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【 CASE REPORT 】

Early Transformation to Classic Hodgkin Lymphoma in a Chemotherapy-naïve Chronic Lymphocytic Leukemia Patient upon Initial Treatment with Ibrutinib

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Abstract:
A 71-year-old woman with a four-year history of chronic lymphocytic leukemia (CLL) received ibrutinib as initial treatment due to progressive anemia and thrombocytopenia. Eleven months after the start of the treatments, although her cytopenia had ameliorated, she developed classic Hodgkin lymphoma, a rare form of Richter's transformation. She was successfully treated with two courses of adriamycin, vinblastin, bleomycin and dacarbazine followed by radiotherapy. In general, several clinical, genetic and molecular factors are associated with Richter's transformation. In addition, our present case suggested that ibrutinib could be a potential risk factor for Richter's transformation in CLL patients.

Key words: CLL, ibrutinib, Richter's transformation

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Introduction

The introduction of ibrutinib, a major Bruton tyrosine kinase inhibitor (BTKi), improves the prognosis of chronic lymphocytic leukemia (CLL), and ibrutinib is now widely used in clinical settings for both relapsed/refractory cases and initially diagnosed cases (1, 2). However, while ibrutinib does induce durable antitumor activity in CLL patients, a significant proportion of patients discontinue therapy due to progression of CLL or transformation to another type of aggressive lymphoproliferative malignancy, known as Richter's transformation (RT) (3).

According to recent clinical studies, approximately 10% to 20% of patients develop RT upon treatment with ibrutinib (3-5). These studies also indicated that RT development during ibrutinib treatment led to unique clinical findings. First, the RT associated with ibrutinib develops earlier in the clinical course than conventional types, with most patients experiencing transformation within one year of the initiation of ibrutinib treatment, which differs from the progression of CLL. Second, relapsed/refractory patients with a history of chemotherapy, especially those treated with purine analog-containing regimens, tended to develop RT during ibrutinib treatment (2). Finally, transformation after ibrutinib treatment tended to lead to unique pathological findings. Several studies analyzing RT after ibrutinib treatment have shown a relatively high incidence of transformation to Hodgkin lymphoma (4, 5).

We herein report a case of CLL transformation to classic Hodgkin lymphoma upon treatment with ibrutinib. Although the patient received ibrutinib as initial chemotherapy, RT occurred within 12 months of the initiation of the ibrutinib regimen.

Case Report

A 71-year-old woman with a 4-year history of untreated CLL was referred to our institution due to progressive anemia and thrombocytopenia. At the time of her referral, the

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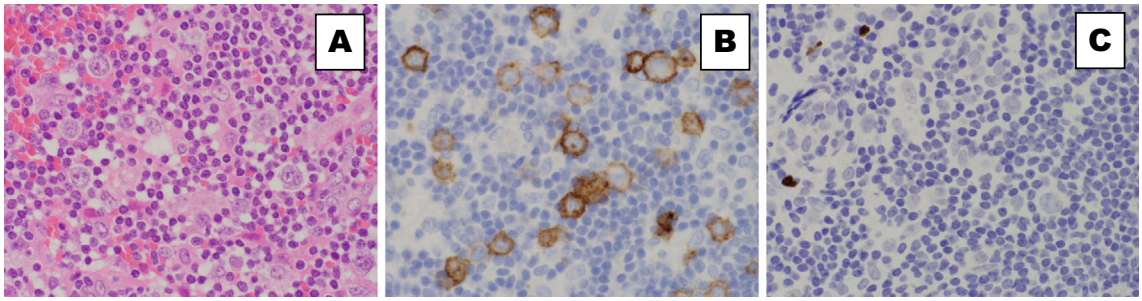

Figure 1. Pathological findings in the lymph nodes. Hematoxylin and Eosin staining showing Reed-Sternberg cells (A). These cells were positive for CD30 (B) but negative for EBV-encoded RNA (C).

patient's complete blood cell counts were as follows: white blood cell count of 23.9×10^9/L, hemoglobin level of 9.2 g/dL and platelet count of 114×10^9/L. Fluorescence *in situ* hybridization (FISH) studies revealed negative results for both del(17)(p13.1) and trisomy 12. A conventional chromosomal analysis indicated 46, XX, inv(9)(p12q13), which is known as a normal variant. We diagnosed her with active disease according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines (6) and started treatment with ibrutinib monotherapy.

Ten months after the initiation of the ibrutinib regimen, the patient showed improvement of leukocytosis, anemia and thrombocythemia, with white blood cell counts of 9.1×10^9/L, Hb of 11.6 g/dL and a platelet number of 157×10^9/L. At this point, she did not show any enlargement of the lymph nodes or splenomegaly. However, 11 months after the initiation of ibrutinib treatment, she showed progressive enlargement of the left submandibular lymph nodes. A surgical biopsy of the enlarged lymph node was performed. A pathological analysis revealed the presence of Reed-Sternberg cells, which were positive for CD30 (Fig. 1). *In situ* hybridization for Epstein-Barr virus (EBV)-encoded small RNAs (EBER) was negative (Fig. 1). Based on these findings, we diagnosed her with RT with mixed cellularity-type classic Hodgkin lymphoma.

At the same time, a bone marrow biopsy sample showed the infiltration of CLL cells positive for CD20, CD5 and LEF-1 (Fig. 2). There was no evidence for the infiltration of Hodgkin lymphoma into the bone marrow. Chromosomal studies of the lymph node biopsy samples revealed that 6 of 20 cells had chromosomal abnormalities: 47, XX, inv(9)(p12 q13), -14, +18, der(?)t(?;14)(?;q11.2). In contrast, the bone marrow samples show a normal variant pattern, as previously confirmed. The patient was treated with two courses of adriamycin, vinblastin, bleomycin and dacarbazine (ABVD) followed by involved-field radiotherapy, and she achieved complete remission of Hodgkin lymphoma. Despite ibrutinib being discontinued after the diagnosis of RT, hematological improvement has been maintained thus far.

Discussion

Historically, the incidence of RT has been reported to be 2-10% among CLL patients (7). Common pathological findings of RT are diffuse large-B cell lymphoma (DLBCL), and less frequently, CLL patients show transformation to Hodgkin lymphoma. Studies performed before the introduction of novel agents, i.e. BTKi or venetoclax, found that the incidence of classic Hodgkin lymphoma transformation was less than 10% that of RT. A retrospective study of 4,121 CLL patients from MD Anderson Cancer Center indicated that only 18 patients (0.4%) developed Hodgkin-like transformation (8). A study from the Mayo Clinic reported that 26 of 3,387 CLL patients (0.7%) showed transformation to Hodgkin lymphoma (9).

Several clinical, genetic and molecular factors have been statistically proven to be associated with RT of CLL (7). An enlarged lymph node exceeding 3 cm in size was established as a risk factor for RT. Regarding chromosomal abnormalities, the presence of trisomy 12, del(17) or del(11q) was considered a risk factor for RT. The absence of del(13) is also a genetic change associated with RT. Molecular studies have identified the disruption of the *TP53* gene, gain-of-function *NOTCH1* mutation, or deletion of *CDKN2A/B* as risk factors for RT (7).

However, these previous findings were mainly drawn from observations based on total cases of RT largely composed of the DLBCL type. Therefore, little is known about the risk factors specifically associated with Hodgkin lymphoma transformation. Case series studies have suggested a possible role of immunosuppression by fludarabine and EBV infection in the transformation to Hodgkin lymphoma; however, others have found no meaningful association (10). Interestingly, recent retrospective studies and a line of case reports have suggested that the incidence of Hodgkin lymphoma transformation was relatively high after BTKi treatment compared to historical data. The Polish adult leukemia group reported that all three patients who developed RT during ibrutinib treatment had a Hodgkin lymphoma phenotype (4, 11). Ahn et al. reported 5 transformation cases in a phase 2 trial with ibrutinib for CLL (5). Among these five cases, two were confirmed to have Hodgkin lymphoma (5). Furthermore, six more CLL cases, including the case presented herein, with Hodgkin lymphoma transformation after BTKi treatment have been reported (12-15). However, most of these cases were relapsed and/or refractory to several pre-

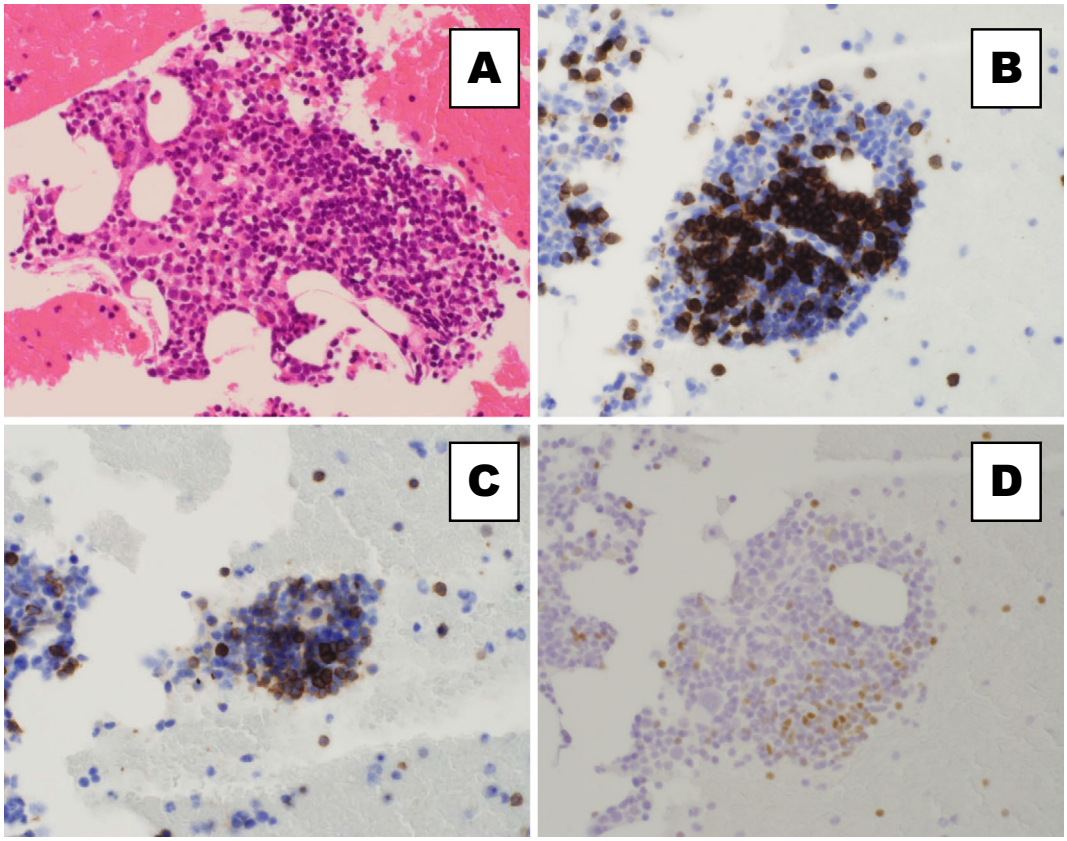

Figure 2. Pathological findings in the bone marrow. Hematoxylin and Eosin staining showing the infiltration of CLL cells (A). These cells were positive for CD20 (B) and CD5 (C) and weakly positive for lymphocyte enhancer-binding factor 1 (LEF-1) (D).

vious lines of chemotherapy, including purine analogs. Therefore, the RT that develops upon BTKi treatment may not be the result of the use of these agents but instead associated with the pretreatment status of the disease (7). Indeed, Taneja et al. reported that two CLL patients with pre-exiting Reed-Sternberg cells in the lymph nodes before the initiation of BTKi treatment transformed to Hodgkin lymphoma (15). This notion is supported by the finding that RT was not observed in a phase 3 study of ibrutinib for chemotherapy-naïve CLL patients (2).

The present findings provide some important information to bear in mind when considering the potential risk of ibrutinib for inducing RT. Our patient did not have a history of chemotherapy and received ibrutinib as a first-line treatment. From a genetics perspective, the patient did not have trisomy of 12 or del(17), both of which are well accepted genetic risk factors for RT (7). In addition, a pathological analysis revealed no contribution from EBV to the transformation of this patient. A chromosomal analysis showed that the transformed cells acquired complex karyotype abnormalities, but the CLL cells did not. These findings suggest that the administration of ibrutinib might have induced genetic instability and progression to transformation in this patient. Importantly, Compagno et al. found that ibrutinib enhanced the expression of activation-induced cytidine deaminase (AID) in CLL cells (16). Since the overexpression of AID induces mutagenic activity, these authors raised concerns about a potential mutagenic risk to patients receiving long-term therapy with ibrutinib (16). Furthermore, a recent observational study indicated the association of a secondary cancer risk with the use of ibrutinib in CLL patients (17).

It is important to consider the potential risk of ibrutinib for inducing transformation and carefully observe the emergence of other types of B-cell neoplasms in CLL patients treated with ibrutinib.

The authors state that they have no Conflict of Interest (COI).

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