of haematopoietic cells. The malignant cells take over the bone marrow and suppress normal haematopoiesis. Complications of leukemia include very high white blood cells (hyperleukocytosis) which could lead to an increase in the blood viscosity and leukostasis.

Objectives: A- To determine the prevalence of hyperleucocytosis in acute and chronic leukaemias of both myeloid and lymphoid types. B- To evaluate the hematological parameters of patients with hyperleucocytosis and those without.

Materials and Method: A total of 247 records of patients with newly diagnosed acute and chronic leukaemias were included in this cross sectional study. A total of 113 acute leukaemias (69 ALL and 44 AML patients) and 134 chronic leukaemias patient records were studied (CML and CLL). The diagnosis of leukaemia was based on criteria of the leukaemic cells in blood and bone marrow (FAB classification). Basic haematological tests (FBC) were done using calibrated automatic blood cell analyzers (CELL DYNE 3500R (USA) & Sysmex KX-21 models (Japan)) with peripheral blood and bone marrow morphological study done by hematopathologist. The diagnostic criteria of the laboratory evidence of hyperleucocytosis was based on the finding in the peripheral blood of white cell counts in excess of 50 , 300 and 800 $\times 10^9$/L in acute leukaemia (AL), chronic myeloid leukaemia (CML) and chronic lymphocytic leukaemia (CLL) patients, respectively.

Results: A relationship between hematological parameters and the type of leukaemia with hyperleucocytosis detected. Hyperleucocytosis found in 21/69 (30%), 22/44 (50%) and 14/134 (13%), ALL, AML and CML patients respectively. A statistically significance lower hemoglobin concentration in AL and CML patients with laboratory evidence of hyperleucocytosis than those without. Also, a statistically significant difference in the total white blood cell count follows the severity of anaemia in acute and chronic myeloid leukaemia patients found. A statistically significance younger age found in ALL patients with hyperleucocytosis than the AML counterpart. Hyperleucocytosis found in 14/31 (45%) of $M_1$to M_3 subtypes whereas it is found in 8/13 (62%) of M_4-M_5 subtypes of AML.

Conclusion: Hyperleucocytosis is more common in the myeloid than in the lymphoid types of leukaemia and associated with significantly lower hemoglobin concentration. It is more common in the monocytic subtype of AML. The severity of anaemia is significantly related to higher circulating total WBC count irrespective of leukaemia type.

Key Word: Acute leukaemia, chronic leukaemia, hyperleucocytosis, myeloid, lymphoid

INTRODUCTION

Acute leukemias (AL) are classified by the FAB (French-American-British) classification system based on the morphology and cytochemical stains. This FAB system is still used {1}.

Leucocytosis in acute leukemia present with high WBC count; a phenomenon known as hyperleukocytosis (WBC count exceeding 50 to 100 x 10^9/L) {2}. Acute lymphoblastic leukaemia (ALL) patients with a profoundly elevated leukocyte count at diagnosis (WBC count $\geq$50 x 10^9/) have poor prognosis. Hyperleukocytosis often represents a medical emergency in AL and the WBC count has a significant effect on the blood viscosity in the microcirculation at a level exceeding 50 x 10^9/L {2}.

About 15% of CML patients present with leukostasis when white cell counts exceeding 300 × 10^9/liter {3}. In CLL: leukocytosis in excess of 800 × 10^9/liter may produce blood hyperviscosity {4}.

Hyperleukocytosis (WBC count $\geq$100 X10^9/L) incidence ranges from 5% to 13% in adult acute myeloid leukemia (AML) and 10% to 30% in adult acute lymphoblastic leukemia (ALL) {5}.

However, in the microcirculation an increase in blood viscosity may be less important than the very high intrinsic viscosity and low deformability of

individual leukaemic blast cells. In addition, the high leucocyte count can affect the blood flow in the circulation of the lung by obstructing microchannels or by forming aggregates and white thrombi in small veins or the leukaemic cells may be invasive, damaging vessel walls. The large amount of fibrin degradation products may directly damage the pulmonary vasculature, leading to respiratory distress syndrome {6,7}.

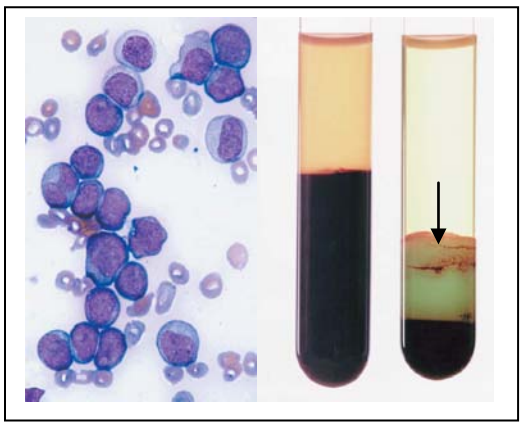

Figure I. Hyperleukocytic in acute myeloid leukemia (N Engl J Med 2003:349:767).

Hyperleukocytosis is associated with leukostasis in the lung, CNS, or genitourinary tract as a result of the intravascular flow-impeding effects of high white cell counts {8}. In AL, Leukostasis can occur with blast counts ≥ 50 $X10^9$/L, and the risk increases significantly with blast counts ≥100 $X10^9$/L {2}.In addition, hyperleukocytosis could also be defined as a blood blast cell count greater than 100 $X10^9$/L {5}. Patients with acute leukemia without hyperleukocytosis (<50 $X10^9$/L) may also develop leukostasis {9,10}. Leukostasis is most common with acute myeloid leukaemia (AML), particularly cases with monocytic differentiation, but can also be seen with ALL, chronic myelogenous leukemia (CML), and rarely chronic lymphocytic leukemia (CLL) {11}.

A high early mortality in patients with AML is correlated with hyperleukocytosis. These patients have metabolic abnormalities, coagulopathy, and multiple organ failure {12}. Acute hyperleukocytosis can mimic several viral, bacterial, and fungal syndromes. If it is not recognized and treated quickly, the mortality rate can be up to 40% {13}. Leukostasis has been described with blast counts of less than 50 $X10^9$/L {14}.

Spurious laboratory data associated with hyperleukocytosis include a falsely elevated platelet count (because white cell fragments are counted as platelets) and falsely prolonged coagulation tests {15}. Examination of a blood smear gives a more accurate assessment of the platelet count in this circumstance. Chemotherapy in hyperleukocytic patients may also lead to a pulmonary leukostatic syndrome, presumably from the effects of rigid blast cells or the effect of the discharge of large amounts of cell contents and resultant cell aggregation {16}.

Hyperleukocytosis with leukostasis is a medical emergency; the blast count must be lowered as soon as possible. Leukapheresis (removal of white cells by an apheresis machine) is used to rapidly reduce the blast count if there is evidence of leukostasis. {17,18}.

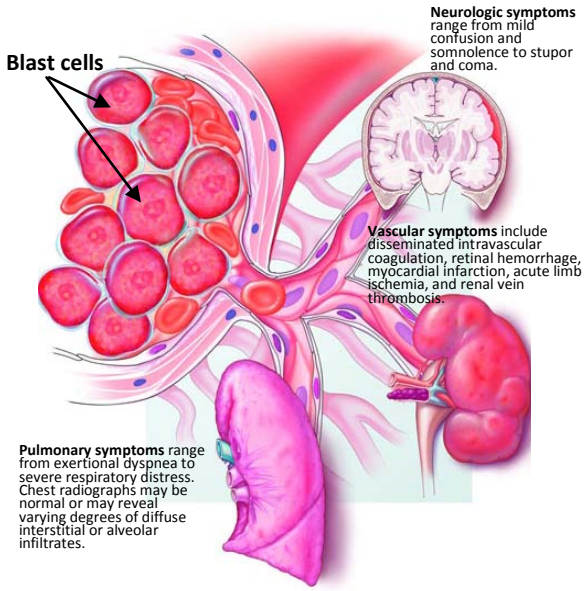

Figure II: Leukostasis, a syndrome caused by the sludging of circulating leukemic blasts in tissue microvasculature {5}.

Hyperleukocytosis (WBC count ≥ 100 x 10^9/L) incidence ranges from 5% to 13% in adult acute myeloid leukemia (AML) and 10% to 30% in adult acute lymphoblastic leukemia (ALL) {5}.

The hyperviscous blood causes slugging of blast cells at the low pressure venous end of the capillary bed, which leads to plugging and eventual rupture of the vessel. The bleeding that then occurs would go unnoticed in most organs, but not in the brain. Patients who undergo induction therapy with hyperleukocytosis are at extreme risk of tumor lysis syndrome, which can be fatal even if recognized early {18}. Patients with ALL are often treated similarly, even though symptoms are less frequent in this condition. Higher total WBC count in acute leukaemia is associated with increased tendency to

bleeding, pulmonary symptoms and haemostasis abnormalities {19}.

Chronic myeloid leukaemia (CML) is a stem cell neoplasia caused by translocation of chromosome 9 and 22 to create what is called Philadelphia chromosome. This translocation leads to uncontrolled cell growth and proliferation. The diagnosis of CLL requires a sustained monoclonal lymphocytosis greater than 5×10^9/liter {4}.

Risk factors for hyperleukocytosis include younger age (it is most commonly seen in infants) certain types of leukemia (microgranular variants of acute promyelocytic leukemia [AML-M3v], acute myelomonocytic leukemia [AML-M4], acute monocytic leukemia [AML-M5], and T-cell ALL), and cytogenetic abnormalities (11q23 translocations or presence of the Philadelphia chromosome){20,21}.

METHODOLOGY

Over seven months (from Nov. 2008 to May 2009), a total of 247 patient records of newly diagnosed acute and chronic leukaemias were included in this cross sectional study. A total of 113 acute leukaemias (69 ALL and 44 AML patients) and 134 chronic leukaemias patient records were studied (CML and CLL). Patient's data were collected in a study form that was designed for the purpose of this study (at the time of initial diagnosis and before receiving any therapy) from the teaching hospitals (mainly Al-Thawra teaching hospital and Al-Gomhori teaching hospital) and Alpha Specialist Medical Center in Sanaa-Yemen.

All the basic haematological tests (FBC) were done using calibrated automated blood cell analyzers (CELL DYNE 3500R (USA) & Sysmex KX-21 models (Japan)). Peripheral blood and bone marrow morphological study done by hematopathologist. The diagnosis of leukaemia was based on criteria of the leukaemic cells in blood and bone marrow.

Laboratory evidence of hyperleucocytosis was based on the finding in the peripheral blood of white cell counts in excess of 50 , 300 and 800 $\times 10^9$/L in AL {1}, CML {2} and CLL {3} patients, respectively.

The mean plus or minus standard deviation (Mean$\pm$ SD) and two sample "t" tests were employed for statistical evaluation of the results using standard methods by computer programs: Excel program under windows 2007 and SPSS programs in University of Thamar /College of Mathematics and Computer Science/Department of Statistics. p-value <0.05 considered statistically significant. Ethical approval of the study protocol obtained from the Ethical Committee.

RESULTS

The distribution of leukaemia patients studied showed that out of the total 113 patients with AL, 69/113 (61.1%) patients were ALL and 44/113 (38.9%) were AML. 108 (81%) out of the total 134 chronic leukaemia patients were CML and 25/134 (18.7%) were CLL. The mean age of ALL patients was 12.1$\pm$11.8 years & the mean age of AML patient was 25.1 $\pm$16.8 (Table 1).

Table 2 reveals that 43 out of total 113 (38%) AL patients had hyperleucocytosis (exceeding 50 $\times 10^9$/L) and 26 (23%) AL patients had hyperleucocytosis (exceeding 100×10^9/L). Hyperleucocytosis found in 14/134 (13%) CML patients (WBC count exceeding 300×10^9/L).

Data depicted in table 3 shows a statistically significance lower hemoglobin concentration in acute and chronic myeloid leukaemias with hyperleucocytosis than those without. Hyperleucocytosis found in 21/69 (30%) of ALL patients while it is present in 22/44 (50%) of AML patients and in 14/134 (13%) CML type of chronic leukaemia. A statistically significance younger age found in ALL patients with hyperleucocytosis than the AML counterpart.

Table 4 showed a statistically significant difference in the total white blood cell count follows the severity of anaemia in acute and chronic leukaemia patients.

Table 5 showed that Hyperleucocytosis found in 14/31 (45%) of $M_1$to M_3 subtypes whereas it is found in 8/13 (62%) of M_4-M_5 subtypes of AML.

DISCUSSION

In the present study, ALL type is more frequent compared to AML and the ALL is predominant in children. The majority 108/134 (81%) of chronic leukaemia is CML type. These figures agree with the known distribution of these diseases {4}

Hyperleucocytosis (WBC count $\geq$50 x 10^9/L) was found in 43/113 (38%) AL patients in the present study (Table 2) which is similar to other study (8/32 (35%) {19}. Lower figure where given by another study (7.3%) {23} which might be attributed to the sample size and the clinical design of the study. Hyperleucocytosis (WBC count $\geq$100 x 10^9/L) was found in 16/69 (23.2%) ALL patients & 10/44 (22.7%) AML patients studied. These figures are comparable with those of other study on ALL {24} and AML patients {25}.

The majority of CML patients (88/108 (81.5%) have total white counts over 100×10^9/L and hyperleucocytosis (white counts over 300×10^9/L) was detected in 14 /108 (13%) CML patients. This agrees with almost all standard works in this regard (Table 2) {3}.

The total WBC count in the majority of CL patients studied (105/108 (97%) CML cases and 25/26 CLL

(96%) cases) were exceeding 50 up to 653×10^9/L, this range is in agreement with the finding of another worker {26}.

A statistically significant lower hemoglobin concentration in patients with hyperleucocytosis than those without identified in both type of leukaemia (Table 3). The severity of anaemia is significantly related to higher circulating total WBC count irrespective of leukaemia type (Table 4). These findings might attributes to the degree of marrow infiltration and the degree of the suppression of erythropiesis that follow the severity of leukaemic burden or it might reflects the body compensatory mechanism to lower the red cell mass in patients with hyperleucocytosis aimed to lower the viscosity of the blood and improve blood flow in the microcirculation of vital organs. Furthermore, it is known that the automatic blood cell analyzer measurement of the hemoglobin is affected by the higher WBC count.

Hyperleukocytosis is more common in AML than in ALL. It is found in 21/69 (30%) of ALL patients while it is present in 22/44 (50%) of AML patients (Table 3). The frequency of early death found to be significantly higher in those with AML compared with ALL patients {8}. Moreover: patients found significantly younger in ALL with hyperleucocytosis than those with AML counterpart (Table 3). These might attribute to the globally known prevalence of ALL in younger age group {1}.

Most AML patients with hyperleukocytic leukaemia (62%) have the monocytic subtype (Table: V). This finding is in accordance with that of another studies {5,18}. The mean of the total WBC count were lower in the granulocytic AML (M1-M3) (114.5 x 10^9/L) than those with monocytic subtype (136.6 x 10^9/L). Leukostasis is usually associated with counts of >100 x10^9/L but acute monocytic leukaemia may present with leukostasis with counts of 50 x10^9/L due to the effects of the large monoblast cells in the development of hyperleucocytosis and its clinical manifestation {16,27,28}. It is suggested that the cell size of leucocytes may be an important factor in the development of hyperviscosity syndromes and organ malperfusion in leukaemic patients {29}.

Earlier, leukostasis was thought to be due presence of critical leukocrit (fractional leukocyte volume) and increased viscosity. Recently, pathogenesis of leukostasis attributes to: sluggish flow with stasis, interaction of endothelium and blast cell leading to aggregation of blast cells in microcirculature, formation of microthrombi, release of toxic granules, endothelial damage, oxygen consumption by leukocytes and tissue invasion {5}.

The interaction of endothelium and blast cell leads to aggregation of blast cell in microcirculation due to difference in expression of adhesion molecule in lymphoblast and myeloblast cell surface. The adhesion molecules expressed on the leukaemic blast cell and their interaction response to the cytokines in the vascular microenvironment is more important than the cell number {30,31}.

Those patients with hyperleukocytosis who undergo induction therapy are at extreme risk of tumor lysis syndrome, which can be fatal even if recognized early {22}. Leukapheresis permits the infusion of blood products and correction of metabolic abnormalities. Chemotherapy in hyperleukocytic patients may lead to a pulmonary leukostatic syndrome, presumably from the effects of rigid, effete blast cells or the effect of the discharge of large amounts of cell contents and resultant cell aggregation {32}.

Therapeutic leukapheresis has been performed in both acute and chronic leukemias. The usual goal is to relieve acute symptoms of hyperleukocytosis, but it has occasionally been used as a primary method of disease control. Leukapheresis reduces the burden of tumor cells subject to chemotherapeutically induced cytolysis and thus the production and the excretion of uric acid {32}. Patients with ALL are often treated similarly, even though symptoms are less frequent in this condition {33}.

The threshold white cell count for pulmonary and/or cerebral dysfunction (leukostasis) in patients with leukemia is not known.

Currently, leukapheresis therapy in CML is reserved for patients who have WBC counts of 300- 500 X10^9/L and signs of leukostasis. The same may be said of CLL. The extent to which the white cell count should be lowered is not known. In practice it is worthwhile to monitor the WBC count until there is a 30 to 50 % decline {31-33}. The short- and long-term benefits of leukapheresis remain in question {34}.

CONCLUSION

Hyperleucocytic leukaemia (HL) represent a particular variant of leukaemia, it require particular attention in diagnosis and treatment. The frequency of hyperleucocytosis in leukaemias is more in the myeloid types and found more in young age group. It is more common in the monocytic subtype of AML. Hyperleucocytosis is associated with lower hemoglobin concentration irrespective of leukaemia type.

RECOMMENDATIONS

Monitoring of the blood viscosity in patients with hyperleucocytic leukaemia recommended with particular attention to blood transfusion during initiation of therapy to prevent leukostasis and the fatal sequences.

Further studies are recommended in the future to study this leukaemia variant with more concern on the associated genetic defects.

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Table I. Distribution of studied patients according to their leukaemia type and age.

				Number (%)		Age (Years)	Number (%)
Leukaemias studied	**Total 247 (100%)**	Acute Leukaemia	ALL	69 (61.1)	Total 113 (100)	< 15	50 (72.5)
						≥ 15	19 (27.5)
			AML	44 (38.9)		< 15	15 (34)
						≥ 15	29 (66)
		Chronic Leukaemia	CML	108 (81)	Total 134 (100)	< 30	25 (23)
						≥ 30	83 (77)
			CLL	26 (19)		< 30	00
						≥ 30	26 (100)

ALL: Acute Lymphoblastic Leukaemia, AML: Acute Myeloid Leukaemia, CML: Chronic Myeloid Leukaemia, CLL: Chronic Lymphocytic Leukaemia.

Table II. Distribution of leucocytes count in leukaemia patients studied.

Leucocyte Parameters		ALL No.(%)	AML No.(%)	Total AL No.(%)	CML No.(%)	CLL No.(%)	Total CL No.(%)
		69 (61.1)	**44 (38.9)**	**113 (100)**	**108 (80.6)**	**26 (19.4)**	**134 (100)**
Total WBC count ($X10^9/L$)	**< 4**	6(8.7)	6(13.6)	12(10.6)	00	00	00
	4 – 11	20(29)	3(6.8)	23(20.4)	00	00	00
	12 – 49	22(31.9)	13(29.5)	35(31)	3 (2.8)	1 (3.8)	4 (3)
	50 – 100	5(7.2)	12(27.3)	17(15)	17(15.7)	7 (26.9)	24 (18)
	> 100-299	16(23.2)	10(22.7)	26(23)	74(68.5)	17(65.4)	91 (68)
	> 300-653	00	00	00	14 (13)	00	14 (13)

ALL: Acute Lymphoblastic Leukaemia, AML: Acute Myeloid Leukaemia, AL: Acute Leukaemia, CML: Chronic Myeloid Leukaemia, CLL: Chronic Lymphocytic Leukaemia, CL: Chronic Leukaemia.

Table III. Relationship of hyperleucocytosis with the leukaemia types and hematological parameters studied.

Parameter			Hyperleucocytosis in Leukaemias		Age (Years)	P-value
			Present	**Absent**		
Leukaemia type	Acute Leukaemia	Total	43/113(38.1%)	70/113(61.9%)		
		ALL	21/ 69(30%)	48/69 (70%)	16 ± 16	**0.03**
		AML	22/44(50%)	22/44 (50%)	26 ± 19	
	Chronic Leukaemia	Total	14/ 134 (13%)	94/134 (87%)		
		CML	14/ 134 (13%)	94/134 (87%)		
		CLL	00	00		
Haematological parameter	Hemoglobin (g/dl)	AL	7.76± 2.48	8.25± 2.63	**0.019**	
		CML	8.45± 1.8	9.5± 2.08	**0.04**	
	WBC count ($\times10^9$/L)	AL	164.71± 115.93	16.06± 13.51	**<0.001**	
		CML	406.6±123.2	178.01±76.9	**<0.001**	
	Platelet count ($\times10^9$/L)	AL	57.57± 95.38	73.74± 138.57	0.1	
		CML	353.07±345.3	481.9±259.9	**0.08**	

ALL: Acute Lymphoblastic Leukaemia, AML: Acute Myeloid Leukaemia, AL: Acute Leukaemia, CML: Chronic Myeloid Leukaemia.

Data presented as mean ±SD, P-value using t-test for two samples, statistically significant change (<0.05), highly significant changes (<0.001).

Table IV. Comparison among haematological parameters according to the severity of anaemia in leukaemias.

	Parameter	Severity of anaemia (Haemoglobin level)			p-value
		SEVERE ANAEMIA **(Hb: <6g/dl)** **Mean±SD.**	*MODERATE ANAEMIA* **(Hb: <6-9g/dl)** **Mean±SD.**	*MILD ANAEMIA* **(Hb: >9g/dl)** **Mean±SD.**	
Hemoglobin (g/dl)	AL	(4.39± 1.0)	(7.39± 1.25)	(10.59± 1.35)	***0.007***
	CML	(5.64±0.24)	(7.7±0.89)	(10.95±1.2)	0.1
	CLL	(4.1± 1.0)	(7.14±0.98)	(11.44±1.6)	0.01
WBC count ($\times 10^9$/L)	AL	(92.26± 149)	(69.38± 78)	(65.42± 93)	***0.03***
	CML	(156.5±70.3)	(249.6±118.5)	(179.5±103.4)	**0.02**
	CLL	(237)	(162.0±120.4)	(144.9±73.5)	**0.2**
Platelet count ($\times 10^9$/L)	AL	(23± 14)	(52.11± 84)	(107.45±171)	0.18
	CML	(460.8±377.0)	(487.7±289.7)	(448.1±255.9)	**0.01**
	CLL	(86±62)	(134.5±110.2)	(245.3±175.7)	0.2

Data presented as mean ±SD, P-value using ANOVA test, statistically significant change (<0.05).
ALL: Acute Lymphoblastic Leukaemia, AML: Acute Myeloid Leukaemia, AL: Acute Leukaemia, CML: Chronic Myeloid Leukaemia.

Table V. Comparison of AML patients with or without hyperleucocytosis according to the granulocytic and monocytic AML Subtypes.

			Granulocytic leukaemia (M_1 to M_3) 31/44 (70%)	**Monocytic Leukaemia** (M_4 & M_5) 13/44 (30%)
AML With hyperleucocytosis	**present**	No. /Total (%)	14/31 (45%)	8/13 (62 %)
		Mean WBC count	114.5	136.6
	absent	No./Total (%)	17/31 (55%)	5/13 (38 %)
		Mean WBC count	15	29

AML subtypes: (M_1 to M_3) (M_4-M_5)