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CASE REPORT

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Ibrutinib treatment of a patient with relapsing chronic lymphocytic leukemia and sustained remission of Richter syndrome

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ABSTRACT

Purpose: Richter syndrome (RS) is a rare event in chronic lymphocytic leukemia (CLL) that is influenced by biological factors and prior CLL treatments. Ibrutinib is a Bruton tyrosine kinase inhibitor that has shown remarkable efficacy in CLL; however, little is known about its relationship to RS. We report a case of ibrutinib efficacy against CLL in a patient with prolonged remission of RS.

Methods: The patient was diagnosed with CLL in 2003. Biological findings at onset included absent ZAP70 expression, mutated IGVH, and NOTCH1 mutation. He was treated with FCR with partial response. In 2013, he progressed to RS, not clonally related to the underlying CLL. The patient was treated with anthracycline- and platinum-based regimens, obtaining a complete remission. After 3 years, he presented a CLL progression with worsening lymphocytosis, anemia, thrombocytopenia, increased splenomegaly, and lymphadenopathies. Positron emission tomography-computed tomography scan excluded pathologic uptake. Thus, he was started on ibrutinib.

Results: At 12 months' follow-up, we observed white blood cell normalization, increased hemoglobin and platelet levels, disappearance of lymphadenopathy, and spleen size reduction. Therapy was well-tolerated with no evidence of RS.

Conclusion: This case demonstrates sustained RS remission in a patient with CLL under ibrutinib therapy, thus improving our knowledge on the use of this new drug in CLL and beyond.

Keywords: Chronic lymphocytic leukemia, Ibrutinib, NOTCH1 mutation, Richter syndrome

Introduction

Chronic lymphocytic leukemia (CLL) is an indolent lymphoproliferative disorder that occasionally transforms to Richter syndrome (RS), a high-grade lymphoma with a poor outcome (1). Richter syndrome occurs in 2% to 8% of patients with CLL and the use of conventional CLL therapies increases the transformation rate. Ibrutinib is a Bruton tyrosine kinase inhibitor that has shown remarkable efficacy in CLL (2); however, little is known about its relationship to RS. We describe the use of ibrutinib in a patient with relapsed CLL who achieved complete remission of an aggressive lymphoma transformation.

Case report

A 73-year-old man was diagnosed with CLL in 2003, after a complete blood count (CBC) showed lymphocytosis and mild thrombocytopenia. Imaging revealed enlarged spleen together with cervical, axillary, and inguinal lymphadenopathy. A bone marrow biopsy showed pathologic findings consistent with CLL. ZAP70 and CD38 expression was absent. Gene mutation analysis revealed mutated IGVH and a subclonal NOTCH1 mutation. In 2008, the patient received treatment with fludarabine, cyclophosphamide, and rituximab, resulting in splenomegaly reduction and stable thrombocytopenia. Five years later, he presented with

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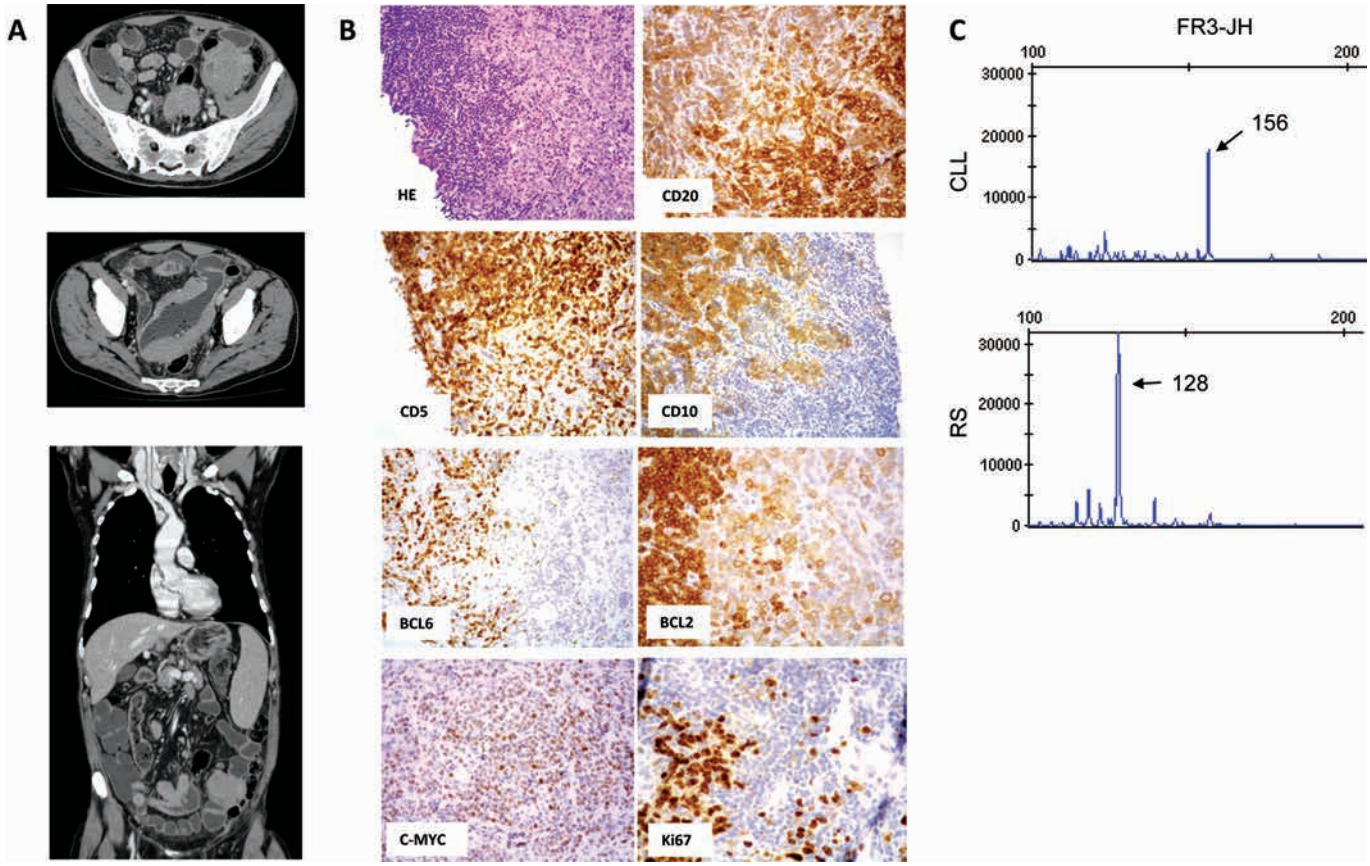

Fig. 1 - (**A**) Computed tomography scan shows 2 abdominal masses: the first of about 14 centimeters in contact with a loop of small intestine, determining stenosis and expansion until the rectovesical pouch; the second of about 7 centimeters between descending colon and proximal sigma. (**B**) Richter transformation in the abdominal mass. Histology shows diffuse infiltration that is composed primarily of large pleomorphic lymphocytes consistent with diffuse large cell lymphoma of germinal center B-cell-like origin. The lymphoma neoplastic cells are positive for CD20, CD10, BCL6, and BCL2 (moderate staining intensity), and negative for CD5. Approximately 80% of the cells are positive for MYC with a mild to moderate intensity of staining. Ki-67 nuclear labeling was about 90%-95%. In some areas, a residual infiltrate of small lymphocytes is present together with the aggressive lymphoma component. Immunophenotyping shows this abnormal lymphoid population to express CD5, CD20 (weak staining intensity), and BCL2 (strong staining intensity), and to be negative for CD10 and BCL6, consistent with preexisting B-cell chronic lymphocytic leukemia (CLL). HE = hematoxylin & eosin. Magnification ×400. (**C**) B-cell clonality results on peripheral blood and biopsy of the abdominal mass. The DNA extracted from paraffin-embedded specimen was analyzed using the IgH Rearrangements Molecular Analysis Kit (Master Diagnòstica). The polymerase chain reaction product obtained from the amplification of the IgH (FR3-JH) segment was run on a 3500 Genetic Analyzer (Applied Biosystems), and results were analyzed with the GeneMapper 5 software. Different FR3-JH rearrangement patterns were observed between CLL and Richter transformation (RS). The upper panel shows a 156 bp clonal peak of the CLL sample. The lower panel shows a 128 bp peak of the RS sample.

abdominal pain due to intestinal obstruction. A computed tomography (CT) scan of the abdomen showed marked splenomegaly (18 cm) and 2 large stenotizing masses (Fig. 1A). Due to concern about possible transformation, a biopsy of the abdominal mass was performed, showing infiltration of large B cells consistent with diffuse large cell lymphoma (Fig. 1B). Immunoglobulin gene rearrangement analysis indicated that the aggressive lymphoma was not clonally related to the underlying CLL (Fig. 1C). Consistent with this result, NOTCH1 mutational burden was lesser than diagnosed CLL. The patient was treated with 6 courses of rituximab with cyclophosphamide, vincristine, liposomal doxorubicin, and prednisone with suboptimal response. Then rituximab, dexamethasone, high-dose cytarabine, and oxaliplatin was given for only one cycle due to cytomegalovirus pneumonia. The CT scan reevaluation documented good response with disappearance of abdominal masses and stable splenomegaly. Starting from January 2016, serial CBCs revealed worsening lymphocytosis, anemia, and thrombocytopenia. A positron emission tomography/CT scan showed increased splenomegaly (24 cm) and multiple lymphadenopathies without F-fluorodeoxyglucose pathologic uptake (Fig. 2A). Fluorescence in situ hybridization showed deleted 13q. In light of these findings, the patient started ibrutinib for progressive CLL. After 9 months of therapy, we observed lymphocyte count normalization together with increased hemoglobin and platelet levels (Fig. 2B). Abdominal and superficial lymph nodes disappeared while spleen size was significantly reduced. Therapy was well-tolerated with no evidence of Richter transformation.

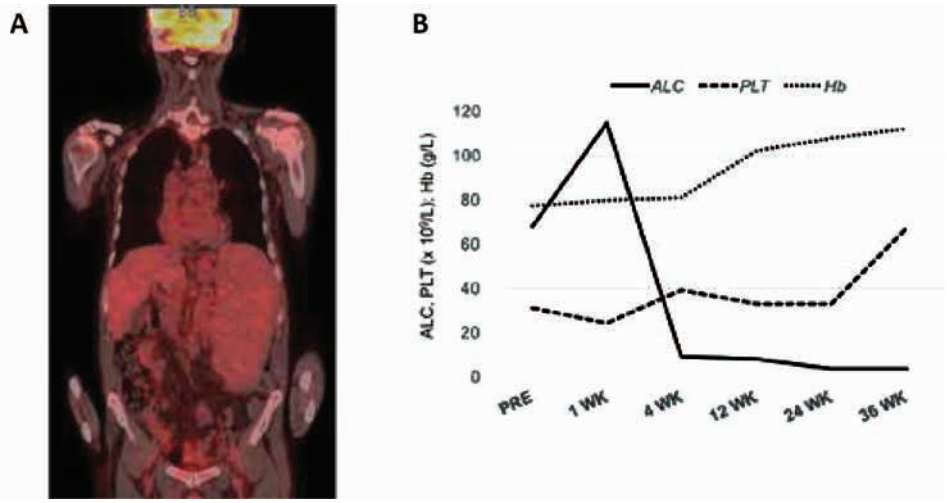

Fig. 2 - (**A**) A positron emission tomography scan performed before ibrutinib treatment shows absence of glucose hypermetabolism of the multiple lymphadenopathy in the axillary, cervical, mediastinal, and abdominal areas. Furthermore, there was a significantly enlarged spleen at 24 centimeters. Uptake and imaging findings were more consistent with indolent chronic lymphocytic leukemia. (**B**) Changes in peripheral blood counts following ibrutinib therapy. ALC = absolute lymphocyte count; Hb = hemoglobin; PLT = platelets.

Discussion

Richter syndrome is a rare event in patients with CLL that is influenced by different biological factors including non-del13q cytogenetics, TP53 disruption, and unmutated IGHV gene (3). Recent studies demonstrated that approximately 80% of RS cases were clonally related to the underlying CLL and displayed a poor outcome. In the remaining 20% of patients, RS represented a de novo diffuse large B cell lymphoma (DLBCL) with an improved median survival of 5 years. In our case, immunoglobulin gene rearrangement analysis showed clonally unrelated RS, which explained treatment efficacy. More recently, NOTCH1 mutation has been described to be a negative CLL prognosticator (4, 5), and a key genetic aberration contributing to transformation to RS (6, 7). In this report, CLL showed a small NOTCH1-mutated subclone whose allelic ratio was reduced at RS, further supporting the diagnosis of a de novo DLBCL.

Data on the contribution of CLL therapy to RS development are controversial. Some studies suggested that a large number of prior therapies increased the risk of RS (8). The incidence of transformation was higher in patients treated with conventional CLL therapy using purine analogues and alkylating agents. In recent years, new drugs targeting the B-cell receptor (BCR) have revolutionized CLL treatment. Despite the growing evidence of high antileukemic efficacy associated with these drugs, their role in RS remains a high research priority. Ibrutinib was one of the first BCR signaling inhibitors with very effective therapeutic activity against CLL that determined a high response rate in previously untreated and relapsed/refractory (R/R) patients (2). The link between ibrutinib treatment and RS transformation of patients with CLL is unclear as data are limited.

To our knowledge, this report indicates for the first time that ibrutinib efficacy against CLL was not associated with RS recurrence in a patient with sustained remission of the aggressive lymphoma. In the phase 1b/2 PCYC-1102 study, the percentage of RS was at the upper limit of the incidence rate described in specific clinical trials (2). However, these patients were heavily pretreated with an average of 3 different chemotherapy regimens and the majority had high-risk disease features. Additionally, many of the transformation events developed shortly after the patient started therapy, suggesting that unrecognized RS likely preexisted treatment initiation. Indeed, in a 3-year follow-up report in 132 patients including R/R and treatment-naive CLL from PCYC-1102 and the extension study PCYC-1103, the number of patients with RS remained at 8 (9). Additional single-center studies confirmed that RS accounts for early progression-related discontinuation of ibrutinib in 4.7% to 5.8% of patients with CLL (10). Conversely, RS was a rare event in patients treated with ibrutinib in the phase 3 study of Ibrutinib (PCI-32765) versus Ofatumumab in patients with R/R CLL (RESONATE) and no transformation was observed in a phase III study of ibrutinib in combination with bendamustine and rituximab in R/R CLL (HELIOS) (11).

Because of a lack of efficacious standard treatment options, the efficacy of ibrutinib was tested on RS, demonstrating the possibility of transient disease control (12). Though limited to case reports, this observation proved that ibrutinib is a novel approach that may have promise in the management of RS. Future trials investigating its use, either as monotherapy or in combination, appear warranted.

Conclusion

Although anecdotal, the case that we report indicates that ibrutinib treatment did not influence the risk of RS relapse, despite the presence of biological and clinical factors associated with CLL transformation. Extended follow-up of large cohorts of patients with CLL will be necessary to fully understand the risk of RS associated with new therapeutic BCR inhibitors, particularly in treatment-naive patients with CLL.

Disclosures

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