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Research article

Clinical presentation and complications of chronic lymphocytic leukemia among Sudanese patients

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Abstract

Chronic lymphocytic leukemia which is the most common leukemia in the western population particularly in the population aged more than 50 years, it is also common in Sudan Patients may present with localized or generalized lymphadenopathy, hepatosplenomegaly, anemia, thrombocytopenia or systemic symptoms. The majority of CLL patients are, however, asymptomatic and the diagnosis can only be achieved by the incidental finding of abnormal complete blood counts (CBC). The aim of this study is to determine the clinical presentations and complications of Sudanese CLL patients diagnosed at radiation & isotopes center (Khartoum), in the period 2008-2012. This is a retrospective prospective study in which one hundred patients were included. The most frequent age group was 70-79 years old (33%), with the male to female ratio of 1.2:1. Only 11% of patients were younger than the age of 50. Clinical findings at

presentation included fever (54%), weight loss (66%),splenomegaly (86%), lymphadenopathy (70%), hepatomegaly (61%), anemia (47%) & thrombocytopenia (52%). About 87% of Sudanese patients were diagnosed incidentally. Only 19%, 9% of patients did immunophenotyping and coomb's test respectively, the majority was positive (77%). Infection was the most common complication (52%), particularly among the elderly patients. This study concluded that the age and gender of Sudanese CLL patients were similar to those of the western countries but our patients came to medical attention, like solid tumors, at a later and more advanced disease. The most common clinical presentation in Sudanese patients was spleenomegaly followed by lymphadenopathy, loss of weight, hepatomegaly, thrombocytopenia and the least presentation was anaemia.

Key words: leukaemia, lymphoid series, spleen, lymph nodes

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by extensive proliferation and accumulation of small lymphocytes in the blood, bone marrow and lymphoid organs [(1)]. CLL is considered to be mainly a disease of the elderly, with a median age at diagnosis of 70 years; however, it is not unusual to make this diagnosis in younger individuals from 30 to 39 years of age [(2)]. The incidence of CLL varies by race and geographic location in the United States, there is a higher incidence among Caucasians as compared with African Americans or Asian Pacific Islanders [(2)]. For no known reasons, the incidence of CLL is very low in Asian countries such as China and Japan, where it is estimated to occur at a frequency that is approximately 10 % in the Western world [(3)] .

Genetic factors rather than environmental factors are the most likely explanation for these differences, since Japanese who settled in Hawaii do not have a higher incidence of CLL than native Japanese [(4, 5)]. Furthermore, there are some similarities in the cytogenetic and molecular genetic characteristics of CLL between Japan and the western world, although one study suggests that the clinical course may be more aggressive [(6)]. The incidence of CLL in Africa is not as low as it is in Asia [(7)].

Clinical presentation of CLL:

There is a wide range of symptoms, physical and laboratory abnormalities among patients with CLL at the time of diagnosis. Patients may present with localized or generalized lymphadenopathy, hepatosplenomegaly, anemia, thrombocytopenia or systemic symptoms. The majority of CLL patients are, however, asymptomatic and the diagnosis can only be achieved by the incidental finding of abnormal complete blood counts (CBC) [(8)].

Approximately 25 percent of patients feel entirely well with no symptoms when a routine blood count reveals an absolute lymphocytosis, leading to a diagnosis of CLL. Five to 10 percent of patients present with the typical "B" symptoms of lymphoma which include one or more of the following: loss of weight ≥10 percent of body weight within the last six months, fever of >100.5ºF (>38ºC) for ≥2 weeks without evidence of infection, drenching night sweats without evidence of infection and fatigue [(9)].

Occasionally, the presenting features are those of an acquired immunodeficiency disorder, manifested by infections mainly respiratory, autoimmune complications such as hemolytic anemia, thrombocytopenia or pure red cell aplasia, or an exaggerated reaction to insect stings or bites (especially mosquito).

Lymphadenopathy is the most common abnormal finding on physical examination of the patient with CLL, present in 50 to 90 percent of patients among various series [(10)]. Lymph node enlargement may be generalized or localized and individual lymph nodes can vary greatly in size. The most commonly affected sites are cervical, supraclavicular, and axillary areas

The spleen is the second most frequently enlarged lymphoid organ, being palpably enlarged in 25 to 55 percent of cases. As is the case with enlarged lymph nodes, the enlarged spleen in CLL is usually painless, and nontender to palpation, with a sharp edge and a smooth firm surface. Painful and infarcted splenic enlargement is an unusual feature of presentation [(10)].

At the time of initial diagnosis an enlarged liver may be noted in 15 to 25 percent of cases [34]. It is usually only mildly enlarged, ranging from 2 to 6 cm below the right costal margin, with a span of dullness to percussion of about 10 to 16 cm. Upon palpation, the liver is usually nontender and firm with a smooth surface [(10)].

Infiltration with CLL cells may occur in any organ, but, at the time of diagnosis, the skin (leukemia cutis-LC) is the most commonly involved non-lymphoid organ. These lesions most commonly involve the face and can manifest as different lesions (macules, papules, plaques, nodules, ulcers, or blisters) [(11)] .

Virtually any lymphoid tissue may be enlarged at diagnosis, including the tonsils. In contrast to other lymphomas, gastrointestinal mucosal involvement is rarely seen in CLL and also meningeal leukemia is unusual at the time of initial presentation. Currently, no curative therapy exists for CLL patients and eventually the patients will end with death either due to lymphoma transformation, associated infections or other unrelated causes. The overall survival of CLL patients varies from less than a year to over 10 years depending on their stages and prognostic features [(1)].

Laboratory abnormalities:

Lymphocytosis is the the most common laboratory abnormality found in CLL in the peripheral blood. Although the absolute blood lymphocyte threshold for diagnosing CLL has been changed at >5000/microL [5 x 10(9)/L] B lymphocytes, a significant proportion of patients present with counts as high as 100,000/microL [100 x 10(9)/L]. CLL cells co express the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23. The levels of surface immunoglobulin, CD20, and CD79b are characteristically low compared with those found on normal B cells [(12)] .In contrast, B-cell PLL cells do not express CD5 in half of the cases, and typically express high levels of CD20 and surface I [(13)].

The triad of neutropenia, anemia and thrombocytopenia may be observed at the time of initial diagnosis, and are usually not severe. These can be related to autoimmune hemolytic anemia, pure red cell aplasia, autoimmune thrombocytopenia, or agranulocytosis. The direct antiglobulin (Coombs') test (DAT) may be positive at some time during the course of the disease in up to 35 percent of cases [13].

Complications:

Chronic lymphocytic leukemia (CLL) is characterized by the progressive accumulation of monoclonal, functionally incompetent lymphocytes. Patients with CLL commonly develop complications associated with an intrinsic immune dysfunction that results in immunodeficiency and the development of autoimmune disorders. Patients with CLL have abnormal cellular and humoral-mediated immune responses due to both quantitative and qualitative defects in immune effector cells. These defects can be due to an underlying disease process or to chemotherapeutic agents used for treatment. Infections account for up to 50 percent of all deaths in patients with CLL [14]. The incidence of major infections is related to the stage of the disease and active treatment [15]. Most infections occur late in the disease course, mainly due to a combination of bone marrow infiltration and therapy-induced immune dysfunction [16, 17].

Anemia is a common complication of advanced CLL and the causes are multifactorial, it may be due to gastrointestinal blood loss secondary to the use of corticosteroids, thrombocytopenia, mucositis or coagulopathy. Other causes can be hypersplenism, marrow suppression secondary to the use of chemotherapy, marrow infiltration by advanced disease, hemolytic anemia and red blood cell aplasia. About one-third of patients with CLL may develop AIHA over the course of their disease unrelated to treatment modality [18], although most series suggest a rate in the range of 4 to 10 percent [19]. The prevalence is related to disease stage, increasing from a rate of approximately 4 percent in Binet stage A to 10 percent in stages B and C. Also the incidence of AIHA may be higher following purine analog treatment

The diagnosis of AIHA is typically made in a patient with an isolated fall in hemoglobin and a positive Coombs' test, indirect hyperbilirubinemia, reticulocytosis, and elevation of serum lactate dehydrogenase (LDH). However, not all patients with AIHA will demonstrate these laboratory findings. In one study, only 18 % of patients with CLL and hemolytic anemia had a positive direct antiglobulin (Coombs') test [20].

Pure red cell aplasia (PRCA) is a rare complication, occurring in approximately 0.5 percent of patients. However, if this disorder is specifically sought for via bone marrow aspiration and absolute reticulocyte count, PRCA may be found in up to 6 percent of patients with CLL [13]. Although it is rare, unlike AIHA, PRCA may occur early in the course of CLL.

Thrombocytopenia can occur at any time in the disease course. If it is present at the time of diagnosis, it is typically mild. A platelet count below 50,000/microL usually occurs only late in the disease. The causes of thrombocytopenia

in patients with CLL can be due to, suppression of platelet production in the presence of extensive tumor burden, autoimmune destruction hypersplenism, infection (particularly sepsis and associated DIC) and chemotherapy [21].

Autoimmune thrombocytopenia (ITP) is diagnosed when a bone marrow biopsy shows an adequate number of megakaryocytes but the peripheral blood has an abnormally low platelet count. This complication occurs in 2 to 3 percent of patients with CLL, and it may be the complaint that initially brings the patient to medical attention [13].

Rarely, agranulocytosis may be encountered in CLL (approximately 0.5 percent). The presence of anemia and/or thrombocytopenia has prognostic implications in CLL. Hypogammaglobulinemia is present in about 8% of patients at the time of initial diagnosis and it may develop in up to two-thirds of patients later in the course of the disease. Usually all three immunoglobulin classes (IgG, IgA, and IgM) are decreased, but in some patients only one or two may be low.

Objectives:

The main objectives of this study are to determine the mode of clinical presentation and the main the complications of chronic lymphocytic leukemia in Sudanese patients.

Methods:

This is a retrospective review of the approved medical records available at radiation & isotope center (Khartoum), Division of Hematology, Department of Medicine. The center is a specialized center dealing with such patients coming from all over Sudan, on patients with chronic lymphocytic leukemia attending the referred clinic. The study included 100 patients; all of them had been diagnosed with CLL with their full records and investigations. Data were collected from 2008 to 2012. Data reviewed and statistical analysis was done using the statistical package for social sciences (SPSS).

Complete blood count was done using automated haematological analyzer (Sysmex).

Results:

In this study the most common age group was (70-79) years as in table (1). Male to female ratio was 1.2:1. Lymphadenopathy and weight loss appear the most common presenting symptoms fig (2). The spleen was enlarged in more than half of our patients (table 4). This study finds a correlation between splenomegaly, the degree of anemia and thrombocytopenia table (9).

The majority of the study group showed lymphocytosis, of whom only (8%) is an absolute count.

Bone marrow biopsy support the diagnosis of CLL in these patients, while only around one fifth performed immunphenotyping studies (fig 4, 5).

Chest infections appear to be one of the most important complications occurring in these patients accounting for (52.5%) as shown in table(4), and it is clear that infections are very common in patients above 60 (table 8).

Anemias and thrombocytopenias appear also to be an important complications (47%, 52% respectively) as in table (3). In this study few patients did DAT, of whom most of them were positive. Table (6) showed that some of those

patients with anemia or thrombocytopenia require at one time blood transfusion or platelets transfusion, not also that some of those patients require the transfusion more than once.

Other complications such as bleeding from skin such as epistaxis, bleeding per rectum are common (14%). Herpes infections complicate some of the cases (4%).

Table (1): Age distribution of CLL patients in Sudan

Age (in yrs)	Number	Percent
40 – 49	11	11.0
50 -59	19	19.0
60 – 69	28	28.0
70 -79	33	33.0
80+	9	9.0

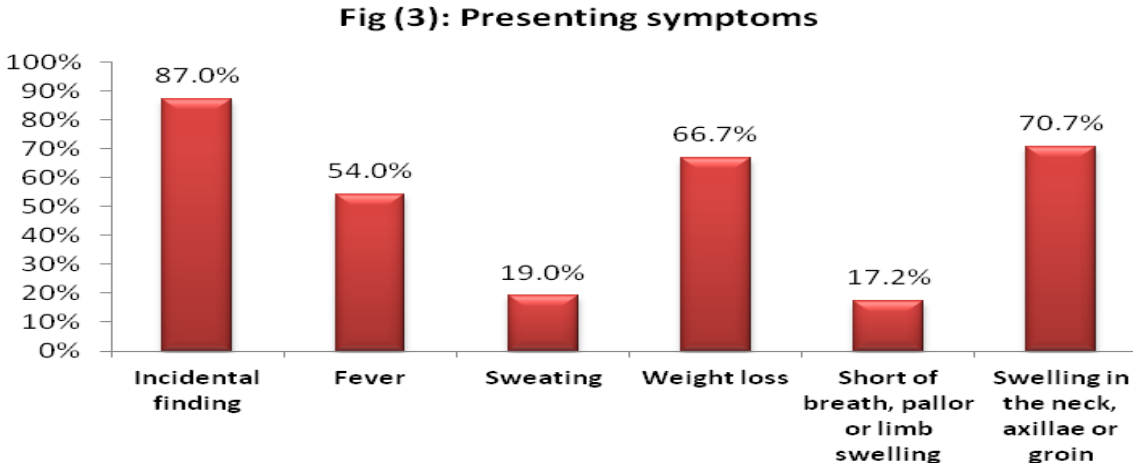

Figure (1) distribution of study population according to presenting symptoms

Table (2) Haematological finding in patients with CLL in Sudanese patients

Result		Frequency	Valid Percent
Lymphocytosis	Yes	98	98.0
	No	2	2.0
	Total	100	100.0
Hb %: normal (10 – 15g)	High	2	2.0
	Low	47	47.0
	Normal	51	51.0
	Total	100	100.0
Platelets (normal 150 -400)	High	2	2.0
	Low	52	52.0
	Normal	46	46.0
	Total	100	100.0
Coomb's test	Positive	7	77.8
	Negative	2	22.2
	Total	9	100.0

Table (3) Bone Marrow and Lymph Node Biopsies in CLL patients

Result		Frequency	Valid Percent
Lymph node biopsy: lymphocytes infiltration	Yes	9	100.0
Bone marrow: Hypercellularity	Yes	99	100.0
Bone marrow: Mature lymphocytes infiltration	Yes	98	98.0
	No	2	2.0
	Total	100	100.0
Bone marrow: Fibrosis	Yes	5	5.9
	No	80	94.1
	Total	85	100.0
Bone marrow: Erythroid& megakaryocytes	Normal	51	63.8
	Reduced	29	36.3
	Total	80	100.0

Table (4) Distribution of Complications in the Study Population

Complication		Frequency	Percent
recurrent chest infection	Yes	52	52.5
	No	47	47.5
	Total	99	100.0
repeated blood transfusion(*)	Yes	20	20.0
	No	80	80.0
	Total	100	100.0
Transfused with platelets(*)	Yes	7	7.1
	No	92	92.9
	Total	99	100.0
bleeding from the skin, mouth or orifices	Yes	14	14.0
	No	86	86.0
	Total	100	100.0
skin lesions (like herpes)	Yes	4	4.0
	No	96	96.0
	Total	100	100.0
Malignant transformation	No	100	100.0

Discussion:

CLL is the most common form of chronic leukemia in the Western countries but whether it is also common in Sudan is not known as there are no enough supporting data. It was consistently found that CLL is the disease of the old age with the median age. In this study more than one third occur at the age group 70-79 years which showed the most frequent occurrence. Male to female ratio in this study 1.2:1 compared to 1.7:1 in the western countries [(2)]. The majority of patients were diagnosed incidentally where patients are discovered while doing routine CBC. The typical B symptoms of lymphoma don't appear clearly in the present study but generally speaking fever, lymphadenopathy and weight loss appear the most common presenting symptoms [(9)]. Comparing to various series in the literature,

lymphadenopathy was present in 50 to 90 percent of CLL patients [10]. That agreed with the finding in this study.The spleen was enlarged in more than half of the patients, compared to 55% in the literature [10]. The percentage expects to be higher as it depends on the imaging techniques. The present study find a correlation between spleenomegaly and the degree of anemia and thrombocytopenia table, the low values may be explained by hypersplenism.

CBCs were done to the majority of the study group which showed lymphocytosis, of whom only few of them were an absolute count. The new guidelines consider the threshold for diagnosis at absolute count of > 5,000 /cum, B lymphocytes and their clonality should be confirmed by flowcytometry [10, 12] .

It is worthy telling that bone marrow biopsies were done to all the patients included in the study, which support the diagnosis of CLL. Chest infections appear to be one of the most important complications occurring in these patients, no exact data was found for the frequency of infections in the literature but it is quite clear that infections account for 50% of deaths in patients with CLL [14]. It is clear that infections were very common in patients above 60 years old. Anemias and thrombocytopenias appear also to be an important complications, although the causes are multifactorial, we can't tell how much frequent are the autoimmune causes, again it is difficult to determine the incidence of (AIHA), about one third of patients might develop AIHA over the course of their disease [18] while 2 to 5 percent of patients develops ITP [21]. In this study DAT was done for few patients, where most of them were positive. Some of those patients with anemia or thrombocytopenia require at one time blood transfusion or platelets transfusion.

Other complications such as skin bleeding, epistaxis and bleeding per rectum were common. Herpes infections complicate some of these cases, but no malignant transformations have been reported, although five to ten percent of CLL patients might have their disease transform into an aggressive large cell lymphoma(Richter's transformation) or prolymphocytic leukemia, while some patients have a higher risk of developing secondary solid tumors [22, 23] .

Conclusion:

This study concluded that CLL is a disease of the elderly in Sudan as elsewhere in the world. The age and gender of Sudanese CLL patients were similar to those reported by the western countries but patients in this study came to the hospital with more severe symptoms and signs such as anemia and hepatosplenomegaly. Infections were the most important complications though as a cause of death had not been tested in these patients.

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