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Haematology

CHARACTERISTICS OF HEMATOLOGICAL MALIGNANCIES IN SOUTH –WEST YEMEN

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ABSTRACT There is paucity of information on patterns of hematological malignancies (HM) in Taiz and IBB governorates situated in the south west of the country . This study was conducted to determine the distribution of various HM among patients who have underwent bone marrow aspiration, in Taiz and Ibb governorates Yemen.

Methods: Retrospective descriptive study of patients diagnosed with HM between September 2016 and October 2020 in the South West Yemen.

The FAB (French-American-British) classification system , immunophenotyping ,BCR ABL and Jack 2 gene mutations have been taken into account in the analysis of the cases .

Results: In this study, a total of 355 cases of HM were registered between September 2016 and October 2020 .Among the 355 registered cases of HM, 50.8 % were males and 49.2 % were females, with a male to female ratio of 1.1 : 1 . By contrast, a female predominance was observed in the case of multiple myeloma (MM), and myeloproliferative neoplasms (MPN) . Acute leukemias were diagnosed in 45.9 % the cases ,followed by chronic leukemias diagnosed in 26.2 % .acute lymphoblastic leukemia (ALL) was the first most common diagnosis seen in 23.6% of H.M cases ,followed by acute myeloblastic leukemia (AML) seen in 22.2%,chronic myeloid leukemia (CML)seen in 14.9% and chronic lymphocytic leukemia (CLL) seen in 11.2 % of H.M respectively .MPN were seen in 16.3 % cases ,MDS seen in 7.1 % ,multiple myeloma seen in 1.8 % .Lymphoma cases encountered in this study were incidentally diagnosed during staging for lymphoma and seen in 2.8 % cases .The majority of HM cases have been observed among patients aged more than 41y (51.5 %) followed by patients aged less than 41 years (48.3 %) of HM . Acute leukemias were the most common HM In adolescents and young adults .

Conclusions: This study provided for the first time the pattern and distribution of HM according to gender , age and presentation symptoms in South West Yemen .Our findings are consistent with other studies done in Yemen and neighboring countries and highlight the needs to establish a national cancer registry as a first step in cancer control in Yemen .

KEYWORDS : Hematological Malignancies ,Yemen, Taiz ,IBB ,Immuno phenotype, BCR/ABL ,JACK2

INTRODUCTION

Cancer is increasingly recognized as the critical public health problem in the world . According to the International Agency for Research on Cancer (IARC) in 2018, there were 18.1 million new cases and 9.6 million deaths from cancer; about one-half of the cases and over one-half of the cancer deaths in the world were in Asia [1].

In the developing world including Middle East there is horrible increase of cancer incidence. The annual number of new cancer cases is expected to double by 2020. Of these up to70 % of the 20 million new cases of cancer are predicted to occur in the developing world. [2]

Hematological malignancies (HM) are a group of cancers that arise from a malignant transformation of cells of the bone marrow or the lymphatic system [3] . According to the study by Ferlay J et al , HMs were estimated to represent about 6.5% of all cancers worldwide in 2012 [4]. Different etiological factors are believed to contribute to the development of these HMs as their incidence varies with geography, age and race/ethnicity. Even though environmental exposure to chemicals (such as pesticides, benzene, smoking etc.), as well as ionizing radiation and infectious agents are believed to be the causes of those malignancies, their exact cause remains unclear [5,6,7]

Leukaemias were among the most common malignancies in children throughout the world; Acute Lymphoblastic Leukaemia, (ALL), accounts for about 30% of all cases of cancers in children[8].

AIM OF THE STUDY

The aim of this study was to describe the pattern of bone marrow aspiration confirmed HM in Taiz and Ibb governorates located in south west Yemen based on common presenting sign and symptoms , age, gender and peripheral blood findings ,immunophenotyping and PCR based techniques namely BCR/ABLE fusion gene and Jack 2 mutations and comparing our results to other research published in Yemen (Taiz ,Sana'a , Aden) and others countries in the region .

MATERIAL AND METHODS

This retrospective descriptive study has been conducted in Specialized Hematological Referral Center in IBB city Yemen (Fig no1.)

One thousand and ten patients underwent bone marrow examination between September 2016 and October 2020 (Saeed et all)[9],among them 355 patients having HM were enrolled in this study, Inform consent was taken from patient and their relative (In childhood cases).[9]

In each case a detailed history with general and systemic examination and routine investigations (complete blood count, blood film study ,reticulocytes count and erythrocytes sedimentation rate and biochemical tests) were carried out prior to bone marrow examination.

The standard technique [10] of bone marrow aspiration was employed obtaining the samples from posterior iliac crest or from sternum by using a biopsy set needle (Disposable bone marrow aspiration and biopsy needles).About 0.5- 1 ml of marrow fluid was obtained and nearly about ten smears prepared. For some patients with acute leukemia, marrow materials were collected and sent to Sana'a Cancer Center laboratory for flow cytometry analysis . Also some patients with CML and MPN whom the diagnosis were not straight forward, specimens were sent for BCR- ABL fusion gene and JAK2 mutation respectively (fig no 2,3).[9,11]

The marrow was examined and interpreted and reviewed with consideration of the patient's clinical examination and laboratory

results . All information about the patients were register in our records including residence, age, gender , clinical features, organomegaly, complete blood picture, other related investigations and bone marrow examination report .

DATA ANALYSIS :
Statistical analysis was done on SPSS.Tables were used for presentation of the data. Percentages of the various categories of HMs and the relationship with demographic variables were explored using percentages in tables.

RESULTS :
355 patients were enrolled in the study between September 2016 –October 2020 ,among them there were 180 (50.8 %) males and 175(49.2 %) females and the M:F =1.1 :1 (Table 1) Mean of age was 33.3 years ,minimum was less than one year and maximum was more than 80 years .

The most common presenting symptoms in acute leukemias were fever ,anemia ,bone pain ,bleeding tendency followed by lymph node enlargement and hepatosplenomegaly .Table no 2 CML and CLL patients had left upper quadrant discomfort due to presence of splenomegaly seen in 47 % and 25 % respectively followed by 22 % in acute leukemias .Table no 2 Lymphadenopathy was seen in 45 % of CLL patients and 23% in ALL Table 3 showed the results of CBC in our patients expressed as mean value of each test .

The first most common diagnosis in our study were acute leukemias (ALL and AML) which were seen in 163 (45.9 %) cases , followed by chronic leukemias (CML and CLL) which were seen in 93 (26.2%) cases .The relative frequencies of them were as follow :

Acute lymphoblastic leukemia ALL , was the most prevalent condition and was seen in 84 patient (23.6 %) and was mostly seen in children and young adults and the FAB LI sub group was seen in 86.9 % followed by FAB L2 and the least was FAB L3 (Table no 4).

The immunophenotyping of the cases showed : B-ALL was seen in 92% of cases and T-ALL 8% of cases .Among cases of B-ALL 77% of cases showed c-ALL and 23% showed proB-ALL[11].

Acute myeloblastic leukemia was the second most prevalent leukemia diagnosed in 79 (22.2 %) of our cases and the FAB M4 and M1 were the most frequent subtypes of AML ,followed by FAB M2,3 and 5 .The diagnosis of AML cases were confirmed by Immunophenotype which show myeloid markers positivity.

Chronic myeloid leukemia (CML) was seen in 53(14. 9 %) patients with M:F was 1.5 :1 and was mostly seen in middle and old aged patients and most of them were seen in chronic phase CML ,and few cases were seen in acceleration phase and in transformation to AML or ALL.

Most cases of CML ,samples of peripheral blood were collected and sent to the Sana'a National Oncology Centre Lab for determination of BCR/ABLE fusion gene by real time PCR technique .The results of BCR/ABL fusion gene results by real time PCR showed 95 % of cases are positive for the mutated gene and 5 % of cases were negative which render theses cases as atypical CML or may be part of MPN which needs confirmation by Jack -2 determinations .

Chronic lymphocytic leukemia was seen in 40 (11.2 %) patients , with M:F was 1 :1,and as usual the disease was mostly seen in older age patient and most of them seen in stage 0 (RAI scoring system) Hairy cell leukemia seen in 2 of CLL cases. The immunophenotyping of these CLL cases were as follow :36 cases show B-CLL phenotype , 2 cases prolymphocytic CLL and 2 cases Hairy cell leukemia [11].

Myeloproliferative disorders (Table no) were seen in 58 (16.3 %) cases with F : M was 2 :1 ; Essential thrombocythemia was the most prevalent seen in 34 (9.5 %) of HM cases followed by myelofibrosis seen in 12 (3.4 %) of HM cases followed by polycythemia rubra vera seen in 10 (2.8 %) cases. Most cases with myeloproliferative disorders peripheral blood samples were collected and sent to the privet I-LAB center in Sana'a for determination of JAK -2 mutations by real time PCR technique .

The results of Jack 2 mutations in our cases were as follow :
40 (68 %) cases show mutated Jack 2 gene and 18(32 %) cases are negative and were mostly cases of MF and PRV cases.

Myelodysplastic syndrome was diagnosed in 25 (7.1 %) cases, with F : M was 1 :1 and was most prevalent in old age group ,and the subgroup refractory anemia (RA) and refractory anemia with excess of blasts (RAEB1-2) were the most prevalent in our cases .

Multiple myeloma was diagnosed in 7 (2 %) cases and was seen in old aged females .Lymphoma was seen in 9(2.5 %) cases and these cases were sent for the propose of staging of the diseases only because the main method of diagnosis is pathological biopsies for this reason we have small number of cases (Table no 4).

DISCUSSION
Hematological Malignancies (HM) in developing countries constitute major problem for patients ,relatives and for physician especially in countries were there are shortage of facilities for diagnosis like flow cytomatry ,cytogenetic and PCR based techniques, shortage of modern treatment of HM especially targeted therapies which nowadays play major role in the increase percentage of disease free survival and percentage of complete remission in the same time absence of bone marrow transplantation centers which constitute major difficulty for cure of many patients who failed to respond to classical treatment and face their inevitable destiny.

Despite the growing burden, cancer is receiving low attention by health policy makers and this could be due to either limited resources, the burdens of communicable diseases , other pressing public health problems, or it may be due to lack of awareness about the magnitude and burden of the diseases both at the present and future [12].

Yemen one of the developing countries who has major shortage of facilities especially nowadays when Yemeni people facing illegal and not fair dirty war since 7 years with major shortage of diagnostic and treatment material, because Yemen is under siege of brutal aggression countries .This study was aimed to give an idea about relative prevalence of HM in Taiz and Ibb governorates Yemen As to our knowledge, no study has investigated the distribution of HM in Taiz and Ibb governorates Yemen. It also remains a mystery whether the pattern of these malignancies follows a similar course to those reported in other countries .

Leukemia is common in Yemen and Acute lymphoblastic leukemia is the most common cancer seen in children in the world[13,14][15,16].

In our study acute lymphoblastic leukemia was the most common HM and accounting for 84(23.6 %) cases of the 355 HMs cases , whereas acute myeloblastic leukemia was the second most common HM accounting for 79(22.2 %) cases , chronic myeloid leukemia (CML)and chronic lymphocytic leukemia (CLL) were the third and the fourth most recurring HMs, accounting for 53(14.9 %) and 40 (11.2 %)of the cases respectively.

This was consistent with the studies done in Taiz Yemen (Radfan) Bawazeer (Aden) , Eretria and Bangladesh[17,18,19,20]

Similar results have been reported from Karachi reveal that ALL was the commonest type (Noor et al., 1989)[21], from Kuwait 44%, Saudi Arabia 34% and UAE 32% (Natneal Belai et al)[19].

Acute myeloblastic leukemia is the second most common HM in our study while previous studies indicated that AML is the first most common diagnosis in Sana'a (45.1 %) and Aden (39.5 %)[22,23] and the ALL is the second most common of adult leukemia(17.7%) in Sana'a (Al-gazaly et al)[22], and in Aden (27.9%) (Abdul Hamid)[24]

In our study lymphoma and multiple myeloma were less prevalent in comparison to studies done in Eastern Morocco [26],Nigeria [27] , Aden[25] which showed that NHL and HD is most prevalent than acute and chronic leukemia in the same time multiple myeloma was prevalent than Yemen[25] Eretria[19] ,in the same time lymphoma cases in our study are less because lymphoma diagnosis is mainly by lymph nodes biopsy not by bone marrow and theses cases send to us for staging proposes only .

From studies discussed HM have shown differences between developed and developing geographical areas ,ethnic /racial origins and between regions in the same country and these differences are due

to differences in socioeconomic states and cultural and environmental factors .

In our study MPN were diagnosed in (16.3 %) of HM cases which is higher than cases diagnosed in Eastern morocco (12.4 %) [26]and the result from Eretria[19] showed less cases with this diagnosis .

Myelodysplastic syndrome was seen in (7.1 %) in our study which was higher prevalence than studies in Eretria (4 %)and Eastern Morocco (3%)[19,26].

We encountered 7 cases (1.8 %) of multiple myeloma and correlated with biochemical, radiological and clinical findings compared to Agazali [13] reported 1.3 % of cases of multiple myeloma in contrast to Eastern Morocco (12.4 %) and Nigeria (20 %) [26,27]where the MM is highly prevalent [26,27,28]and these differences because of geographical , race and ethnic and environmental factors.

Anemia was constant finding in acute leukemia, MDS ,Lymphoma and multiple myeloma with Hb concentration between 7- 9 g /dl (see Table no 3) .In acute leukemia anemia was associated with throm bocytopenia (mean platelets 45.5x10^9 /l) and leucocytosis(mean WBC 55.2X10^9/L).

Chronic leukemias were associated with mild anemia ,leukocytosis and normal or reduced platelets(CLL).MPN were associated with platelet count more the 10^6x10^9/L especially ET subtype .MDS as usual is associated with pancytopenia (see table no 3)

The predominant age group in our leukemia patients were between 0.5 years and 20 years especially ALL cases ,while AML between 11 -40 years .CML was mostly seen between 21 -60 y and CLL , MDS and MM Were seen between 41-80 years .MPN were seen between 20-60 years .The most common presentation symptoms in our acute leukemia patients were ;fever ,pallor, bone pain and splenomegaly .Chronic leukemia patients presented mostly with pallor , splenomegaly and lymph nodes enlargement especially in CLL patients. This results are consistent with results reported by Abdul Hamid Aden Yemen [24] .

The immunophenotyping of the ALL cases showed : B-ALL which was seen in 92% of cases and T-ALL 8% of cases .Among cases of B-ALL 77% of cases showed c-ALL and 23% showed proB-ALL [11].Cases of AML showed myeloid markers mainlyCD34,CD33 ,CD117,CD13,and glycophorin A^{+}.[11] see Fig no2 .

The immunophenotyping of CLL cases were as follow :36 cases show B-CLL phenotype , 2 cases prolymphocytic CLL and 2 cases Hairy cell leukemia [11].

The results of BCR/ABL fusion gene by real time PCR in our cases of CML showed 95 % of cases are positive for the mutated gene and 5 % of cases were negative which render theses cases as atypical CML or may be part of MPN which needs confirmation by Jack -2 determinations [29] see Fig no 2.

The results of Jack 2 mutations in our MPN cases were as follow :
40 (68 %) cases show mutated Jack 2 gene and 18(32 %) cases are negative and were mostly cases of MF and ET cases which need detection of other mutations related to these conditions [29] see Fig no 1.

CONCLUSION:

This study provided for the first time the pattern and distribution of HM in Taiz and Ibb governorates situated in South West Yemen taking in account age ,gender ,presentation symptoms ,CBC ,immuno phenotyping BCR /ABL fusion gene and JAK 2 mutated gene by PCR based techniques .

Acute lympbhoblastic leukemia was the most common HM accounting for 23.6 % of all cases , followed by acute myeloblastic leukemia 22.2 %, CML 14.9 % ,CLL 11.2 % ,MPN 16.3 % ,MDS 7.1 % , Lymphoma 2.8 % ,and MM 1.8 % . Our findings are consistent with other studies done in Yemen and neighboring countries .

The outcome of acute leukemia in our country still poor because of multiple factors such as shortage of diagnostic techniques ,modern treatment ,absence of bone marrow transplantation centers, unfair war and aggression against Yemeni people for 7 years .

Recommendation :
Urgent need for national cancer registry ,introduction of modern diagnostic technology in every governorate ,urgent need for bone marrow transplantation center ,greater vigilance in the diagnosis and introduction of modern treatment of HM especially acute leukemia.

We are grateful to Mr. EEHAB SAIF AL ZAGEER for his valuable help in the registration of cases and typing of the paper.

Table no 1 Hematological malignancies according to number of patient and sex

	Disease	M	F	Total number	%
1	A.L.L	46	38	84	23.6
2	A.M.L	41	38	79	22.2
3	C.M.L	33	20	53	14.9
4	C.L.L	20	20	40	11.2
5	M.P.D	21	37	58	16.3
6	M.D.S	13	12	25	7.1
7	Lymphoma	6	3	9	2.8
8	Multiple Myeloma	0	7	7	1.8
ToTal		180	175	355	100%

Table no 2: Percentage of common presentation symptoms of our cases in different HM

	Disease	Fever	Anemia	Splenomegaly	Pancytopenia	Bone Pain	L.N.E
1	A.L.L	92%	94%	22%	24%	90%	21%
2	A.M.L	94%	95%	28%	35%	80%	7%
3	C.M.L	5%	28%	47%	0	27%	0
4	C.L.L	9%	18%	41%	0	5%	45%
5	M.P.D	0	0	11%	0	0	0
6	M.D.S	24%	32%	5%	42%	0	0
7	Lymphoma	90%	25%	25%	0	7%	92%
8	Multiple Myeloma	28%	57%	0	0	42%	0

Table no 3 : Mean Value of CBC IN Our Cases with Hematological Malignancies

Disease	Hb g/dL	WBC X10^9	PLX10^9	ESR/h	MCV fL	MCH pg	MCHC g/L	Retics %
A.L.L	7.9	55.2	45.3	83	83.1	28.1	33.2	0.8
A.M.L	7.2	32.1	114.2	112	85.2	28.9	32	2.4
C.M.L	10.2	174.7	416.9	31	84.3	29.1	34	1
C.L.L	11.5	77.5	199.9	52	86.5	28.3	32	0.8
M.P.D	11.1	22.2	1,147.2	19	72.6	23.5	32	0.6
M.D.S	9.1	4.3	101.3	70	87.1	29.6	33	1.5
Lymphoma	9.2	4.3	172.6	70	78.5	26.9	33	1.2
Multiple Myeloma	8.8	4.8	177.8	97.9	88.3	29.1	33	0.8

Table no 4 : Distribution of Hematological malignancies according to number ,gender and age groups

	Disease	<1 y	1-10 y	11-20 y	21-30y	31-40y	41-60 y	>60 y	N / %
1	A.L.L	6	29	25	8	4	6	6	84 / 23.6%
2	A.M.L	0	8	17	9	5	23	17	79 / 22.2%
3	C.M.L	0	0	4	13	10	20	6	53 / 14.9%
4	C.L.L	0	0	0	0	2	12	26	40 / 11.2 %
5	M.P.D	0	0	0	10	14	24	10	58 / 16.3%
6	M.D.S	0	0	0	0	6	10	9	25 / 7.1%
7	Lympho ma	0	0	1	2	2	3	1	9 / 2.8 %
8	Multiple Myeloma	0	0	0	0	0	2	5	7 / 1.8%

Fig no 1 :Location of Taiz and IBB governorates in the map of Yemen

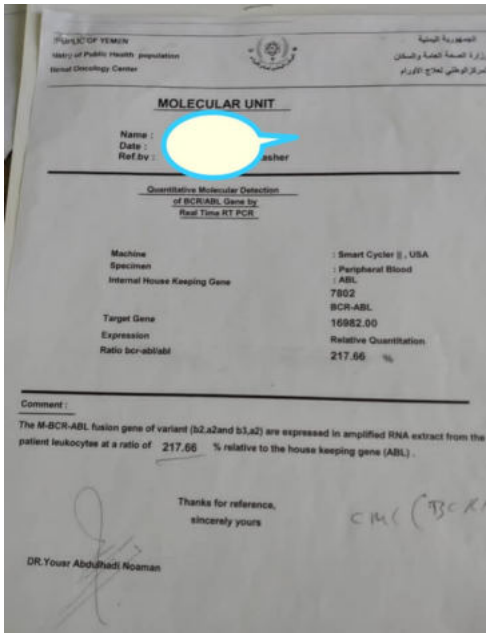

Fig no 2:Example of BCR/ABL fusion gene result in Yemen

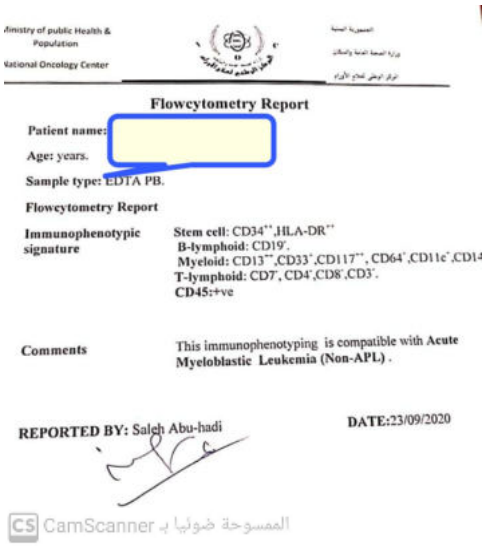

Fig no 3:Example of Immunophenotype result in Yemen

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