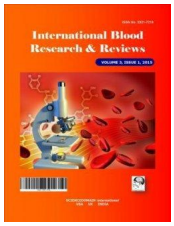

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Clinical and Haematological Pattern of Chronic Lymphocytic Leukaemia in Sudanese Patients

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Authors' contributions

This work was carried out in collaboration between both authors. Author RAEMA designed the study, performed the statistical analysis, wrote the protocol and wrote the manuscript. Author IMO managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: Chronic lymphocytic leukemia is the most frequent adult leukemia in Western countries accounting for 25 to 30% of all leukemic patients. The clinical and haematological features vary from patient to patient. The aim of this study is to describe the clinical presentation of chronic lymphocytic leukemia, to evaluate haematological patterns of the disease in the peripheral blood and bone marrow and to correlate them with the clinical stage of the disease.
Study Design: This is a retrospective descriptive study.
Place and Duration: Radio Isotope Centre Khartoum (RICK), haematology laboratory during the period of January 2010 to December 2011.
Methodology: The data were collected at the haematology laboratory from patients' records as well as from a special questionnaire designed for this study. Clinical data, complete blood count, bone marrow examination and immunophenotyping results were used.
Results: Out of 98 cases studied 69 (70.4%) were males and 29 (29.6%) were females. Sixteen patients (16.3%) were less than 50 years old (young patients) and 82 (83.7%) were more than 50

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years of age (elderly patients). 49.1% of the patients were from western Sudan. Eight patients (8.2%) were asymptomatic. Absolute lymphocyte count above 5× 10^9/L had significant association with diffuse pattern of infiltration (*P* value=0.035) and was not significantly associated with advanced Rai stage (stage III 32.6%, Rai stage IV 22.8%) (P value=0.710).

Conclusion: Clinical and haematological pattern of chronic lymphocytic leukaemia in Sudanese patients has comparable results with previous studies in other parts of the world. Most of the patients were elderly male, from western Sudan presented with nonspecific symptoms, generalized lymphadenopathy and leukocytosis. The majority of patients presented in advanced stage at the diagnosis.

Keywords: Chronic lymphocytic leukemia; clinical presentation; hematological findings; pattern of infiltration and staging of chronic lymphocytic leukaemia.

1. INTRODUCTION

Lymphoproliferative disorders are a set of disorders characterized by the abnormal proliferation of lymphocytes into a monoclonal lymphocytosis. The two major types of lymphocytes are B cells and T cells, which are derived from pluripotent hematopoietic stem cells in the bone marrow [1].

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of mature-appearing lymphocytes in the blood, bone marrow, lymph nodes, and spleen. The Chronic lymphocytic leukemia (CLL) cells are monoclonal B lymphocytes that express CD19, CD5, and CD23, with weak or no expression of surface immunoglobulin (Ig), CD20, CD79b, and FMC7 [2]. Chronic lymphocytic leukemia (CLL) accounts for 22.6% of all leukemias, and the incidence is 3.35 to 3.69 per 100,000 per year for men and 1.61 to 1.92 per 100,000 per year for women [3]. The disease is rare in young people but the incidence rises in the fourth decade. Several factors are involved in the pathogenesis of Chronic Lymphocytic Leukemia (CLL), including antigen stimulation within specific microenvironments and failure to undergo apoptosis [4].

In at least 50% of patients, the disease is diagnosed by chance, following a routine blood examination [4]. Constitutional symptoms are present in approximately 15% of patients at diagnosis, with night sweats, weight loss, and fatigue being more frequent than disease-related fever [5]. Physical examination generally reveals non tender, painless, and mobile lymphadenopathy [6], splenomegaly, or hepatomegaly. Manifestations of bone marrow (BM) involvement, particularly significant anemia (hemoglobin <11 g/dl) or thrombocytopenia (platelets count < 100 × 10^9/l), are noted at presentation in 15% of CLL patients. A positive direct antiglobulin test (DAT) is present in about 20% of patients at diagnosis [7].

Morphologically, the lymphocytes in blood films are small and show scanty cytoplasm and a characteristic pattern of nuclear chromatin clumping; the nucleolus is inconspicuous [4]. The peripheral blood should exhibit an increase in the number of small mature-appearing lymphocytes to >5,000/µl, which are (CD19 + CD20 +) and they should fulfil the characteristic CLL phenotype, i.e. CD5 +, CD23 +, weak or negative staining with FMC7 and CD79b, and weak expression of monoclonal surface membrane immunoglobulin (staining for κ or λ) [8].

The BM aspirate smear must show >30% of all nucleated cells to be lymphoid. Although the type of marrow infiltration (diffuse *vs.* nondiffuse) reflects the tumor burden and provides some prognostic information, recent results suggest that the prognostic value of BM biopsy may now be superseded by new prognostic markers [9].

A marrow aspirate/biopsy is not required for diagnosis but may be useful under the following circumstances:

- To assess normal marrow reserve and to establish the cause of anemia and thrombocytopenia for patients with Rai stage III or IV disease. Thus, the anemia/thrombocytopenia may be related to marrow replacement by CLL but could be secondary to other causes, e.g., myelodysplasia, red cell aplasia, autoimmune cause, or iron deficiency.
- To confirm that there is no paratrabecular localization or cyclin D1 staining in atypical cases [10].

- To assess the pattern of marrow infiltration, this is of prognostic value.
- To assess response following chemotherapy. As discussed later, obtaining a minimal residual disease (MRD)–negative marrow following chemotherapy predicts for a prolonged remission [11].

There are two widely accepted staging methods for use in both patient care and clinical trials: the Rai system and the Binet system [12]. The original Rai classification was modified to reduce the number of prognostic groups from 5 to 3 [13]. As such, both systems now describe 3 major subgroups with discrete clinical outcomes.

The modified Rai classification defines low-risk disease as patients who have lymphocytosis with leukemia cells in the blood and/bone marrow (lymphoid cells > 30%; formerly considered Rai stage 0). Patients with lymphocytosis enlarged nodes at any site, and splenomegaly and/or hepatomegaly (lymph nodes being palpable or not) are defined as having intermediate-risk disease (formerly considered Rai stage I or stage II). High-risk disease includes patients with disease-related anemia (as defined by a hemoglobin [Hb] level < 110 g/L [11 g/dL]; formerly stage III) or thrombocytopenia (as defined by a platelet count < 100×10^9/L; formerly stage IV)[14].

Staging is based on the number of involved areas, as defined by the presence of enlarged lymph nodes of greater than 1 cm in diameter or organomegaly, and on whether there is anemia or thrombocytopenia. Areas of involvement considered for staging are presented below:

1. Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of lymph nodes is enlarged).
2. Axillae (involvement of both axillae counts as one area).
3. Groins, including superficial femorals (involvement of both groins counts as one area).
4. Palpable spleen.
5. Palpable liver (clinically enlarged).

Stage A: Hb 100 g/L (10 g/dL) or more and platelets 100×10^9/L or more and up to two of the above areas involved.

Stage B: Hb 100 g/L (10 g/dL) or more and platelets 100×10^9/L or more and organomegaly greater than that defined for stage A (i.e., three or more areas of nodal or organ enlargement).

Stage C: All patients who have Hb less than 100 g/L (10 g/dL) and/or a platelet count less than 100×10^9/L, irrespective of organomegaly [14] .

Chronic lymphocytic leukemia (CLL) has different clinical and haematological features and varies from patient to patient. It also has different immunophenotypic markers therefore studying these groups of patients with chronic lymphocytic leukaemia and their clinical and haematological features can provide clues about the pattern of presentation and the diagnostic findings and may help in the management, assessment of the response and prognosis. To the best of our knowledge no such study has been published in Sudan in order to show the clinical and haematological pattern of chronic lymphocytic leukaemia and our work aims to fill in the gap in this aspect.

2. MATERIALS AND METHODS

2.1 Study Design

This is a retrospective descriptive study designed to study the demographical, clinical and haematological patterns of chronic lymphocytic leukaemia in Sudanese patients attending the Radio Isotope Centre Khartoum (RICK) in the period from January 2010 to December 2011.

2.2 Study Area

The study was conducted at Radio Isotope Centre Khartoum (RICK) laboratory, department of haematology. Radio Isotope Centre Khartoum (RICK) is the major national oncology hospital in Khartoum providing diagnostic, therapeutic, training and research services.

2.3 Study Population and Sampling

Patients diagnosed as having chronic lymphocytic leukaemia, based on flow cytometry results, during the set period of the study were included in the study.

2.4 Data Processing

Data were entered and analyzed using statistical analysis soft wired SPSS (statistical package for social sciences) 11.5 version.

2.5 Ethical Considerations

This study poses no physical risk to participants. The Radio Isotope Centre Khartoum (RICK) general manager and the head of the laboratory service approved this study. Each participant was assigned a unique identification number. Collected data were secured and used only for research purposes.

2.6 Methodology

Data were collected from records by filling a special questionnaire designed for the study. Clinical data, complete blood count, bone marrow examination (two bone marrow aspiration slides which were already stained by Wright stain and two trephine biopsies, one stained using Haematoxylin & Eosin (H&E) stain and the other using silver stain) and immunophenotyping results were revised and reinterpreted. Fibrosis was graded according to World Health Organization (WHO)-defined 4-point scoring system (0-3) [15].

3. RESULTS

Out of 98 cases studied 69 (70.4%) were males and 29 (29.6%) were females. The average age of patients ranged between (46-75) years with predominance of male (*P* value =0.323) [Fig. 1].

Almost half of the patients were from the western part of Sudan (49.1%), 26 (26.5%) from Northern Sudan, 16 (16.3%) from Central Sudan, 6 (6.1%) and 2 (2%) were from Eastern and Southern Sudan.

Eight patients (8.2%) were asymptomatic and were diagnosed accidentally during a routine examination. Most of patients presented non-specific symptoms (53%) followed by fever (28.6%), weight loss (6.1%) and night sweating (4.1%). Generalized lymphadenopathy was seen in 91.8% of patients, hepatosplenomegally in 37.8%, splenomegally in 20.4% and hepatomegally in 3.1%. Most of patients presented leucocytosis (88.8%) and 86.7% had anemia with hemoglobin <11 g/dl. Thrombocytopenia with platelet count <100 x 10^9/L was seen in 49 cases (50%).

Collectively, our data showed that the median white blood cell count and absolute lymphocyte counts were 107.670×10^9/L and 87.136×10^9/L respectively. The most common pattern of lymphocytes infiltration in bone marrow was the diffuse one (75.5%) and occurred mostly in age group 46-60 years (*P* value=0.093). This was followed by interstitial pattern in 20.4% (common between age group 61-75 years) and nodular pattern 4.1% (common between age group 61-75 years) [Table 1].

The relationship between the absolute lymphocyte count and the pattern of infiltration and Rai staging system is shown in [Fig. 2] and [Table 2].

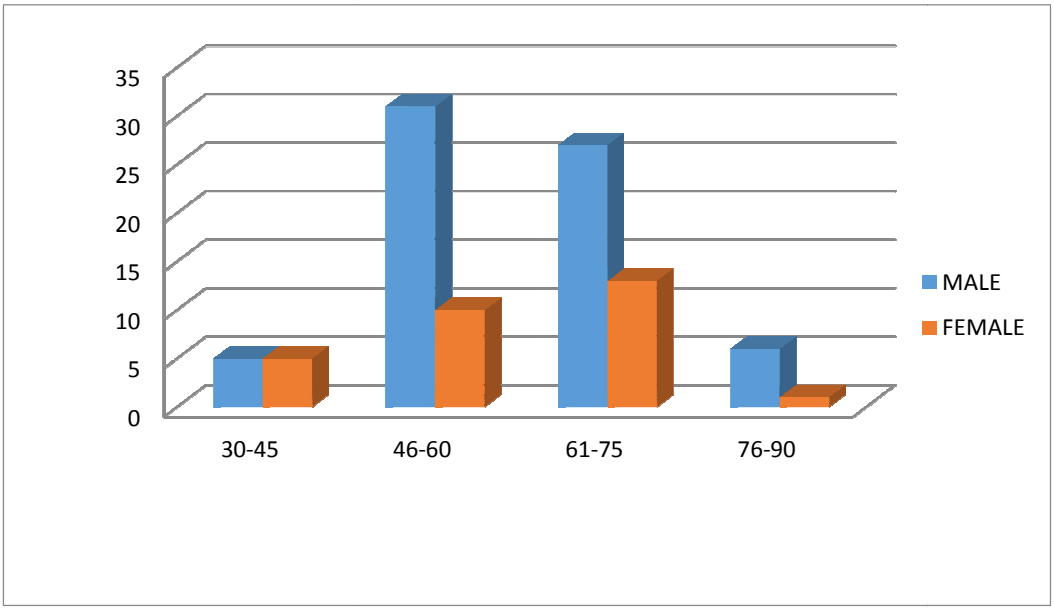

Fig. 1. Age groups according to the gender (n=98)

Table 1. Pattern of infiltration in relation to age group (n=98)

			Infiltration			Total
			Diffuse	Nodular	Interstitial	
Age groups	30-45	Count	7	1	2	10
		% within Age Groups	70%	10%	20%	100.0%
		% within Infiltration	9.5%	25.0%	10.0%	10.0%
	46-60	Count	35	0	6	41
		% within Age Groups	85.4%	.0%	14.6%	100.0%
		% within Infiltration	47.3%	.0%	30.0%	41.0%
	61-75	Count	29	3	8	40
		% within Age Groups	72.5%	7.5%	20%	100.0%
		% within Infiltration	39.2%	75.0%	40.0%	40.0%
	76-90	Count	3	0	4	7
		% within Age Groups	42.9%	.0%	57.1%	100.0%
		% within Infiltration	4.1%	.0%	20.0%	7.0%
Total		Count	74	4	20	98
		% within Age Groups	76.0%	4.0%	20.0%	100.0%
		% within Infiltration	100.0%	100.0%	100.0%	100.0%

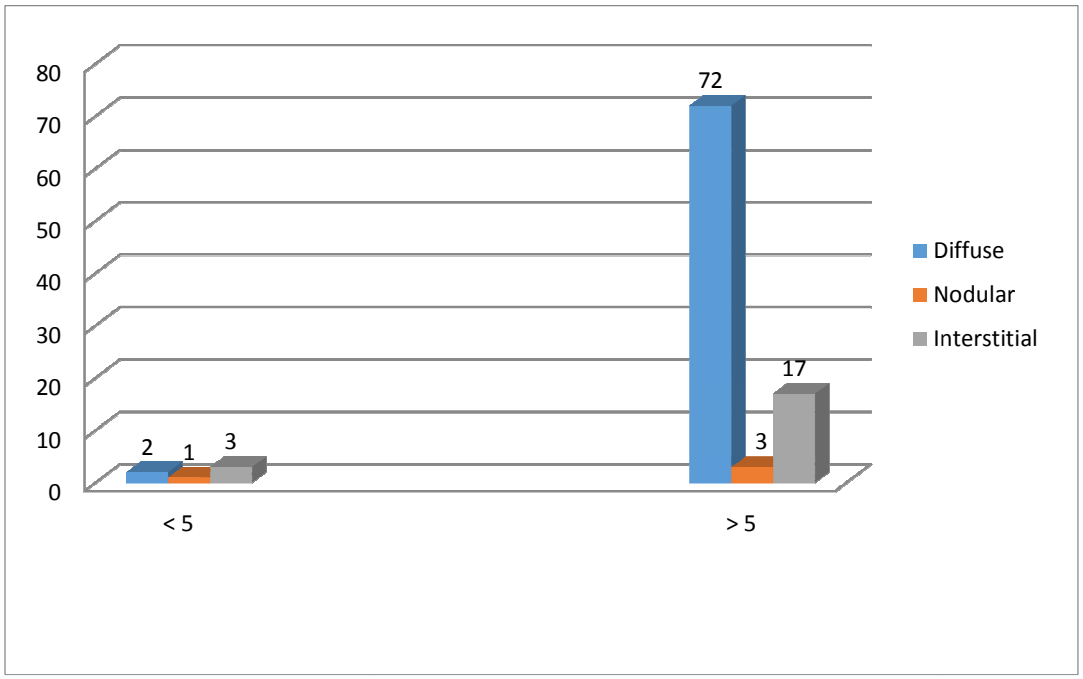

Fig. 2. Absolute lymphocyte count in relation to pattern of infiltration (n=98)

Table 2. Absolute lymphocytes count in relation to Rai staging system (n=98)

			Rai staging					Total
			Stage 0	Stage I	Stage II	Stage III	Stage IV	
Absolute lymphocytes count group	< 5	Count	0	2	2	1	1	6
		% within Absolute lymphcyte count groups	.0%	33.3%	33.3%	16.7%	16.7%	100.0%
		% within Rai classification	.0%	11.1%	9.5%	3.1%	4.3%	6.1%
	> 5	Count	6	16	19	30	21	92
		% within Absolute lymphcyte count groups	6.5%	17.4%	20.7%	32.6%	22.8%	100.0%
		% within Rai classification	100.0%	88.9%	90.5%	96.8%	95.5%	93.9.0 %
Total		Count	6	18	21	31	22	98
		% within Absolute lymphcyte count groups	6.1%	18.4%	21.4%	31.6%	22.5%	100.0%
		% within Rai classification	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Grade 0 fibrosis in the bone marrow was seen in (63.2%) of patients, grade 1 in 10.2%, grade 2 in 18.4% and grade 3 in 8.2%.

Stage III was the common stage of Rai staging system in 31.6% of patients followed by stage IV in 22.5%, stage II in 21.4%, stage I in 18.4% and stage in 0 6.1% with male predominance in all stages (*P* value=0.587).

Fifty two cases (53.1%) were class (C) according to international working party classification (Binet), 32.7% were class (B) and 14.3% were class (A) with male predominance in all classes (*P* value=0.697) (53.1%).

4. DISCUSSION

Chronic lymphocytic leukemia is the most common leukemia amongst adults in the Western countries, accounting for 25- 30% of all leukemias. The prevalence of chronic lymphocytic leukemia in Sudan is unknown. Statistics from the Radio Isotope Centre-Khartoum (RICK) revealed that the percentage of new cases of Chronic lymphocytic leukemia (CLL) were 2.54% in 2010 and 2.38% in 2011 of all leukaemia.

Most reported studies on CLL are from the Western world, and no comparable studies have been done for the Sudanese population. There are some similarities and differences between this study and other studies conducted around the world.

Chronic lymphocytic leukemia (CLL) is a disease of the elderly population with median age of 70 years, with 81% of the patients being diagnosed at age 60 years or older [16]. The median age in this study was 60 years. In this study there was also a higher percentage (16.3%) of young Chronic lymphocytic leukemia (CLL) patients (<50 years) than that reported in similar studies conducted by Mauro et al. [17] in Italy (10%) and by Karmiris et al. [18] in Britain (12%). The male to female ratio was 2.4:1 in this study. In literature the sex ratio has been reported as 1.5-2:1 as mentioned by Karmiris et al. [18] and Molica et al. [19]. This male predominant in this study may be due to the fact that males are comparatively more exposed to occupational and environmental carcinogens as has been suggested by Bhutani et al. [20]. In the present study almost half of the patients were from western Sudan (49.1%) and this may be due to environmental or genetic susceptibility.

The literature has reported an accidental diagnosis of Chronic Lymphocytic Leukemia (CLL) in about 30-35% cases [19,6]. Our data, regarding accidental diagnosis, showed a considerable lower percentage (8.2%) something that may be due to lack of improvement in the

diagnostic methods and health care system in Sudan.

The most common presenting symptom in CLL was lymphadenopathy in studies conducted by Molica et al. [19] and Omoti et al. [21], and similar findings were also observed in our study. Hepatomegaly and splenomegaly were present in 3.1% and 20.4% of cases respectively in contrast to 10% and 20% as reported by Rozman et al. [22] in a study done in Spain. The median white blood cell count and absolute lymphocytes count were 107.670 $\times 10^9$/L and 87.136$\times 10^9$/L respectively in this study which is higher than that reported by Agrawal et al. [23] in India.

According to the World Health Organization (WHO) classification, lymphocytosis in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma is defined as an absolute lymphocytes count of at least 10×10^9/L, but the diagnosis of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma can still be made with a lower absolute lymphocyte count (ALC) if morphologic and immunophenotypic features are typical of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [24].

In this study the most common pattern of infiltration in the bone marrow was the diffuse pattern, 75.5% of cases, followed by the interstitial, 20.4% of case, and the nodular pattern in 4.1% od cases. This differs from a study conducted by Baliakas et al. [25] in which the interstitial pattern predominated among the others patterns.

In this study 6.1% of patients had an absolute lymphocyte count (ALC) $<5\times 10^9$/L along with less extensive bone marrow infiltration (*P value*=0.035) and early stage of Chronic Lymphocytic Leukaemia than patients with absolute lymphocyte count (ALC) > 5×10^9/L. Similar data have been previously reported by Tsimberidou et al. [26].

Fibrosis was seen in 36.7% of cases and this may be due to secondary myelofibrosis which is not an uncommon event in Chronic Lymphocytic Leukaemia, occurring in 20–30% of all cases [27]. These data are consistent with work presented by Shatseva et al. [28] in a study conducted in Russia where 60% of Chronic Lymphocytic Leukaemia patients had bone marrow fibrosis.

Due to the fact that developed countries have better health care systems there is a likelihood that CLL patients will be diagnosed in the early stages [19]. Work by Rozman and Montserrat revealed that about 50 – 60% of patients with Chronic Lymphocytic Leukaemia in developed countries are diagnosed with stage 0 and I disease and 10 – 20% with advanced stages [6]. In this study only 24.5% of patients were diagnosed with stage 0 and I while the majority of patients, 54.1%, was diagnosed with stage III and IV. These results show that most of the patients are diagnosed during late stages. Similar results were also observed in India by Gogia et al. [29] in which 26% of patients were diagnosed during stage 0 and I and 41% during stage III and IV. The reason for this is that in developing countries the health care infrastructure is not up to international standards due to lack of funds and resources.

5. CONCLUSION

The median age of CLL patients in Sudan was 60 years. Patients' ages ranged between 46-75 years with male prevalence. Almost half of the patients were from western Sudan. The most common clinical presentation were nonspecific complains and generalized lymphadenopathy. Anaemia, thrombocytopenia and leukocytosis were the most common haematological findings in complete blood count. The majority of patients were presented with a diffuse pattern of infiltration in the bone marrow and advanced clinical stage.

CONSENT

It is not applicable.

ACKNOWLEDGEMENTS

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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QUESTIONNAIRE

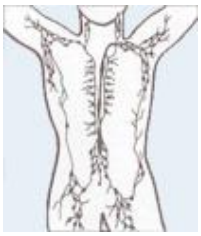
University of Khartoum
The Graduate College
Medical and Health Studies Board

Questionnaire about clinical and haematological pattern of Chronic Lymphocytic Leukaemia in Sudanese patients from Jan 2010- Dec 2011.

ID no: ☐ Name …… Dr. In charge: …… Tel: .....
Age: …….. sex…… Tribe……..

Clinical data: **Lymph nodes**

Symptoms	Score	O/E	
No complain		Spleen	
Fever		Liver	
Weight loss			
Night sweating			
Swelling			
N.S.C			



CBC results:

Hb	TWBCs	PLt	RBCs	Lymph %	ALC

Bone Marrow results:

Mega	Erythoid	Myeloid	Lymph %	Infiltration	Fibrosis in T.B

Rai stage …….. IWP classification ……..

Date: ……

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/17779