

Chronic Lymphocytic Leukemia: Autoimmune Presentations in A tertiary Care Hospital of Lahore

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^{1,2,4} Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Final approval of the version to be published, ³ Drafting the work or revising it critically for important intellectual content ⁶ Active participation in active mythology

Funding Source: None

Conflict of Interest: None

Received: Aug 11, 2021

Accepted: Mar 03, 2022

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ABSTRACT

Objective: To determine the frequency of presenting features and complications in chronic lymphocytic leukemia.

Methodology: This descriptive study was conducted at the Hematology department, King Edward Medical University and affiliated hospitals, from 20 July to 20 December 2017. For every patient, a thorough clinical and dermatological examination, abdominal ultrasound and bone marrow examination was done. A fresh blood sample for CBC, immune profile, and serum testing was collected by a syringe using aseptic technique. A complete blood count was carried out and chemical examination was done. Reticulocyte count was performed and direct antiglobulin test using coomb's reagent was done. Every patient was evaluated for the criteria of SLE and was categorized accordingly.

Results: Out of the 150 patients enrolled in the study, 122(81.3%) were male and 28(18.7%) were female. The mean age was 65.8 ± 1.33 years with the majority of patients falling in the group of 71- 80 years. Out of 150 patients, 40 (26.7%) had Coombs test positive. Most of the patients who had Coombs positive were in stage 4 CLL. The patients who presented with complications such as paraneoplastic pemphigus were 1 out of the 150 patients. Splenomegaly was found in 87.3 % of all CLL patients where 13.33% presented with massive splenomegaly. Angioedema was found in 2 out of 150 patients. No case of SLE, Sjogren's syndrome, Churg strauss Syndrome, Vasculitis or Richters Transformation was found.

Conclusion: Detection of complications in a significant number of CLL patients is related to disease progression and overall survival. The treatment modalities are different in different causes of anaemia and complications due to CLL. It will help the clinicians in modifying the treatment and decreasing the misery of patients due to co morbidities.

Keywords: CLL, Autoimmune anaemia, complications of CLL.

Cite this article as: Rashid A, Rashid M, Aslam N, Sheikh H, Kashif A, Khanum A. Chronic Lymphocytic Leukemia: Autoimmune Presentations in A tertiary Care Hospital of Lahore. *Ann Pak Inst Med Sci.* 2021; 18(1):15-19. doi. 10.48036/apims.v18i1.613

Introduction

CLL is characterized by proliferation, accumulation, and sustained increase of morphologically mature but functionally incompetent lymphocytes. Autoimmune phenomena are a well-known complication of lymphoproliferative diseases. Autoimmune Haemolytic Anaemia is the most frequent autoimmune disorder associated with CLL although patients may present with widespread immune complications.

Chronic lymphocytic leukaemia (CLL) is characterised by accumulation of CD5+ monoclonal B cells in primary and secondary lymphoid tissues. Genetic defects and stimuli originating from the microenvironment concur to the selection and expansion of the malignant clone. It is the most prevalent lymphoid malignancy in the western countries, with an estimated incidence of approximately 15,000 new diagnoses per year.(1) The median age at diagnosis is 72 years. The diagnosis of chronic lymphocytic leukaemia (CLL) is based on clinical and

laboratory features. The initial diagnostic investigations are morphology and immunophenotype. These tests should be complemented with molecular genetics and/or histology to exclude other B-cell disorders of small lymphocytes. The clinical course of patients with B-cell chronic lymphocytic leukemia (CLL) is often made complicated by autoimmune phenomena that mainly target blood cells. Complications can occur in up to a quarter of all patients during the course of the illness. It is not true to say that autoimmunity is confined to the formed elements of the blood since conditions such as paraneoplastic pemphigus and acquired angioedema do occur in CLL, but nonhematologic autoimmunity is very rare indeed(2). Autoimmunity is usually caused by loss of self-tolerance resulting in a pathologic immune response to autologous blood cells. Most cases of AIHA and ITP are caused by high-affinity polyclonal IgG directed against red blood cells (RBCs) or platelet antigens.(3) (4)Autoantibodies specific for RBCs are detectable by the direct antiglobulin test in up to 20% of patients with advanced CLL but cause AIHA in only a minority of these patients.

The diagnosis of CLL requires the presence of $5 \times 10^9/L$ B lymphocytes in the peripheral blood, sustained for at least 3 months. CLL cells coexpress the surface antigen CD5 together with the B-cell antigens CD19, CD20, and CD23.

Each clone of leukemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains. The staging methods of chronic lymphocytic leukaemia that are currently in use throughout the world are the Rai and the Binet systems. In the three-stage Rai system low risk encompasses Rai stage 0, with the clinical features of lymphocytosis in blood and bone marrow only. Intermediate risk encompasses stage I, with lymphocytosis and enlarged nodes, and stage IV with lymphocytosis plus splenomegaly and or hepatomegaly (nodes positive or negative). Infections are the major cause of morbidity and mortality in patients with chronic lymphocytic leukemia (CLL). Predisposition to infection in CLL is mediated through various abnormalities, including both the immune defects inherent in the primary disease (impairment in humoral and cellular immunity) and in the further immunosuppression related to the management of CLL. Hypogammaglobulinemia is probably the most important immune defect in terms of the risk of severe bacterial infections, its frequency and severity progressing with the duration of the disease.

Methodology

This descriptive study was conducted in the Hematology Department of King Edward Medical University and affiliated hospitals during a period six months after the approval of the synopsis, from 20 July to 20 December 2017. The sampling technique used was non-probability purposive sampling. Sample size of 150 patients was estimated by using a 95% confidence level. 7% margin of error, with expected frequency of complications in patients of chronic lymphocytic leukaemias was taken as 19.4%. Newly diagnosed cases and cold cases of chronic lymphocytic leukaemia that had not taken any treatment with age up to 85 years were included. Patients on treatment or having been treated for chronic lymphocytic leukaemia were not included. Patients who had received transfusion within last three months and known cases of autoimmune disorders like systemic lupus erythematosus, lupus nephritis, pemphigus vulgaris and giant cell arthritis were excluded. Patients taking drugs known to cause haemolytic anaemia like quinidine, penicillin, and methyl dopa and on steroid therapy were not included.

For every patient, a detailed history, clinical examination, skin biopsy, and CBC was run on a fresh 3 ml blood sample containing EDTA using Automated Haematology Analyzer (*Sysmex KX-21*). Reticulocyte count was done by supravital staining. Direct antiglobulin test using antihuman globulin, Bilirubin and Lactate dehydrogenase levels were measured using XN 1000. Data was entered and analysed on SPSS version 20 computer software and program for data analysis. Quantitative variables including age of the patient, complete blood counts and bilirubin levels, reticulocyte count and lactate dehydrogenase levels were presented as mean \pm standard deviation. Qualitative variables including autoimmune haemolytic anaemia, gender, AHA, massive splenomegaly were presented as frequency/percentages. Data was entered and analysed on SPSS version 20, computer software and program for data analysis. Quantitative variables including age of the patient, complete blood counts and bilirubin levels, reticulocyte count and lactate dehydrogenase levels were presented as mean \pm standard deviation. Qualitative variables including autoimmune haemolytic anaemia, gender, AHA, massive splenomegaly were presented as frequency/percentages. Data for age, gender and duration of CLL was stratified. Post stratification chi square test was applied and P value ≤ 0.05 was considered as significant

Results

In our study, 150 patients of CLL were enrolled. Enrolled patients age ranged from 40-85 years with mean age of 65.8 ± 1.5 years with maximum number of 45 (30%) patients falling in the group of 71-80 years. (Figure 2) Maximum number of patients 50 (33.3%) fell in stage II (according to Binet classification) followed by 45 (30%) in stage III, 42 patients (28%) in stage IV, 12 (8%) in stage I and only 1 patient (0.675) in stage 0.

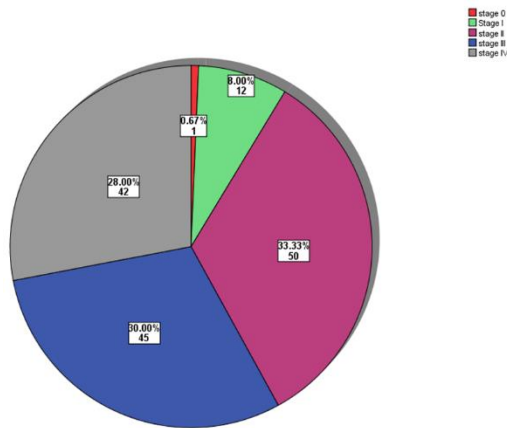


Figure 1. CCL patients presenting with different stages of diseases

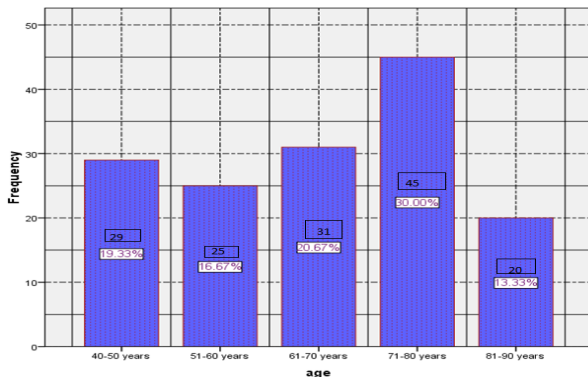


Figure 2. Age distribution group wise in patients of CLL

The mean haemoglobin of all CLL patients was $9.8 \text{ g/dl} \pm 2.62$. 15 % of patients were suffering from anemia. Mean Bilirubin levels in CLL patients were $1.3 \pm 0.5 \text{ mg/dL}$ (Figure 4) and a much higher mean of $3.5 \pm 1.45 \text{ mg/dL}$ in patients who had haemolytic anemia. The patients who presented with complications such as paraneoplastic pemphigus were 1 out of 150 patients. Splenomegaly was found in 87.3 % of all CLL patients with 13.33% presenting with massive splenomegaly. (Figure 3) Angioedema was found in 2 out of 150 patients. No case

of SLE, Sjogren s syndrome Churg strauss Syndrome, Vasculitis or Richters Transformation was found.

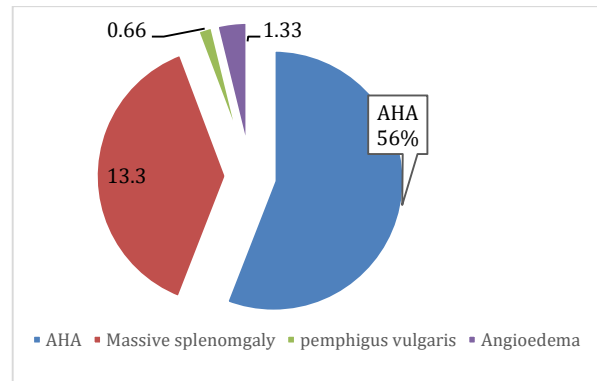


Figure 3. Autoimmune Complication of CLL

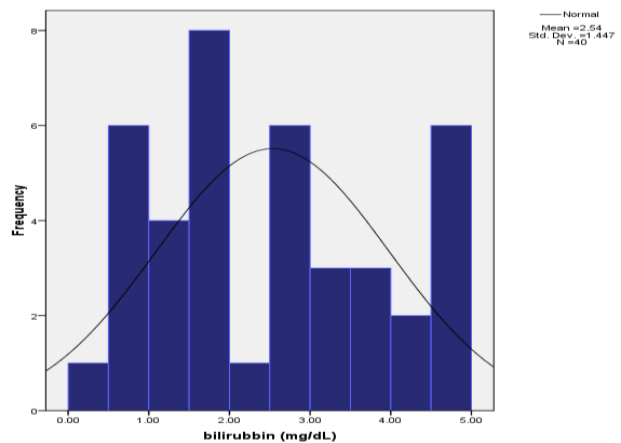


Figure 4. Bilirubin level in patients of CLL

Discussion

In this study, we included 150 patients with a diagnosis of CLL. This was a prospective cross sectional survey which was conducted in a well-equipped tertiary care unit. The mean age of the patients in our study was 65.8 ± 1.5 years with the maximum number of patients falling in the group of 71-80 years. While in another local study by Ehsan AY et al,^{6,7} the mean age of cohort was 62.84 years. The majority of the patients in our study were male, i.e. 81.33% with a male to female ratio of 4.3:1.

Oppezo P et al⁸ conducted a study showing that 63% of the population under study was male. Another study conducted in the Hospital Clinic of Barcelona, which divided their patients into two groups from 1980-1994 and from 1995-2008 showed Median age of patients presenting with clinical features was higher in patients diagnosed between 1980 and 1994 than in those seen from 1995 to 2004 (68 vs 64 years; $P = .005$). The distribution by age group revealed a trend toward younger ages at diagnosis,

with a significant increase in the proportion of patients younger than 70 years old (55.9% vs. 63%; $P = .039$). There was also increased prevalence of men in both groups (54.3% vs 58.4%; $P = \text{NS}$).⁸ In our study, the maximum number of patients 50 (33.3%) fell in stage II (according to Binet classification), followed by 45 (30%) in stage III, 42 patients (28%) in stage IV, 12 (8%) in stage I and only 1 patient (0.675) in stage 0. In the study mentioned above conducted in Barcelona, majority of patients were from Binet stage A (75.6%) and minimum were from stage C (8.8%), and 15.6% from stage B.^{9,10}

Our results also showed that the mean haemoglobin of all CLL patients was $9.8 \text{ g/dl} \pm 2.62$. Around 15 % of patients were suffering from anemia. Another study similar to ours conducted from November 2002 to December 2008, in which 112 young patients (<65 years) diagnosed with CLL were included. There were 62 males and 50 females, with a median age of 52 years (range 29–68). Eighty-one percent were in Binet stage A, 19% were in stages B/C. Rai stage 0 was recorded in 61% of patients, I/II in 33.5%, III/IV in 5.5%. Their median haemoglobin was 14 in all 112 cases and Hb 14.2 in stage A patients that was 90.^{11,12} Autoimmune Hemolytic Anemia is a well-known complication of Chronic Lymphocytic Leukemia. In our study, out of 150 patients, 40 (26.7%) had Coombs positive. Most of the patients having Coombs positive were in stage 4. A study managed at the Institute of Hematology of the University "La Sapienza" of Rome Fifty-two cases of autoimmune hemolytic anemia (AHA) were observed within a series of 1203 patients (4.3%) with chronic lymphocytic leukemia (CLL). Nineteen were recorded at the time of CLL diagnosis and 33 during the clinical follow-up.¹¹

Our results showed that patients with splenomegaly was found in 87.3% of all CLL patients and 13.33% presented with massive splenomegaly. In a study conducted in University of California, San Francisco results showed that lymphoma was the commonest hematologic disease associated with both splenomegaly and massive splenomegaly. The chronic leukemias, chronic lymphocytic leukemia (CLL) (10%), were twice as common as the acute leukemias for splenomegaly and six times more common for massive splenomegaly. (23%)¹² Another study conducted in Northern Nigeria, 4 out of 30 patients with splenomegaly, had Chronic Lymphocytic Leukemia.^{13,14} Our study also showed that 2 out of 150 patients had acquired angioedema. There is a well-known link between acquired angioedema and lymphoplasmacytic disorders.^{15,16} In a study that studied

this relationship, they noted that while reviewing 32 patients with Acquired angioedema, nine (28%) had lymph proliferative disease.^{17,18,19}

Conclusion

Detection of complications in a significant number of CLL patients is related to disease progression and overall survival. The treatment modalities are different for different causes of anaemia and complications due to CLL. This will help clinicians modify the treatment and decrease the misery of patients due to co morbidities.

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