CASE REPORT

A BIZARRE PROGRESSION OF CHRONIC LYMPHOCYTIC LEUKAEMIA INTO DIFFUSE LARGE B-CELL LYMPHOMA

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A 65-year-old male presented with complaints of weakness, lethargy, abdominal pain, and low-grade fever for the last few months. His examination revealed generalized lymphadenopathy and splenomegaly. A subsequent laboratory workup revealed atypical lymphoid cells with prominent double-bright positivity of CD19 and CD5 markers. Further investigations revealed deletion of the ATM (11q22.3) gene, and by other diagnostic factors, the patient was diagnosed with B-cell chronic lymphocytic leukaemia. Thus, treatment was initiated with oral chemotherapy followed by rituximab-bendamustine. After three weeks, he presented to the emergency room with a fever and worsening abdominal pain. On examination, massive splenomegaly was found. After stabilization, a bone marrow biopsy revealed findings which, in light of the clinical symptoms, were consistent with Richter's transformation of B-Cell chronic lymphocytic leukaemia into Diffuse large B-Cell Lymphoma.

Keywords: Diffuse large B-Cell lymphoma; B-Cell chronic lymphocytic leukaemia; Richter's transformation

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INTRODUCTION

B-cell chronic lymphocytic leukaemia (BCLL), as the name suggests, is a variant of blood cancer which exhibits uncontrolled growth of the white blood cell (WBC) known as the B-lymphocyte.[1] This disease is characterized by the accumulation of monoclonal B-lymphocytes which arise from CD5+ lymphocytes.[2] This disease may remain clinically silent. Conversely, it may also present with lymphadenopathy, hepatomegaly, anaemia, thrombocytopenia, and splenomegaly. Chronic lymphocytic leukaemia (CLL) cells can be distinguished from normal B-cell populations by biomarkers which include CD19, CD5, and CD23 in the presence of low surface immunoglobulin levels.[3] On microscopy, so-called "smudge cells," may be observed, which are a result of cytoskeletal defects in affected cells, resulting in a distinctive image on peripheral blood smear.[4] Although the pathogenesis of chronic lymphocytic leukaemia remains unclear, models have been proposed in order to attempt to shed light on this process. One such model posits that naive B-cells may undergo T-cell dependent or T-cell independent reactions, both of which produce antigen-experienced B-cells that may initiate monoclonal B-cell lymphocytosis.[1] The most appropriate treatment options for Chronic Lymphocytic Leukaemia are decided based on multiple factors which include the presence of specific genetic aberrations, age, comorbidities and immunoglobulin heavy chain (IGHV) mutational status. Ibrutinib, an oral inhibitor of Bruton tyrosine kinase (BTK), commonly used therapy for chronic lymphocytic leukaemia can lead to pseudo-Richter's transformation.[5]

CASE PRESENTATION

A 65-year-old male with no known comorbidities was referred to the Out-Patient Department (OPD) for evaluation of lymphocytosis. He had a history of weakness, lethargy, abdominal pain, and low-grade fever in the last few months. On physical examination, he had generalized lymphadenopathy and splenomegaly, 6 cm below the left costal margin. His complete blood count showed haemoglobin 8.1 gm/dL, white blood count 143 x 10^9/L and platelets 95 x 10^9/L. Immunophenotyping by flow cytometry was also performed, which showed: CD45: 97%, CD19: 92%, CD20: 91%, CD22: 44%, cCD79a: 65%, CD23: 64%, CD5: 92%, CD38: 72%, CD200: 96%, HLA-DR: 96%, KAPPA: 51%, whereas CD34, TDT, CD3, cCD3, CD4, CD8, CD7, CD10, CD13, CD33, MPO, CD14, FMC7 & LAMBDA were all negative. Double bright positivity of CD19 & CD5 was prominent. Further investigations revealed serum creatinine 2.30 mg/dl, uric acid 4.10 mg/dl, calcium 8.20 mg/dl, LDH 326 U/L. His renal function tests normalized with intravenous (IV) fluid hydration and a whole-body computed tomography (CT) scan was done with contrast which showed multiple enlarged lymph nodes at the

cervical, mediastinum and axillary region along with splenomegaly (18cm). Prognostic workup showed deletion of ATM gene (11q22.3) in 67% of 200 nuclei scored by fluorescence in situ hybridization (FISH) assay. The patient was diagnosed with B-cell chronic lymphocytic leukaemia with a Rai score of IV (high) and Binet score C. As the patient could now be classified in the high-risk category per these scales, he was advised treatment with chemo-immunotherapy, however; due to financial constraints, he was reluctant for treatment with parenteral chemotherapy. Hence, he was started on a treatment regimen with chlorambucil and prednisolone. In the meanwhile, arrangements for financial resources were started for him. After 2 cycles of this regimen, there was an improvement in the complete blood counts. However, his abdominal pain, spleen size, and B-symptoms were not improving. Meanwhile, Rituximab and bendamustine were started and he responded well and was discharged in stable condition.

After 3 weeks, he presented again with a fever and worsening abdominal pain. On examination, he exhibited massive splenomegaly to the extent of the umbilicus. Complete blood count showed: haemoglobin 4.8 gm/dL, white blood count: 3.5x10^9/L, platelets 19 x 10^9/L. Peripheral film review showed large atypical lymphocytes having scanty basophilic cytoplasm with vacuolization (Figure 1A). The patient was managed with broad-spectrum intravenous antibiotics. After stabilization, a bone trephine biopsy was performed which showed bone marrow aspirate with large atypical lymphocytes. These lymphocytes have basophilic cytoplasm along with vacuolation (Figure 1B). Bone trephine also showed a completely effaced architecture with a monotonous infiltrate of atypical lymphoid cells (Figure 1C) which strongly expressed CD20 but was negative for CD 05 (Figure 1D). Immunophenotyping by flow cytometry was repeated again which showed: CD45: 64%, CD19: 43%, CD20: 32%, CD22: 22%, cCD79a: 44%, CD23: 33%, CD5: 00%, CD38: 24%, CD200: 37%, HLA-DR: 15%, FMC7: 14%, whereas CD34, TDT, CD3, cCD3 CD4, CD8, CD7, CD10, CD13, CD33, MPO, CD14 & LAMBDA were all negative. Double bright positivity of CD19 & CD5 as well as KAPPA was absent.

Therefore, the patient's worsening splenomegaly, pancytopenia, bone marrow biopsy and flow cytometry findings were consistent with Richter's transformation of B-Cell chronic lymphocytic leukaemia into Diffuse large B-Cell Lymphoma. The patient eventually developed sepsis, multiple organ failure and ultimately succumbed to death.

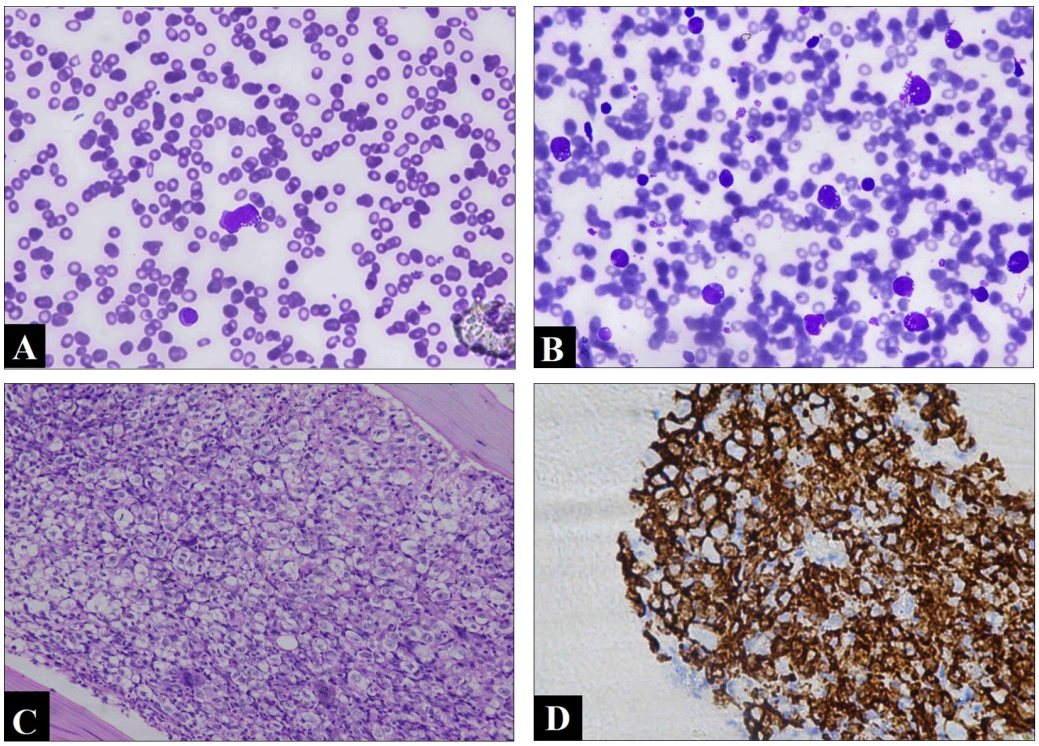

Figure-1: Peripheral film, bone marrow biopsy, and bone trephine histology
Peripheral Film (A), Bone Marrow Biopsy (B), and Bone Trephine (C, D)

DISCUSSION

The seriousness of Chronic Lymphocytic Leukaemia drastically increases as patients undergo Richter's transformation, which describes the progression of this disease into a new disease state: diffuse large B-cell lymphoma or the traditionally observed Hodgkin lymphoma.[5] Approximately 2–10% of chronic lymphocytic leukaemia patients undergo Richter's transformation into Diffuse large B-Cell Lymphoma, which alters the indolent disease course into one which is far more aggressive in nature.[6] Richter's transformation is characterized by B-type symptoms (weight loss, fever, night sweats), a dramatic increase in the size of the patient's lymph nodes (lymphoma) or spleen, hypercalcemia, and increased lactate dehydrogenase.[7] In contrast to chronic lymphocytic leukaemia, which exhibits variable prognostic outcomes, the diffuse large B-Cell lymphoma resulting from Richter's transformation has a much poorer prognosis.[8] Some studies have been conducted in order to investigate the factors which contribute to the risk of Richter's transformation in patients with Chronic Lymphocytic Leukaemia. The findings of such publications provide evidence that the genetic and biological features of the patient as well as the previously received therapies, may all influence the risk of Richter's transformation.[7] Despite these findings, the exact mechanism by which these factors contribute to a higher risk of Richter's transformation remains unclear.

In Conclusion, Richter's transformation is a rare phenomenon in which chronic lymphocytic leukaemia progresses into an aggressive lymphoma. Although the exact mechanisms behind this pathology remain unclear, various studies allude to multifactorial aetiology. These case reports which document the variable presentations of this disease help clinicians in identifying a rapidly declining patient who may have incurred this transformation and now faces an even poorer prognosis.

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