



Case Report

Asymptomatic Chronic Lymphocytic Leukemia – presenting as Gastric lymphoma – A Case Report with Review of Literature

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ABSTRACT:

A 60 year old known diabetic male patient attends medical outpatient department for routine diabetic checkup. Clinical examination remains unremarkable. Diabetic status was also under control. Routine complete hemogram showed Total Leucocyte count (TLC) of 2.1 lakhs/cu.mm and Absolute Lymphocytosis of $10 \times 10^9/L$. Peripheral smear revealed more than 85% of atypical lymphocytes. Peripheral blood subjected for Flow cytometric analysis and Immunochemistry showed positivity to B cell markers. Patient was diagnosed as a case of asymptomatic chronic lymphocytic leukemia (CLL); Rai stage 0 and anti-leukemic management was initialized. After two weeks, patient presented with generalized gastrointestinal symptoms – diarrhea, vomitings, gastritis, colic etc. Clinical examination was once again uneventful and endoscopy was performed. There was no evident macroscopic lesion. Biopsy from slightly elevated mucosa showed similar cells as that of B-CLL. Thus, further management was planned and case was diagnosed as Extranodal gastric lymphoma with infiltration of B-CLL. We present here a rare case of Asymptomatic CLL presenting as Gastric lymphoma. This report accentuates the precedence of combined and cumulative approach of clinician and a pathologist in present case which led to early diagnosis and management of the patient.

KEY WORDS: Asymptomatic CLL, Gastric lymphoma.

INTRODUCTION:

Chronic Lymphocytic Leukemia (CLL) is the most common type of leukemia in the elderly age group. It is a mature form of B cell lymphoid leukemia [1]. The majority of patients with CLL are asymptomatic at the time of diagnosis. Some patients may have lymphadenopathy, organomegaly etc [2]. The usual presenting manifestations of CLL are due to infiltration of lymphoid organs; ensuing complications are mainly an autoimmune phenomenon and infections [3]. We present here a case of asymptomatic form of CLL with a mass per abdomen, which on evaluation was diagnosed as Gastric lymphoma (Extranodal infiltration of CLL). As such this is a very rare complication with a limited number of cases reported in literature.

CASE REPORT:

A 60 year old male, came to medical outpatient department for regular health checkup. The patient was a known diabetic. Clinical examination was uneventful. Routine laboratory investigations were performed for which blood and urine samples were collected. Urine was positive for Glucose and Albumin. Fasting blood sugar and post prandial blood sugar, blood urea and serum creatinine levels were within normal range. Hemoglobin was 9.8 gms%. Total leucocyte count (TLC) was 2.1 lakhs/cu.mm and showed absolute lymphocytosis of $10 \times 10^9/L$ (initially performed in Sysmex KX-21N™ Automated Hematology Analyzer). Peripheral smear showed increased TLC. Differential leucocyte count was done – which revealed Neutrophils – 6; Lymphocytes – 86; Eosinophils – 3; Monocytes – 3; Basophils – 2. Normocytic normochromic red blood cells were present. The lymphocytes were numerous, small cells showing round nucleus and scant or nil cytoplasm, chromatin was clumped and nucleoli were inconspicuous. No cleaved cells or prolymphocytes. A few smudge cells were also

observed. Mild degree of thrombocytopenia was evident. (Platelet count – 80,000/cu.mm) (Fig: 1,2). With this clinical and hematological picture the patient was re-evaluated. There was palpable spleen tip 2cms below the costal margin but there was no hepatomegaly or adenopathy. Thus, the case was diagnosed as an asymptomatic chronic lymphocytic leukemia. The patient was admitted and further plan of management was formulated. The patient refused for bone marrow aspiration. The blood sample was collected and subjected for Flow cytometric immunophenotyping which demonstrated a dominant B-cell population expressing positivity to Non-lineage marker CD45; B-lineage markers CD19, CD20, CD22, CD23, CD11c, CD38, CD5(B & T Lineage marker), ZAP70 (Fig: 3). Thus, the picture was strongly suggestive of the B - cell disorder and was finally diagnosed as Asymptomatic Chronic lymphocytic leukemia. The patient was referred to Hematology/Medical oncology departments for further management. The patient was prescribed Chlorambucil, Fludarabine and steroids which was given in cycles in a staged manner.

After 2 weeks, the patient came to the emergency ward with complaints of pain abdomen, diarrhea, vomitings, dyspepsia and infrequent episodes of malena from since five days. Clinical examination was uneventful except for a small ill-defined mass in the umbilical quadrant 5 cms above the umbilicus over the right lateral aspect of mid line. X-ray chest postero-anterior view and X-ray abdomen antero-posterior views were normal. Ultrasound abdomen revealed a normal abdominal study. As the hematological picture was showing normal hemoglobin value and platelet count except for increased TLC and lymphocytosis, an endoscopy was planned. Endoscopy showed mild congestion of gastric mucosa and a small mucosal elevation measuring around 1 x 1.5 cms near to the pyloric end at the greater curvature. Endoscopic biopsy was taken from the mucosal elevation and subjected for histopathological examination. The sections

stained with hematoxylin and eosin revealed intestinal metaplasia of the gastric glands. The interglandular and submucosal areas show infiltration with numerous atypical lymphocytes and other lymphocytes in various stages of maturation (Fig: 4). Morphology of the cells was similar to the cells observed in the peripheral smear. Thus, the lesion was diagnosed as Gastric lymphoma (Extranodal CLL). The patient was kept under palliative treatment with Rituximab. The patient was advised to attend follow up clinic every week. The gastrointestinal symptoms were not under control. Thus, high risk consent was taken from the patient and relatives and partial gastrectomy was performed, the specimen was subjected to histopathological examination. Gross examination showed specimen measuring 5.6 x 7.2 cms with small nodular, ulcerated lesion 1.5 x 0.8 cms size (Fig:5).

Histopathological examination showed similar features as that of specimen of endoscopic biopsy, margins were clear from infiltration of the tumor cells (Fig: 6). The patient was discharged on the 12th post-operative day without any complications. The patient is still attending follow up clinic and the gastrointestinal symptoms are under control. Patient has not developed any adenopathy or organomegaly and is still continuing the conventional treatment for CLL.

DISCUSSION:

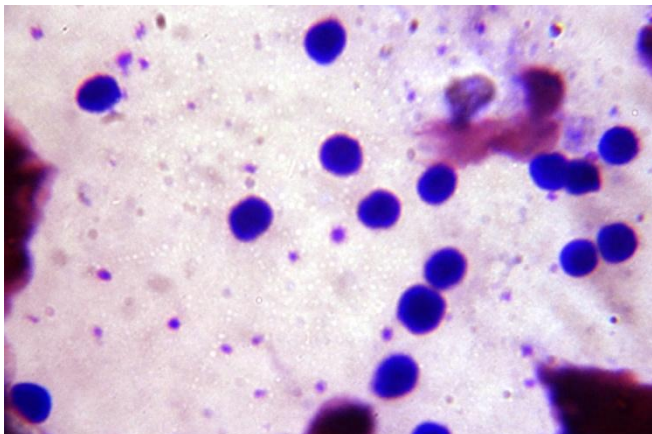
CLL is clinically heterogeneous disease. It is a chronic B cell lymphoproliferative disorder of middle and old age. It is characterized by proliferation of CD5+ mature lymphocytes in blood, bone marrow and lymphoid tissues. An accumulative disease of low proliferative activity with defective apoptosis. In west CLL is the most common form of chronic leukemia (25-30%). In Asia it is very uncommon (2-3%). A disease of elderly (median age – 55 years) with slightly higher incidence in males (1.7:1) [4]. It is very rare in children [5].

The clinical course of CLL is usually indolent and depends on the stage of presentation. A typical case shows features of fatigue, weakness, frequent infections, lymphadenopathy and organomegaly [4]. But in an early stage disease all the above features might be absent. A small percentage of patients with CLL eventually progress to diffuse large B cell lymphoma or Richter's transformation with poor treatment outcome [6-8]. A sudden weight loss, organomegaly or increased systemic lymphadenopathy in a patient with CLL would raise a suspicion of Richter's transformation clinically [2]. The diagnosis of early stage disease is usually made on the basis of peripheral smear examination and complete hemogram evaluation, which is performed as a part of a routine hematological evaluation for any other disease [4]. The same scenario is evident in present case. In asymptomatic cases the patients may have anemia and thrombocytopenia as a result of marrow replacement by CLL cells or immune mediated destruction of mature blood elements [2]. Hematological examinations reveal absolute lymphocytosis more than $10 \times 10^9 / L$. These lymphocytes are monoclonal B cells expressing the CD5 antigen. The similar cells are found in the bone marrow aspirate also. In classical CLL more than 90% of cells in peripheral blood are mature lymphocytes. Smudge cells are also seen. Bone marrow, 30% - 95% of lymphocytes [4,5]. The diagnosis is established mainly by Flow cytometric immunophenotyping and Immunohistochemistry (IHC) in the present era. These studies in turn give information regarding the response to treatment and prognosis. CLL shows positivity to B cell antigens CD19, CD20, CD23 and CD5 (B and T lineage marker); either Kappa or Lambda chain surface Ig which confirms monoclonality. CLL cells also express low density towards CD22, CD79a, CD43 and HLA-DR. These cells are negative for CD10, FMC7, CD79b and Cyclin D1.

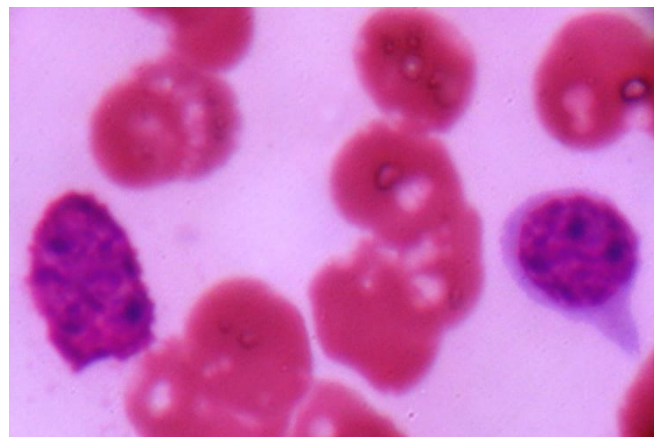
The CD38 positivity has been reported in cases with unmutated variable regions of

immunoglobulin heavy chain (IgVH) genes and worse clinical outcome[9-11].

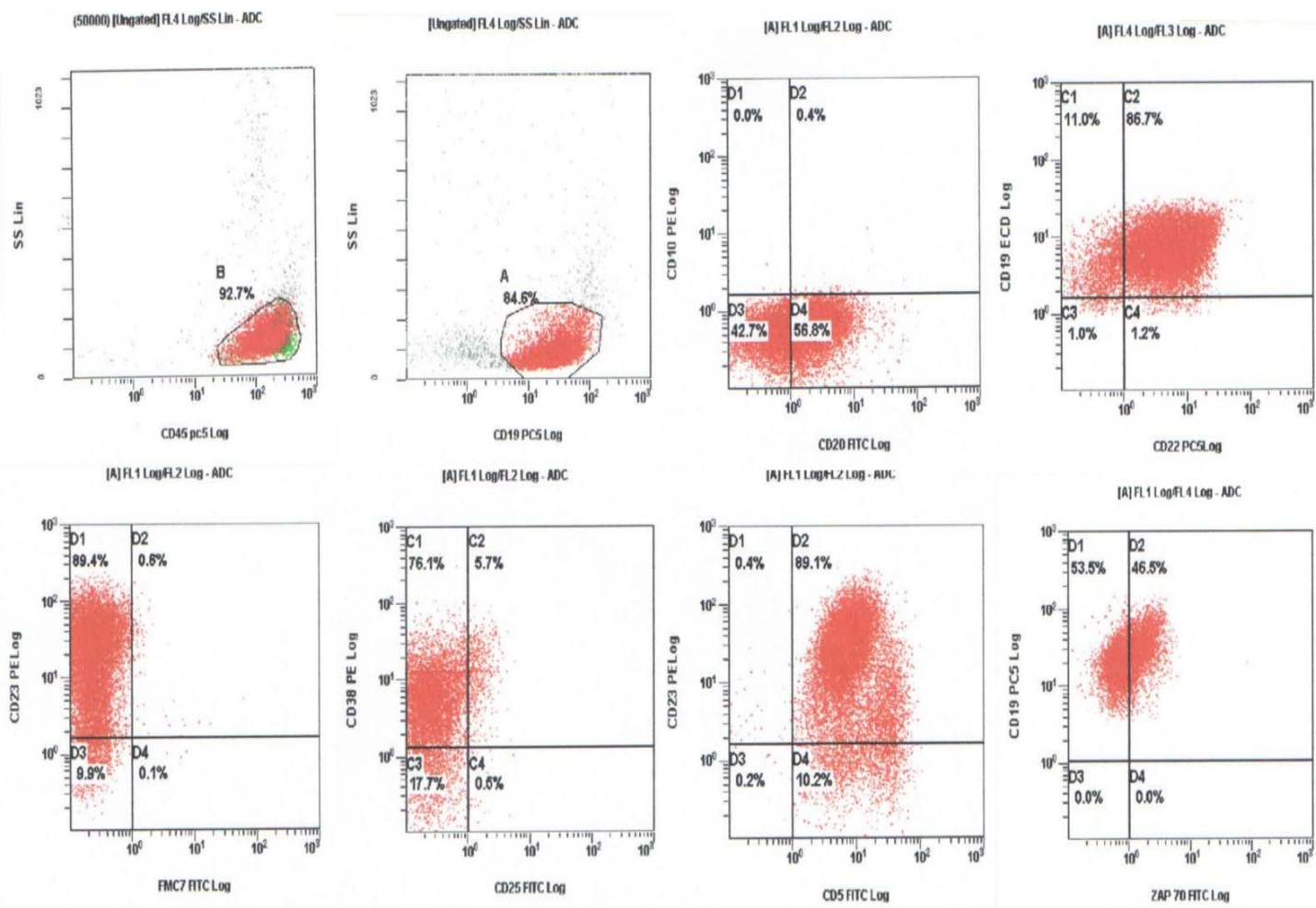
1. Photomicrograph – Peripheral smear, Leishman’s stain (100x).Absolute - lymphocytosis.



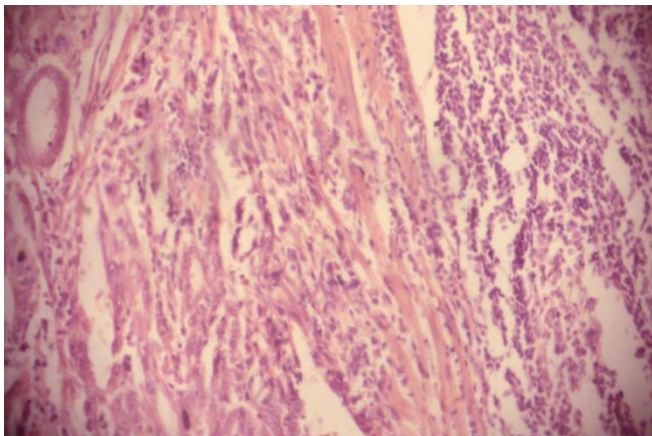
2. Photomicrograph – Peripheral smear, Leishman’s stain (400x). Smudge cells.



3. Flow cytometric immune phenotyping – Positive for B cell markers.



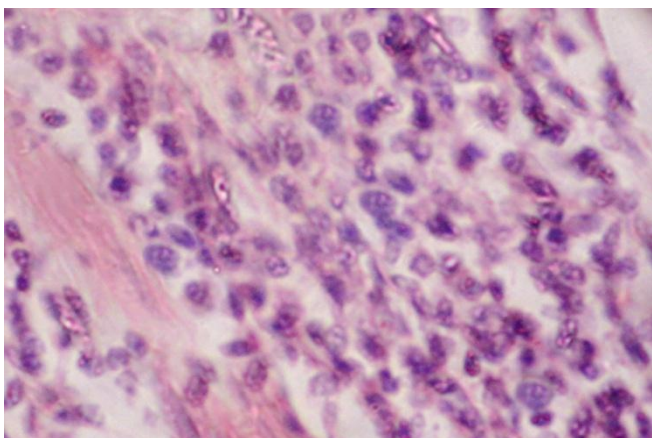
4. Photomicrograph – Endoscopic biopsy (100x). Gastric glands showing Intestinal metaplasia and atypical lymphocytic aggregates



5. Gross -Resected partial gastrectomy H&E, specimen. Ulcerative nodule (inside circle)



6. Photomicrograph – Resected specimen, H&E, (400x). Atypical lymphocytic aggregates and atrophic gastric glands



ZAP70 is a surrogate marker for IgVH mutation status, patients with more than 20% expression have a worse prognosis [4]. The cytogenetic abnormalities are evaluated by Fluorescence in situ hybridization studies. Deletion 13q14 is the most common disorder (50%) followed by Trisomy 12 (20-30%). 13q14 correlates with long survival while other cytogenetic abnormalities are reportedly associated with poor prognosis. Clinical staging of CLL is also an another path of prognostic evaluation. Rai staging system and Binet staging systems are two widely used ones.

Present case can be included under Rai [12] stage 0 and Binet [13] stage B. Extranodal involvement has been usually reported in lung, pleura, skin, central nervous system and kidney. These patients have a progressive illness and should undergo complex lines of treatment. The prognosis is obviously ominous [14]. The incidence of gastrointestinal tract involvement in CLL is low, even in postmortem studies. Historically it is reported to be uncommon (5-13%) [15]. The patients with gastrointestinal involvement can be asymptomatic or can present with abdominal pain, chronic colitis, chronic gastritis, persistent diarrhea, gastrointestinal hemorrhage is not uncommon [16,17]. Gonzalves et al., reported a similar case with gastrointestinal tract invasion without any features of Richter's syndrome [16]. Kuse and Lueb also reported similar cases but clinical symptoms were not reported [18]. The majority of cases evaluated by endoscopy are macroscopically unremarkable. But sometimes the presence of solid mass or ulcerative lesion can be encountered. Microscopic findings of the endoscopic biopsy reveal chronic gastritis, atrophic mucosa and atypical lymphoid aggregates. The tissue subjected for Flow

cytometry and Immunohistochemistry show positivity for markers of B-CLL.

Treating CLL is a very challenging task. The literature suggests B-CLL as an incurable disease despite new treatment strategies including chemotherapy and monoclonal antibody combinations; Hematopoietic stem cell transplantation etc., [14]. The strategy of treatment is based on clinical staging systems – Rai [12] staging and Binet [13] staging. The most common treatment for patients with typical B-CLL has been Chlorambucil / Fludarabine alone or in combination. The combination of Rituximab (375-500 mg/m² day 1); Fludarabine (25 mg/m² days 2-4 on cycle 1 and 1-3) in subsequent cycles and Cyclophosphamide (250 mg/m² with Fludarabine) achieves complete response in 69% of patients. Bendamustine, an alkylating agent is highly effective and is vying with Fludarabine as the primary treatment of choice. In case of Extranodal diseases as in the present case, combination regimens including Rituximab are highly effective. Allogeneic bone marrow transplantation can be curative in young patients, but is associated with significant treatment related mortality rate [5].

CONCLUSION:

In conclusion, CLL coexisting with Gastric lymphoma (Extranodal infiltration of CLL) is an extremely rare presentation which poses a diagnostic challenge due to varied asymptomatic clinical presentation, normal macroscopic appearance on endoscopy and minimal mucosal changes in microscopy. A cumulative effort of the clinicians and pathologists in evaluating the patient by careful clinical, hematological, histopathological and immunohistochemical approach has led us to the accurate path of diagnosis and management, which turned out as a boon to the patient where an asymptomatic CLL was diagnosed and a symptomatic fatal gastric lymphoma was taken care off.

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