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Chronic Lymphocytic Leukemia in an Adolescent Girl: A Case Report and Clinico-Pathologic Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author NM and HK analyzed and interpreted the patient data regarding the hematological disease. Author SJ did interpretation of histopathology of mass biopsy. Authors NJ and AS performed the clinical examination of the patient and provided clinical details for manuscript. Authors NM, HK and AS was a major contributor in writing the manuscript. Authors NJ and SJ did critical review of the manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Chronic lymphocytic leukemia (CLL) in pediatric age is rare in the literature. It is a common disease of older adults, characterized by clonal proliferation and progressive accumulation of monoclonal B-cell lymphocytes. The diagnosis is established by immunophenotyping and prognosis is defined by staging system (Rai and Binet), as well as by several biological and genetic markers. We report a case of CLL diagnosed in an adolescent girl presented at 16 years of age. The case is being reported to improve awareness regarding this rare entity in children.

Case Presentation: A 16 year old female presented with fever, weight loss and cervical lymphadenopathy. After baseline workup, lymph node biopsy, bone marrow biopsy along with immunohistochemistry and flowcytometry on peripheral blood was performed to establish the diagnosis. The clinico-pathologic features including extensive immunophenotyping were consistent with CLL.

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Discussion: Management guidelines for older adults are very well established but no standardized protocol exists for pediatric age group. We offered her Fludarabine and Cyclophosphamide as first line regimen and she responded well and achieved remission after four cycles. Unfortunately disease relapsed within two years. At this time, determination of optimum therapeutic protocol was a unique challenge as hematopoietic stem cell transplant (HSCT) was not available at our institute.
Conclusion: CLL is an extremely rare malignancy in childhood and adolescence. Therefore age specific treatment protocols are not established. Reporting this case will help in eliciting the high index of suspicion among pathologists and oncologists for this exceptionally unusual and life threatening disease so that delays can be avoided.

Keywords: Chronic lymphocytic leukemia; pediatric; immunophenotyping; flowcytometry.

1. INTRODUCTION

Chronic lymphoproliferative disorders are a wide group of malignancies that is exceptionally rare in children and adolescence. Chronic lymphocytic leukemia (CLL) although common in adults, is extremely rare in pediatric population. It is characterized by proliferation of phenotypically mature malignant B lymphocytes, mostly in the peripheral blood, bone marrow and lymph nodes [1]. The diagnosis requires a monoclonal B-cell count greater than or equal to 5x10E9/L, with the characteristic morphological and immunophenotypic features of CLL in the peripheral blood. Circulating malignant cells have a unique immunophenotype comprised of a variety of B cell markers as well as expression of CD5 antigen in absence of other pan-T cell markers [2]. In addition to immunophenotyping, nowadays usually other laboratory investigations like cytogenetics and molecular diagnostic techniques are utilized to determine the prognosis.

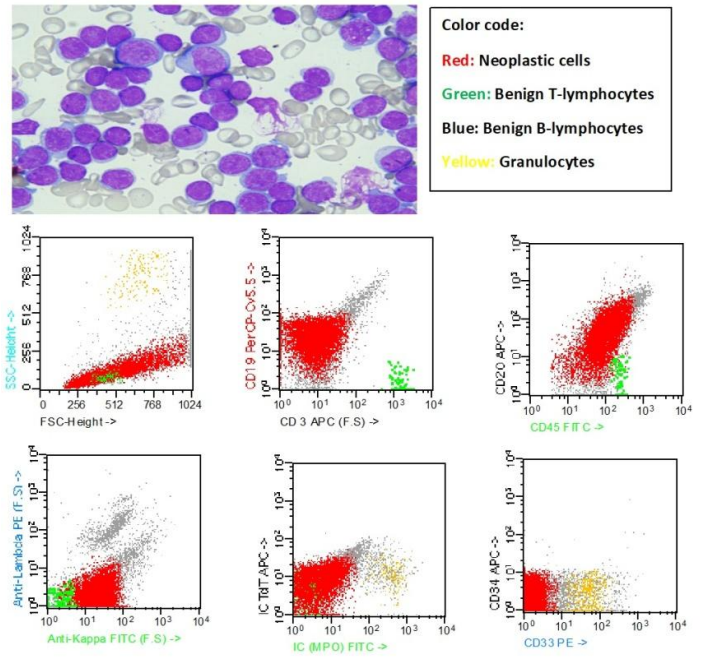
CLL is the most common lymphoproliferative disorder diagnosed in middle aged and elderly adults in West and accounts for about 25% of all leukemias [3]. It is uncommon in Asian Countries, and constitutes 5% of all hematological malignancies in Pakistan [4]. It is unlikely to occur before 45 years of age, and the median age for diagnosis is 72 years [3]. As stated above, chronic leukemia is exceptionally uncommon in children, and it constitutes less than 5% of all childhood leukemias [5]. Only a few cases of pediatric CLL have been reported in previous literature [5-7,8].

Here, we report a case of a 16 year old female who presented with clinical and laboratory findings consistent with CLL. The diagnosis was confirmed by excisional lymph node biopsy, bone marrow biopsy and immunophenotyping by flow cytometry on peripheral blood.

2. CASE PRESENTATION

A 16 year old female presented with complaints of intermittent fever, fatigue and neck swelling for 1.5 years. Patient has taken multiple antibiotics, steroids and antituberculous therapy (ATT) in last one year and her condition was not improved. There was no history of lymphoproliferative disorder or any other malignancy in family. On physical examination, enlarged cervical and supraclavicular lymph nodes and massive hepatosplenomegaly observed. CT scan neck, chest and abdomen was done which showed wide spread disease above and below the diaphragm along with splenic involvement. Serum LDH was 3581U/L however direct coombs test was negative. Baseline complete blood count (CBC) revealed Hb 3.5g/dl, total leukocyte count (TLC) 980x10E9/L and platelet 151x10E9/L. Blood film examination showed lymphocytosis along with many smudge cells. Morphologically intact cells were mostly small in size, having high nuclear to cytoplasmic ratio, clumped nuclear chromatin, indistinct nucleoli with regular nuclear outlines and scant amount of pale agranular cytoplasm. Few medium sized lymphoid cells also appreciated with vesicular nuclei, single prominent nucleoli and moderate amount of pale basophilic, agranular cytoplasm. Immunophenotyping by flowcytometry (Fig. 1) was done on peripheral blood using following panel of markers:

Tdt, CD34, CD45, IC CD3, IC MPO, CD19, CD20, CD22, CD79a, CD5, CD10, CD23, FMC-7, Anti-Kappa, Anti-Lambda, CD25, ZAP-70, CD3, CD4, CD8, CD13,CD33, CD15 and CD66c.



Immunophenotypic analysis was performed on BD FACS Calibur four color flowcytometer and analyzed by Paint-A-Gate software. It revealed 83% neoplastic cells which express CD45, CD19 (dim), CD20, CD22, CD5, and Anti-Kappa (dim). Rest of the markers mentioned in above panel were negative. Cervical lymph node biopsy report was also consistent with Flowcytometry on peripheral blood. In addition to above markers, a panel of immunohistochemical markers was tested on cell block that revealed negativity for CD99, CD117, bcl-6 and cyclin-D1; positive for bcl-2 and Ki-67 positive in approximately 10% of neoplastic cells. Overall features were consistent with low grade B-cell lymphoproliferative disorder favoring CLL. Bone marrow biopsy showed interstitial infiltration by small mature lymphocytes (Fig. 2).

Flourescence in situ hybridization (FISH) analysis performed on bone marrow and found to be negative for TP53 mutation. Chemotherapy started with Fludarabine and Cyclophosphamide. Her CBC showed normal counts and liver and spleen also regressed after the first cycle of chemotherapy. Total four cycles of this regimen given and marked improvement observed in subsequent laboratory parameters as well as in physical examination findings.

She remained in remission as follow-up visits showed no abnormal findings. After two years, she again presented with high grade fever, body aches and bilateral neck swelling. There was no hepatosplenomegaly at this time however other features raised suspicion of relapse. On examination there was generalized lymphadenopathy. CBC revealed Hb 11.2g/dl, TLC 214x10E9/L, and platelet 492x10E9/L. Excisional lymph node biopsy from right axilla (Fig. 3) and repeat flowcytometry on peripheral blood (Fig. 4) was performed to exclude possibility of other lymphoproliferative disorder. Immunophenotypic analysis of peripheral blood at the time of relapse was performed on BD FACS CANTO II eight color flowcytometer and analyzed by FACS DIVA software using following panel of markers:

Tdt, CD45, IC CD3, IC MPO, CD19, CD20, CD200, CD5, CD10, CD23, FMC-7, Anti-Kappa, Anti-Lambda, CD25, ZAP-70

It revealed 86% neoplastic cells which express CD45, CD19, CD20, CD5, CD200 and Kappa (dim positive). At this time, dim partial expression of CD23 was observed. Rest of the markers mentioned in above panel were negative.

Microscopic examination of lymphoid tissue showed diffuse sheets of small sized mononuclear cells with scanty cytoplasm, coarse nuclear chromatin and hyperchromasia. Following panel of immunohistochemical markers was performed:

CD20, CD5, CD23, Cyclin-D1, BCL-2, CD43, Ki-67, CD3, CD10, CD21

Diffuse bright positivity observed for CD20, CD5, BCL-2, and CD43 while CD23 was scattered positive in only few neoplastic cells. Ki-67 showed very low proliferative index. Rest of the above mentioned markers were negative. It was indeed a rare challenging case. Lymph node biopsy exhibit low grade lymphoproliferative disorder with immunohistochemical features again consistent with small lymphocytic lymphoma (SLL)/CLL) with atypical immunophenotype in terms of CD23 expression. The patient was selected as a candidate for bone marrow transplant (BMT). Family counseled and referred out for HSCT. However, it could not be done due to financial constraints. Dexamethasone and allopurinol given for a week then chlorambucil was started along with supportive treatment. After initial stabilization, patient lost to follow up and unfortunately expired.

3. DISCUSSION

This is indeed a rare challenging case to diagnose and manage as it is an extremely uncommon malignancy to occur in children and only a number of cases have been reported to date [3,5-10]. CLL is virtually never encountered in our pediatric oncology settings. Due to patient's young age, an exhaustive evaluation was undertaken to rule out other diagnoses. Not only age, female gender of our patient was also against the male preponderance (M:F ratio 1.7-2:1) associated with CLL [11].

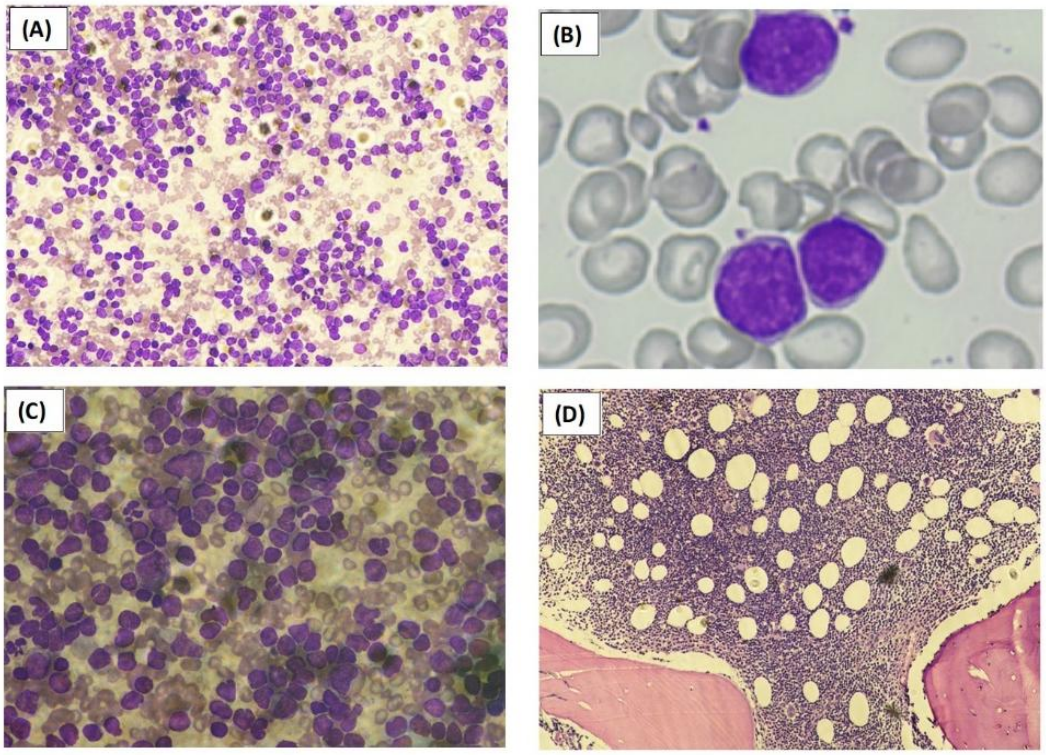


Figure2: (A & B) Peripheral blood film showing hyperleukocytosis, absolute lymphocytosis and smudge cells (C) Bone marrow aspirate exhibiting infiltration by mature lymphocytes (D) H&E stained section of bone marrow trephine biopsy showing interstitial infiltration by lymphocytes.

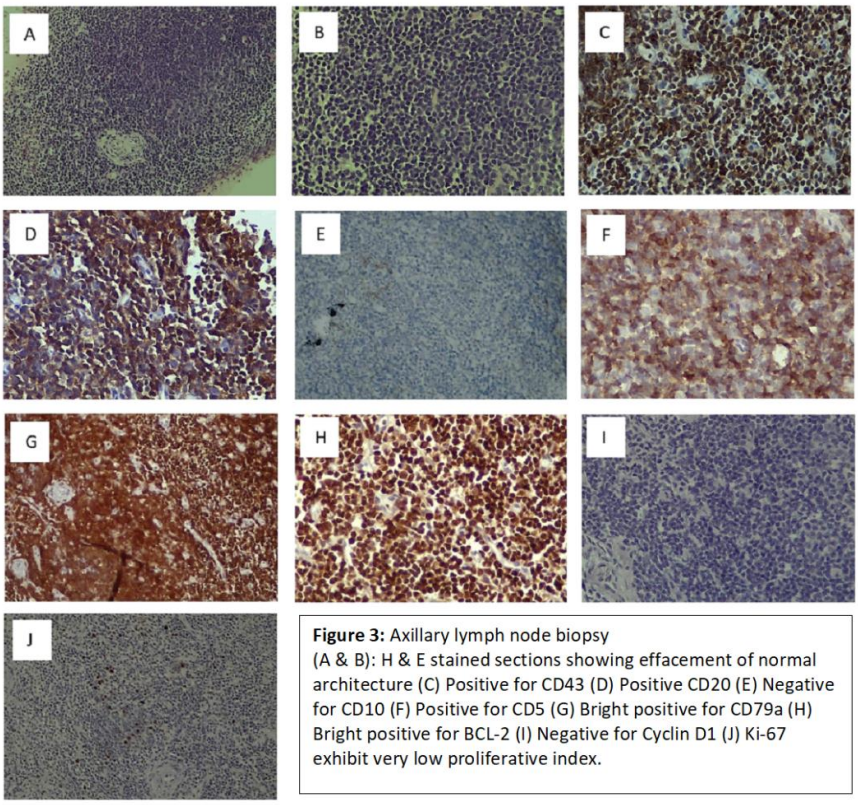
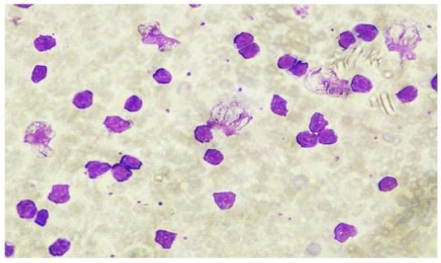


Figure 3: Axillary lymph node biopsy
(A & B): H & E stained sections showing effacement of normal architecture (C) Positive for CD43 (D) Positive CD20 (E) Negative for CD10 (F) Positive for CD5 (G) Bright positive for CD79a (H) Bright positive for BCL-2 (I) Negative for Cyclin D1 (J) Ki-67 exhibit very low proliferative index.



COLOR CODE:
Red: Neoplastic cells
Green: T- Lymphocytes
Blue: B-lymphocytes
Yellow: Granulocytes

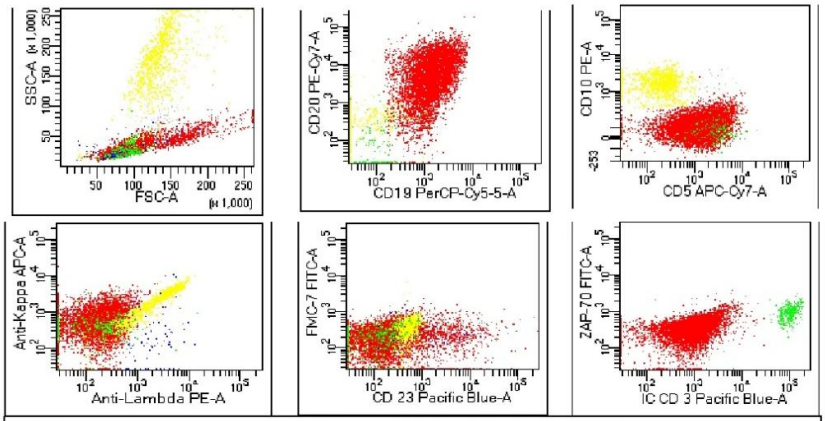


Figure 4: Immunophenotypic analysis by Flowcytometry on peripheral blood (at relapse) using mononuclear gating show positivity for CD20, CD19, CD5, dim positivity for kappa and dim partial expression of CD23 while no expression of lambda, IC CD3 and ZAP-70.

Most CLL cases in the West are incidentally diagnosed in asymptomatic patients by routine blood sample analysis. Other patients present with lymphadenopathy, splenomegaly, anemia, or thrombocytopenia. Our patient presented with lymphadenopathy, hepatosplenomegaly and hyper leukocytosis. Lymphadenopathy is observed in approximately 80% of CLL cases often with cervical and axillary lymph nodes bilaterally and symmetrically being affected [12]. Splenomegaly is usually mild to moderate and is observed in approximately 50% of cases while hepatomegaly is less frequent. Autoimmune hemolytic anemia often associated with CLL was not observed in our patient evidenced by negative direct coombs test performed on multiple occasions during the course of disease. According to reported literature, 15% of patients with CLL have positive direct coombs test including the cases without anemia [12]. LDH level increases with disease progression and it is also observed in our patient. Other complications associated with this disorder include immune deficiency leading to repeated infections, autoimmune complications, secondary malignancies, and Richter transformation.

The key feature in CLL pathogenesis is the progressive accumulation of CD5-positive B-cells because of a failure in programmed cell death or apoptosis. In addition to small lymphocytes, pro-lymphocytes are also observed but they constitute <15% of lymphoid cells as seen in this case. Interstitial pattern of bone marrow infiltration was observed in present case however para-trabecular and diffuse patterns also reported, later is associated with disease progression. Neoplastic cells in CLL exhibit a characteristic immunophenotypic profile that includes bright expression of CD19, CD5, CD23, CD200; dim expression of CD22, CD79b, CD20, CD43, CD11c, sIgκ or sIgλ, sIgM while no expression of CD10, CD103, CyclinD1 and FMC7. Our patient demonstrated classic morphology and immunophenotype consistent with the diagnosis of CLL according to WHO classification of tumors of hematopoietic and lymphoid tissues [2]. The only limiting feature was dim partial expression of CD23 that raised possibility of atypical CLL.

CLL cases with an atypical immunophenotype (i.e. negative for CD5, negative for CD23 or positive for FMC7) have been reported in literature [3,13]. Atypical CLL is a variant found in approximately 25% of patients with CLL. Although atypical variant has a more aggressive course compared to typical CLL, it is not usually reported. CD 200 and ROR1 are recently identified highly characteristic markers for CLL [14]. Bright positivity of CD200 was observed in present case which helped to exclude leukemic phase of mantle cell lymphoma. The expression of CD200 emerged as a powerful marker to distinguish mantle cell lymphoma from CLL and therefore better recognize atypical CLL. Negativity of FMC7 and cyclin-D1 were additional supporting features to rule out leukemic phase of mantle cell lymphoma. ROR1 couldn't tested in present case due to unavailability in our laboratory. ZAP-70, a very important prognostic marker was also negative in this case. Increased expression of ZAP-70 indicates a poor prognosis, whereas negative ZAP-70 indicates a greater chance of survival [8]. Other markers are CD38 and CD49d which play important role in prognostication.

The most frequent cytogenetic abnormalities are deletion 13, deletion 11q, trisomy 12, deletion 6q and deletion 17p which are associated with some peculiar clinical features and outcome. Deletion 17p is observed in 5-50% of cases and usually associated with TP53 mutations which was negative in our patient. Other mutations such as MYD88, NOTCH-1, SF3B1 and BIRC3 can be observed in 5-15% of cases. Atypical CLL showed relatively higher incidence of markers associated with poor prognosis like trisomy 12, unmutated IgVH and CD38 expression [15,13].

The first line regimen for young and fit patients is FCR (Fludarabine, Cyclophosphamide and Rituximab). Response rate with FCR is encouraging in adults with 30-40% achieving MRD negative complete remission. Although FCR is considered as first line treatment option, potential myelotoxicity, immunosuppression, frequent infections and reproductive issues are of major concern in younger patients. Our patient responded well to Fludarabine and cyclophosphamide at the time of diagnosis. While, at relapse, she was advised bone marrow transplant but couldn't done due to financial constraints. She subsequently showed improvement and went into remission however this patient had a very aggressive form of the disease and relapsed after two years. CLL in adults usually responds well to treatment with a chance of 60-70% complete remission [16]. No significant difference is reported in clinical

outcomes between CLL and its atypical variant. [17] In young patients, it usually recurs after standard therapy; subsequent therapies may be effective but less durable and ultimately these patients become treatment refractory [18]. This patient's early relapse and aggressive clinical course led to consideration of allogenic transplant that couldn't be done due to various factors therefore chlorambucil was started to manage relapse.

Chemoimmunotherapy is the standard first-line approach for CLL. Treatment is initiated when the disease becomes symptomatic, and survival is high following treatment. Due to scarcity of data, specific treatment protocol for pediatric patients is not established yet. With a better understanding of CLL biology, there has been steady progress in treatment in recent years. Several new drugs (e.g. Ibrutinib, Venetoclax) have been approved with different mechanisms of action. Novel approaches with durable disease control and less toxicity have to be identified for pediatric patients.

4. CONCLUSION

In conclusion, CLL is a very rare disease in pediatric age group and it may develop secondary to mutations. This case report demonstrates the presentation and disease course of CLL in children and will definitely add as a reference to limited number of reported cases in this age group.

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CONSENT

The parents of patient provided written informed consent to the publication of the case details.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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